CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021368/S-020

Trade Name: **CIALIS**

Generic Name: **Tadalafil**

Sponsor: **Eli Lilly and Company**

Approval Date: 10/06/2011

Indications: CIALIS® is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of:

- erectile dysfunction
- the signs and symptoms of benign prostatic hyperplasia
- ED and the signs and symptoms of BPH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021368/S-020 and S-021

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Sofia S. Khan, PharmD
Manager, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, Indiana, 46285

Dear Dr. Khan:

Please refer to your Supplemental New Drug Applications (sNDAs) dated December 3 and 6, 2010, received December 6, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cialis® (tadalafil) tablets, 5mg.

We acknowledge receipt of your amendments dated December 10, 2010, February 25, March 18 and 30, April 12 and 20, May 13, June 23, September 1 (2), 2, 15 (3), and 30, 2011.

These "Prior Approval" supplemental new drug applications provide for

> Supplement 20: treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
>
> Supplement 21: treatment of erectile dysfunction (ED) and the signs and symptoms of BPH.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the

patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies for each supplement, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021368/S-020 and NDA 021368/S-021**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because benign prostatic hyperplasia and erectile dysfunction do not exist in children.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling for these indications. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and a package insert, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Division Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SCOTT E MONROE
10/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CIALIS safely and effectively. See full prescribing information for CIALIS.

CIALIS (tadalafil) tablets, for oral use

Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Indications and Usage:	
Benign Prostatic Hyperplasia (1.2)	10/2011
Erectile Dysfunction and Benign Prostatic Hyperplasia (1.3)	10/2011
Dosage and Administration:	
Dosage and Administration (2)	10/2011
CIALIS for Once Daily Use for Benign Prostatic Hyperplasia (2.3)	10/2011
CIALIS for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia (2.4)	10/2011
Use in Specific Populations (2.6)	10/2011
Concomitant Medications (2.7)	10/2011
Warnings and Precautions:	
Warnings and Precautions (5)	10/2011
Alpha-blockers and Antihypertensives (5.6)	10/2011
Renal Impairment (5.7)	10/2011
Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH (5.14)	10/2011

----------INDICATIONS AND USAGE----------

CIALIS® is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of:

- erectile dysfunction (ED) (1.1)
- the signs and symptoms of benign prostatic hyperplasia (BPH) (1.2)
- ED and the signs and symptoms of BPH (ED/BPH) (1.3)

----------DOSAGE AND ADMINISTRATION----------

- *CIALIS for use as needed*
  - ED: Starting dose: 10 mg as needed prior to sexual activity. Increase to 20 mg or decrease to 5 mg based upon efficacy/tolerability. Improves erectile function compared to placebo up to 36 hours post dose. Not to be taken more than once per day (2.1).
- *CIALIS for once daily use*
  - ED: 2.5 mg taken once daily, without regard to timing of sexual activity. May increase to 5 mg based upon efficacy and tolerability (2.2).
  - BPH: 5 mg, taken at approximately the same time every day (2.3)
  - ED and BPH: 5 mg, taken at approximately the same time every day (2.3, 2.4)
- CIALIS may be taken without regard to food (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 2.5 mg, 5 mg, 10 mg, 20 mg (3).

----------CONTRAINDICATIONS----------

- Administration of CIALIS to patients using any form of organic nitrate is contraindicated. CIALIS was shown to potentiate the hypotensive effect of nitrates (4.1).
- History of known serious hypersensitivity reaction to CIALIS or ADCIRCA® (4 2).

----------WARNINGS AND PRECAUTIONS----------

- Patients should not use CIALIS if sex is inadvisable due to cardiovascular status (5.1).
- Use of CIALIS with alpha blockers, antihypertensives or substantial amounts of alcohol (≥5 units) may lead to hypotension (5.6, 5.9).
- CIALIS is not recommended in combination with alpha blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. Caution is advised when CIALIS is used as a treatment for ED in men taking alpha blockers. (2.7, 5.6, 7.1, 12.2)
- If taking potent inhibitors of CYP3A4, dose should be adjusted: CIALIS for use as needed: ≤10 mg every 72 hours. For once daily use: dose not to exceed 2.5 mg (5.10).
- Patients should seek emergency treatment if an erection lasts >4 hours. Use CIALIS with caution in patients predisposed to priapism (5.3).
- Patients should stop CIALIS and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of Non Arteritic Ischemic Optic Neuropathy (NAION). Discuss increased risk of NAION in patients with history of NAION (5.4).
- Patients should stop CIALIS and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.5).
- Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms (5.14).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥2%) include headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- CIALIS can potentiate the hypotensive effects of nitrates, alpha blockers, antihypertensives or alcohol (7.1).
- CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase CIALIS exposure. For concomitant use with potent CYP3A4 inhibitors, dose adjustment may be needed (2.7, 5.10, 7.2).
- CYP3A4 inducers (e.g. rifampin) decrease CIALIS exposure (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment (2.6, 5.8, 8.6):

- Mild or Moderate: Dosage adjustment may be needed.
- Severe: Use is not recommended.

Renal Impairment (2.6, 5.7, 8.7):

- Patients with creatinine clearance 30 to 50 mL/min: Dosage adjustment may be needed.
- Patients with creatinine clearance less than 30 mL/min or on hemodialysis: For use as needed: Dose should not exceed 5 mg every 72 hours. Once daily use is not recommended.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Erectile Dysfunction

CIALIS® is indicated for the treatment of erectile dysfunction (ED).

1.2 Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

1.3 Erectile Dysfunction and Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

2 DOSAGE AND ADMINISTRATION

Do not split CIALIS tablets; entire dose should be taken.

2.1 CIALIS for Use as Needed for Erectile Dysfunction

- The recommended starting dose of CIALIS for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity.
- The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.
- CIALIS for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of CIALIS, this should be taken into consideration.

2.2 CIALIS for Once Daily Use for Erectile Dysfunction

- The recommended starting dose of CIALIS for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.
- The CIALIS dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability.

2.3 CIALIS for Once Daily Use for Benign Prostatic Hyperplasia

The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day.

2.4 CIALIS for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia

The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

2.5 Use with Food

CIALIS may be taken without regard to food.

2.6 Use in Specific Populations

Renal Impairment

CIALIS for Use as Needed

- Creatinine clearance 30 to 50 mL/min: A starting dose of 5 mg not more than once per day is recommended, and the maximum dose is 10 mg not more than once in every 48 hours.
- Creatinine clearance less than 30 mL/min or on hemodialysis: The maximum dose is 5 mg not more than once in every 72 hours *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

Erectile Dysfunction

- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Benign Prostatic Hyperplasia and Erectile Dysfunction/Benign Prostatic Hyperplasia

- Creatinine clearance 30 to 50 mL/min: A starting dose of 2.5 mg is recommended. An increase to 5 mg may be considered based on individual response.
- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Hepatic Impairment

CIALIS for Use as Needed

- Mild or moderate (Child Pugh Class A or B): The dose should not exceed 10 mg once per day. The use of CIALIS once per day has not been extensively evaluated in patients with hepatic impairment and therefore, caution is advised.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

- Mild or moderate (Child Pugh Class A or B): CIALIS for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

2.7 Concomitant Medications

Nitrates

Concomitant use of nitrates in any form is contraindicated *[see Contraindications (4.1)]*.

Alpha Blockers

ED — When CIALIS is coadministered with an alpha blocker in patients being treated for ED, patients should be stable on alpha-blocker therapy prior to initiating treatment, and CIALIS should be initiated at the lowest recommended dose *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

BPH — CIALIS is not recommended for use in combination with alpha blockers for the treatment of BPH *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

CYP3A4 Inhibitors

CIALIS for Use as Needed — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of CIALIS is 10 mg, not to exceed once every 72 hours *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

CIALIS for Once Daily Use — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose is 2.5 mg *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow:
2.5 mg tablets debossed with "C 2 1/2"
5 mg tablets debossed with "C 5"
10 mg tablets debossed with "C 10"
20 mg tablets debossed with "C 20"

4 CONTRAINDICATIONS

4.1 Nitrates

Administration of CIALIS to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates *[see Clinical Pharmacology (12.2)]*.

4.2 Hypersensitivity Reactions

CIALIS is contraindicated in patients with a known serious hypersensitivity to tadalafil (CIALIS or ADCIRCA®). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

Evaluation of erectile dysfunction and BPH should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing CIALIS, it is important to note the following:

5.1 Cardiovascular

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including CIALIS, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention. *[See Contraindications (4.1) and Patient Counseling Information (17.1)]*.

Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for CIALIS, and therefore until further information is available, CIALIS is not recommended for the following groups of patients:

- myocardial infarction within the last 90 days
- unstable angina or angina occurring during sexual intercourse
- New York Heart Association Class 2 or greater heart failure in the last 6 months
- uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension
- stroke within the last 6 months.

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects *[see Clinical Pharmacology (12.2)]*. While this effect should not be of consequence in most patients, prior to prescribing CIALIS, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

5.2 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should be aware that CIALIS for once daily use provides continuous plasma tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, anti-hypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol *[see Drug Interactions (7.1, 7.2, 7.3)]*.

5.3 Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

CIALIS should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

5.4 Eye

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors *[see Adverse Reactions (6.2)]*.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

5.5 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.1, 6.2)]*.

5.6 Alpha-blockers and Antihypertensives

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha blockers and antihypertensive medications *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

Caution is advised when PDE5 inhibitors are coadministered with alpha blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

ED

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose.
- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other antihypertensive drugs.

[See Dosage and Administration (2.7) and Drug Interactions (7.1)].

BPH

- The efficacy of the co-administration of an alpha-blocker and CIALIS for the treatment of BPH has not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure lowering, the combination of CIALIS and alpha-blockers is not recommended for the treatment of BPH. *[See Dosage and Administration (2.7), Drug Interactions (7.1), and Clinical Pharmacology (12.2.)]*.
- Patients on alpha-blocker therapy for BPH should discontinue their alpha-blocker at least one day prior to starting CIALIS for once daily use for the treatment of BPH.

5.7 Renal Impairment

CIALIS for Use as Needed

CIALIS should be limited to 5 mg not more than once in every 72 hours in patients with creatinine clearance less than 30 mL/min or end-stage renal disease on hemodialysis. The starting dose of CIALIS in patients with creatinine clearance 30 – 50 mL/min should be 5 mg not more than once per day, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. *[See Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

ED

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min *[see Use in Specific Populations (8.7)]*.

BPH and ED/BPH

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min. In patients with creatinine clearance 30 – 50 mL/min, start dosing at 2.5 mg once daily, and increase the dose to 5 mg once daily based upon individual response *[see Dosage and Administration (2.6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.8 Hepatic Impairment

CIALIS for Use as Needed

In patients with mild or moderate hepatic impairment, the dose of CIALIS should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

CIALIS for once daily use has not been extensively evaluated in patients with mild or moderate hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

5.9 Alcohol

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Clinical Pharmacology (12.2)]*.

5.10 Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)

CIALIS is metabolized predominantly by CYP3A4 in the liver. The dose of CIALIS for use as needed should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole *[see Drug Interactions (7.2)]*. In patients taking potent inhibitors of CYP3A4 and CIALIS for once daily use, the maximum recommended dose is 2.5 mg *[see Dosage and Administration (2.7)]*.

5.11 Combination With Other PDE5 Inhibitors or Erectile Dysfunction Therapies

The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take CIALIS with other PDE5 inhibitors, including ADCIRCA.

5.12 Effects on Bleeding

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. CIALIS has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although CIALIS has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

5.13 Counseling Patients About Sexually Transmitted Diseases

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

5.14 Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH

Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Tadalafil was administered to over 9000 men during clinical trials worldwide. In trials of CIALIS for once daily use, a total of 1434, 905, and 115 were treated for at least 6 months, 1 year, and 2 years, respectively. For CIALIS for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

CIALIS for Use as Needed for ED

In eight primary placebo-controlled clinical studies of 12 weeks duration, mean age was 59 years (range 22 to 88) and the discontinuation rate due to adverse events in patients treated with tadalafil 10 or 20 mg was 3.1%, compared to 1.4% in placebo treated patients.

When taken as recommended in the placebo-controlled clinical trials, the following adverse reactions were reported (*see* Table 1) for CIALIS for use as needed:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS (10 or 20 mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for CIALIS for Use as Needed for ED

Adverse Reaction	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing[a]	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

[a] The term flushing includes: facial flushing and flushing

CIALIS for Once Daily Use for ED

In three placebo-controlled clinical trials of 12 or 24 weeks duration, mean age was 58 years (range 21 to 82) and the discontinuation rate due to adverse events in patients treated with tadalafil was 4.1%, compared to 2.8% in placebo-treated patients.

The following adverse reactions were reported (*see* Table 2) in clinical trials of 12 weeks duration:

Table 2: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in the Three Primary Placebo-Controlled Phase 3 Studies of 12 weeks Treatment Duration (Including a Study in Patients with Diabetes) for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=248)	Tadalafil 2.5 mg (N=196)	Tadalafil 5 mg (N=304)
Headache	5%	3%	6%
Dyspepsia	2%	4%	5%
Nasopharyngitis	4%	4%	3%
Back pain	1%	3%	3%
Upper respiratory tract infection	1%	3%	3%
Flushing	1%	1%	3%
Myalgia	1%	2%	2%
Cough	0%	4%	2%
Diarrhea	0%	1%	2%
Nasal congestion	0%	2%	2%
Pain in extremity	0%	1%	2%
Urinary tract infection	0%	2%	0%
Gastroesophageal reflux disease	0%	2%	1%
Abdominal pain	0%	2%	1%

The following adverse reactions were reported (*see* Table 3) over 24 weeks treatment duration in one placebo-controlled clinical study:

Table 3: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in One Placebo-Controlled Clinical Study of 24 Weeks Treatment Duration for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=94)	Tadalafil 2.5 mg (N=96)	Tadalafil 5 mg (N=97)
Nasopharyngitis	5%	6%	6%
Gastroenteritis	2%	3%	5%
Back pain	3%	5%	2%
Upper respiratory tract infection	0%	3%	4%
Dyspepsia	1%	4%	1%
Gastroesophageal reflux disease	0%	3%	2%
Myalgia	2%	4%	1%
Hypertension	0%	1%	3%
Nasal congestion	0%	0%	4%

CIALIS for Once Daily Use for BPH and for ED and BPH

In three placebo-controlled clinical trials of 12 weeks duration, two in patients with BPH and one in patients with ED and BPH, the mean age was 63 years (range 44 to 93) and the discontinuation rate due to adverse events in patients treated with tadalafil was 3.6% compared to 1.6% in placebo-treated patients. Adverse reactions leading to discontinuation reported by at least 2 patients treated with tadalafil included headache, upper abdominal pain, and myalgia. The following adverse reactions were reported (*see* Table 4).

Table 4: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with CIALIS for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Three Placebo-Controlled Clinical Studies of 12 Weeks Treatment Duration, including Two Studies for CIALIS for Once Daily Use for BPH and One Study for ED and BPH

Adverse Reaction	Placebo (N=576)	Tadalafil 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Additional, less frequent adverse reactions (<1%) reported in the controlled clinical trials of CIALIS for BPH or ED and BPH included: gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Back pain or myalgia was reported at incidence rates described in Tables 1 through 4. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g., codeine) was used. Overall, approximately 0.5% of all subjects treated with CIALIS for on demand use discontinued treatment as a consequence of back pain/myalgia. In the 1-year open label extension study, back pain and myalgia were reported in 5.5% and 1.3% of patients, respectively. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Incidence rates for CIALIS for once daily use for ED, BPH and BPH/ED are described in Tables 2, 3 and 4. In studies of CIALIS for once daily use, adverse reactions of back pain and myalgia were generally mild or moderate with a discontinuation rate of <1% across all indications.

Across all studies with any CIALIS dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials of CIALIS for once daily use or use as needed. A causal relationship of these events to CIALIS is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

Body as a Whole — asthenia, face edema, fatigue, pain

Cardiovascular — angina pectoris, chest pain, hypotension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia

Digestive — abnormal liver function tests, dry mouth, dysphagia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage

Musculoskeletal — arthralgia, neck pain

Nervous — dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo

Renal and Urinary — renal impairment

Respiratory — dyspnea, epistaxis, pharyngitis

Skin and Appendages — pruritus, rash, sweating

Ophthalmologic — blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids

Otologic — sudden decrease or loss of hearing, tinnitus

Urogenital — erection increased, spontaneous penile erection

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CIALIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and Cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of CIALIS without sexual activity. Others were reported to have occurred hours to days after the use of CIALIS and sexual activity. It is not possible to determine whether these events are related directly to CIALIS, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.1)]*.

Body as a Whole — hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis

Nervous — migraine, seizure and seizure recurrence, transient global amnesia

Ophthalmologic — visual field defect, retinal vein occlusion, retinal artery occlusion

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including CIALIS. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.4)]*.

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including CIALIS. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of CIALIS, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Warnings and Precautions (5.5)]*.

Urogenital — priapism *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Potential for Pharmacodynamic Interactions with CIALIS

Nitrates — Administration of CIALIS to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Dosage and Administration (2.7), Contraindications (4.1), and Clinical Pharmacology (12.2)]*.

Alpha-Blockers — Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, tamsulosin or alfuzosin. *[See Dosage and Administration (2.7), Warnings and Precautions (5.6), and Clinical Pharmacology (12.2)]*.

Antihypertensives — PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. *[See Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*.

Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. *[See Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)]*.

7.2 Potential for Other Drugs to Affect CIALIS

[See Dosage and Administration (2.7) and Warnings and Precautions (5.10)].

Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H_2 Antagonists (e.g. Nizatidine) — An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors — CIALIS is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

CYP3A4 (e.g., Ketoconazole) — Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone *[see Dosage and Administration (2.7)]*.

Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

HIV Protease inhibitor — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure *[see Dosage and Administration (2.7)]*.

Cytochrome P450 Inducers — Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

CYP3A4 (e.g., Rifampin) — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of CIALIS for once daily use; the magnitude of decreased efficacy is unknown.

7.3 Potential for CIALIS to Affect Other Drugs

Aspirin — Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Cytochrome P450 Substrates — CIALIS is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 (e.g. Theophylline) — Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 (e.g. Warfarin) — Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

CYP3A4 (e.g. Midazolam or Lovastatin) — Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin.

P-glycoprotein *(e.g. Digoxin)* — Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25 mg/day) in healthy subjects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B — CIALIS (tadalafil) is not indicated for use in women. There are no adequate and well controlled studies of CIALIS use in pregnant women. Animal reproduction studies in rats and mice revealed no evidence of fetal harm.

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to tadalafil doses greater than 10 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 16 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

In a rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, a reduction in postnatal survival of pups was observed. The no observed effect level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day. This gives approximately 16 and 10 fold exposure multiples, respectively, of the human AUC for the MRHD of 20 mg.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

8.3 Nursing Mothers

CIALIS is not indicated for use in women. It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk.

Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

8.4 Pediatric Use

CIALIS is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years has not been established.

8.5 Geriatric Use

Of the total number of subjects in ED clinical studies of tadalafil, approximately 25 percent were 65 and over, while approximately 3 percent were 75 and over. Of the total number of subjects in BPH clinical studies of tadalafil (including the ED/BPH study), approximately 40 percent were over 65, while approximately 10 percent were 75 and over. In these clinical trials, no overall differences in efficacy or safety were observed between older (>65 and ≥75 years of age) and younger subjects (≤65 years of age). Therefore no dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered. *[See Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). *[See Dosage and Administration (2.6) and Warnings and Precautions (5.8)]*.

8.7 Renal Impairment

In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80 mL/min. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.8-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol

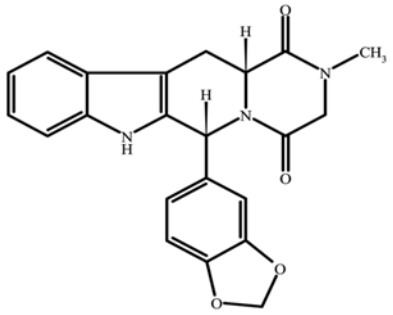
(unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance 30 to 50 mL/min. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. *[See Dosage and Administration (2.6) and Warnings and Precautions (5.7)]*.

10 OVERDOSAGE

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to tadalafil elimination.

11 DESCRIPTION

CIALIS (tadalafil) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

CIALIS is available as almond-shaped tablets for oral administration. Each tablet contains 2.5, 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenal cortex). *In vitro*, tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

12.2 Pharmacodynamics

Effects on Blood Pressure

Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing

systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure When Administered with Nitrates

In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of CIALIS in patients taking any form of nitrates is contraindicated *[see Contraindications (4.1)]*.

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (*see* Figure 1).

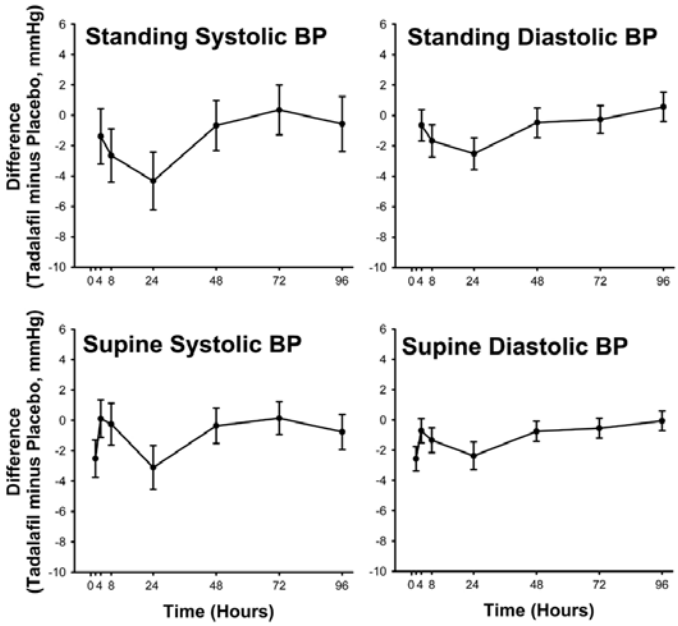


Figure 1: Mean Maximal Change in Blood Pressure (Tadalafil Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of Tadalafil 20 mg or Placebo

Therefore, CIALIS administration with nitrates is contraindicated. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1)]*.

Effect on Blood Pressure When Administered With Alpha-Blockers

Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents in healthy male subjects *[see Dosage and Administration (2.7) and Warnings and Precautions (5.6)]*. In four studies, a single oral dose of tadalafil was administered to healthy male subjects taking daily (at least 7 days duration) an oral alpha-blocker. In two studies, a daily oral alpha-blocker (at least 7 days duration) was administered to healthy male subjects taking repeated daily doses of tadalafil.

Doxazosin — Three clinical pharmacology studies were conducted with tadalafil and doxazosin, an alpha[1]-adrenergic blocker.

In the first doxazosin study, a single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (N=18 subjects). Doxazosin was administered at the same time as tadalafil or placebo after a minimum of seven days of doxazosin dosing (*see* Table 5 and Figure 2).

Table 5: Doxazosin (8 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg
Supine	3.6 (-1.5, 8.8)
Standing	9.8 (4.1, 15.5)

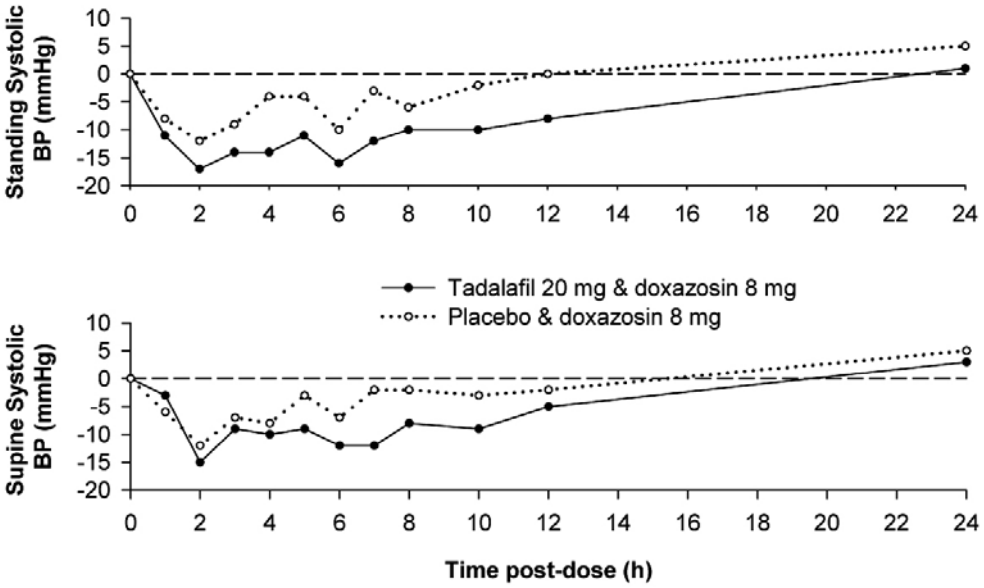


Figure 2: Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mm Hg or a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. There were nine and three outliers following administration of tadalafil 20 mg and placebo, respectively. Five and two subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mm Hg, while five and one subject were outliers due to standing systolic BP <85 mm Hg following tadalafil and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of tadalafil. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported.

In the second doxazosin study, a single oral dose of tadalafil 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (N=72 subjects) was conducted in three parts, each a 3-period crossover.

In part A (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 a.m. Tadalafil was administered at either 8 a m., 4 p.m., or 8 p.m. There was no placebo control.

In part B (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 p m. Tadalafil was administered at either 8 a m., 4 p.m., or 8 p.m. There was no placebo control.

In part C (N=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a m. In this part, tadalafil or placebo were administered at either 8 a.m. or 8 p m.

The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in Table 6 and Figure 3.

Table 6: Doxazosin (8 mg/day) Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg at 8 a.m.	Tadalafil 20 mg at 8 p m.
Ambulatory Blood-Pressure Monitoring (ABPM)	7	8

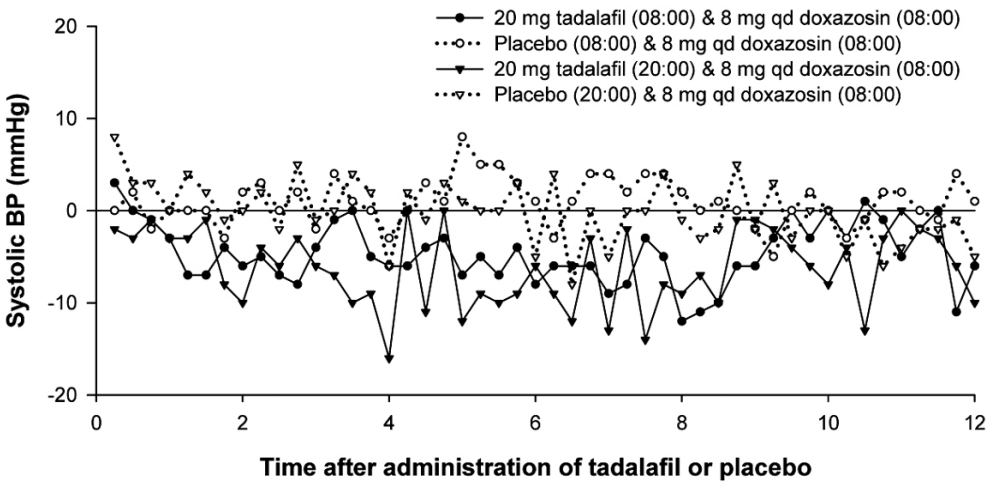


Figure 3: Doxazosin Study 2 (Part C): Mean Change from Time-Matched Baseline in Systolic Blood Pressure

Blood pressure was measured by ABPM every 15 to 30 minutes for up to 36 hours after tadalafil or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mm Hg were recorded or one or more decreases in systolic blood pressure of >30 mm Hg from a time-matched baseline occurred during the analysis interval.

Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of tadalafil and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 a.m. dosing of tadalafil or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mm Hg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of >30 mm Hg following tadalafil and placebo, respectively.

During the 24-hour period after 8 p.m. dosing, 17 subjects were categorized as outliers following administration of tadalafil and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mm Hg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mm Hg, following tadalafil and placebo, respectively.

Some additional subjects in both the tadalafil and placebo groups were categorized as outliers in the period beyond 24 hours.

Severe adverse events potentially related to blood-pressure effects were assessed. In the study (N=72 subjects), 2 such events were reported following administration of tadalafil (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to tadalafil dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase.

In the third doxazosin study, healthy subjects (N=45 treated; 37 completed) received 28 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. After 7 days, doxazosin was initiated at 1 mg and titrated up to 4 mg daily over the last 21 days of each period (7 days on 1 mg; 7 days of 2 mg; 7 days of 4 mg doxazosin). The results are shown in Table 7.

Table 7: Doxazosin Study 3: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure		**Tadalafil 5 mg**
Day 1 of 4 mg Doxazosin	Supine	2.4 (-0.4, 5.2)
	Standing	-0.5 (-4.0, 3.1)
Day 7 of 4 mg Doxazosin	Supine	2.8 (-0.1, 5.7)
	Standing	1.1 (-2.9, 5.0)

Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours post dose on the first day of each doxazosin dose, (1 mg, 2 mg, 4 mg), as well as on the seventh day of 4 mg doxazosin administration.

Following the first dose of doxazosin 1 mg, there were no outliers on tadalafil 5 mg and one outlier on placebo due to a decrease from baseline in standing systolic BP of >30 mm Hg.

There were 2 outliers on tadalafil 5 mg and none on placebo following the first dose of doxazosin 2 mg due to a decrease from baseline in standing systolic BP of >30 mm Hg.

There were no outliers on tadalafil 5 mg and two on placebo following the first dose of doxazosin 4 mg due to a decrease from baseline in standing systolic BP of >30 mm Hg. There was one outlier on tadalafil 5 mg and three on placebo following the first dose of doxazosin 4 mg due to standing systolic BP <85 mm Hg. Following the seventh day of doxazosin 4 mg, there were no outliers on tadalafil 5 mg, one subject on placebo had a decrease >30 mm Hg in standing systolic blood pressure, and one subject on placebo had standing systolic blood pressure <85 mm Hg. All adverse events potentially related to blood pressure effects were rated as mild or

moderate. There were two episodes of syncope in this study, one subject following a dose of tadalafil 5 mg alone, and another subject following coadministration of tadalafil 5 mg and doxazosin 4 mg.

Tamsulosin — In the first tamsulosin study, a single oral dose of tadalafil 10, 20 mg, or placebo was administered in a 3 period, crossover design to healthy subjects taking 0.4 mg once per day tamsulosin, a selective alpha[1A]-adrenergic blocker (N=18 subjects). Tadalafil or placebo was administered 2 hours after tamsulosin following a minimum of seven days of tamsulosin dosing.

Table 8: Tamsulosin (0.4 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	**Tadalafil 10 mg**	**Tadalafil 20 mg**
Supine	3.2 (-2.3, 8.6)	3.2 (-2.3, 8.7)
Standing	1.7 (-4.7, 8.1)	2.3 (-4.1, 8.7)

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points) following administration of tadalafil 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood-pressure effects were reported. No syncope was reported.

In the second tamsulosin study, healthy subjects (N=39 treated; and 35 completed) received 14 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. Daily dosing of tamsulosin 0.4 mg was added for the last seven days of each period.

Table 9: Tamsulosin Study 2: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure		**Tadalafil 5 mg**
Day 1 of 0.4 mg Tamsulosin	Supine	-0.1 (-2.2, 1.9)
	Standing	0.9 (-1.4, 3.2)
Day 7 of 0.4 mg Tamsulosin	Supine	1.2 (-1.2, 3.6)
	Standing	1.2 (-1.0, 3.5)

Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose on the first, sixth and seventh days of tamsulosin administration. There were no outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points). One subject on placebo plus tamsulosin (Day 7) and one subject on tadalafil plus tamsulosin (Day 6) had standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood pressure were reported. No syncope was reported.

Alfuzosin — A single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]-adrenergic blocker (N=17 completed subjects). Tadalafil or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing.

Table 10: Alfuzosin (10 mg/day) Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	**Tadalafil 20 mg**
Supine	2.2 (-0.9,-5.2)
Standing	4.4 (-0.2, 8.9)

Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85 mm Hg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.

Effects on Blood Pressure When Administered with Antihypertensives

Amlodipine — A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

Angiotensin II receptor blockers (with and without other antihypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing,

ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril — A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

Effects on Blood Pressure When Administered with Alcohol

Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in one study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Effects on Exercise Stress Testing

The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.

Effects on Vision

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupilometry. Across all clinical studies with CIALIS, reports of changes in color vision were rare (<0.1% of patients).

Effects on Sperm Characteristics

Three studies were conducted in men to assess the potential effect on sperm characteristics of tadalafil 10 mg (one 6 month study) and 20 mg (one 6 month and one 9 month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo, although these differences were not clinically meaningful. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

Effects on Cardiac Electrophysiology

The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide) -controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QT_c (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QT_c (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

12.3 Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once per day dosing and exposure is approximately 1.6-fold greater than after a single dose. Mean tadalafil concentrations measured after the administration of a single oral dose of 20 mg and single and once daily multiple doses of 5 mg, from a separate study, (*see* Figure 4) to healthy male subjects are depicted in Figure 4.

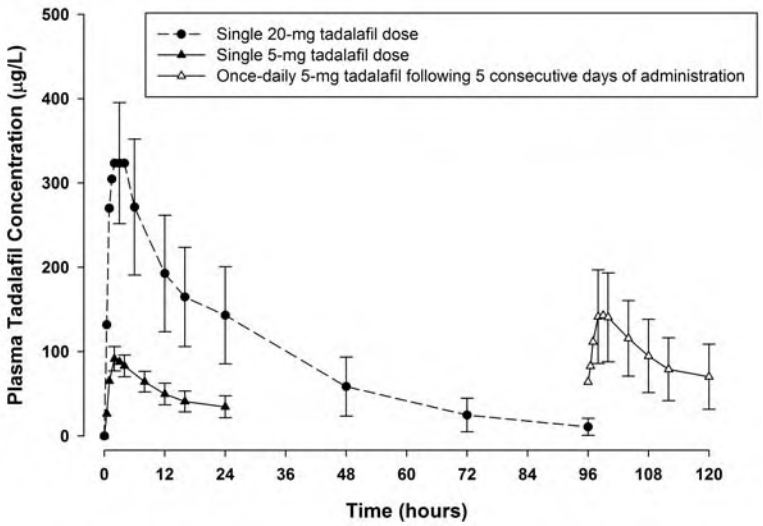


Figure 4: Plasma tadalafil concentrations (mean ± SD) following a single 20-mg tadalafil dose and single and once daily multiple doses of 5 mg

Absorption — After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food.

Distribution — The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism — Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Excretion — The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Geriatric — Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered *[see Use in Specific Populations (8.5)]*.

Pediatric — Tadalafil has not been evaluated in individuals less than 18 years old *[see Use in Specific Populations (8.4)]*.

Patients with Diabetes Mellitus — In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Patients with BPH — In patients with BPH following single and multiple-doses of 20 mg tadalafil, no statistically significant differences in exposure (AUC and C_{max}) were observed between elderly (70 to 85 years) and younger (≤60 years of age) subjects. No dose adjustment is warranted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, the exposures in human males given Maximum Recommended Human Dose (MRHD) of 20 mg.

Mutagenesis — Tadalafil was not mutagenic in the *in vitro* bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes or the *in vivo* rat micronucleus assays.

Impairment of Fertility — There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 20 mg.

There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

13.2 Animal Toxicology and/or Pharmacology

Animal studies showed vascular inflammation in tadalafil-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 2- to 33-fold above the human exposure (AUCs) at the MRHD of 20 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1- and 6-month studies at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. The abnormal blood-cell findings were reversible within 2 weeks after stopping treatment.

14 CLINICAL STUDIES

14.1 CIALIS for Use as Needed for ED

The efficacy and safety of tadalafil in the treatment of erectile dysfunction has been evaluated in 22 clinical trials of up to 24-weeks duration, involving over 4000 patients. CIALIS, when taken as needed up to once per day, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

CIALIS was studied in the general ED population in 7 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12-weeks duration. Two of these studies were conducted in the United States and 5 were conducted in centers outside the US. Additional efficacy and safety studies were performed in ED patients with diabetes mellitus and in patients who developed ED status post bilateral nerve-sparing radical prostatectomy.

In these 7 trials, CIALIS was taken as needed, at doses ranging from 2.5 to 20 mg, up to once per day. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted.

Several assessment tools were used to evaluate the effect of CIALIS on erectile function. The 3 primary outcome measures were the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF is a 4-week recall questionnaire that was administered at the end of a treatment-free baseline period and subsequently at follow-up visits after randomization. The IIEF EF domain has a 30-point total score, where higher scores reflect better erectile function. SEP is a diary in which patients recorded each sexual attempt made throughout the study. SEP Question 2 asks, “Were you able to insert your penis into the partner’s vagina?” SEP Question 3 asks, “Did your erection last long enough for you to have successful intercourse?” The overall percentage of successful attempts to insert the penis into the vagina (SEP2) and to maintain the erection for successful intercourse (SEP3) is derived for each patient.

Results in ED Population in US Trials — The 2 primary US efficacy and safety trials included a total of 402 men with erectile dysfunction, with a mean age of 59 years (range 27 to 87 years). The population was 78% White, 14% Black, 7% Hispanic, and 1% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>90%) patients reported ED of at least 1-year duration. Study A was conducted primarily in academic centers. Study B was conducted primarily in community-based urology practices. In each of these 2 trials, CIALIS 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Table 11). The treatment effect of CIALIS did not diminish over time.

Table 11: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two Primary US Trials

	Study A			Study B		
	Placebo	CIALIS 20 mg		Placebo	CIALIS 20 mg	
	(N=49)	(N=146)	p-value	(N=48)	(N=159)	p-value
EF Domain Score						
Endpoint	13.5	19.5		13.6	22.5	
Change from baseline	-0.2	6.9	<.001	0.3	9.3	<.001
Insertion of Penis (SEP2)						
Endpoint	39%	62%		43%	77%	
Change from baseline	2%	26%	<.001	2%	32%	<.001
Maintenance of Erection (SEP3)						
Endpoint	25%	50%		23%	64%	
Change from baseline	5%	34%	<.001	4%	44%	<.001

Results in General ED Population in Trials Outside the US — The 5 primary efficacy and safety studies conducted in the general ED population outside the US included 1112 patients, with a mean age of 59 years (range 21 to 82 years). The population was 76% White, 1% Black, 3% Hispanic, and 20% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (90%) patients reported ED of at least 1-year duration. In these 5 trials, CIALIS 5, 10, and 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Tables 12, 13 and 14). The treatment effect of CIALIS did not diminish over time.

Table 12: Mean Endpoint and Change from Baseline for the EF Domain of the IIEF in the General ED Population in Five Primary Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	15.0 [0.7]	17.9 [4.0]	20.0 [5.6]	
		p=.006	*p<.001*	
Study D				
Endpoint [Change from baseline]	14.4 [1.1]	17.5 [5.1]	20.6 [6.0]	
		p=.002	*p<.001*	
Study E				
Endpoint [Change from baseline]	18.1 [2.6]		22.6 [8.1]	25.0 [8.0]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	12.7 [-1.6]			22.8 [6.8]
				p<.001
Study G				
Endpoint [Change from baseline]	14.5 [-0.9]		21.2 [6.6]	23.3 [8.0]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

Table 13: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 2 ("Were you able to insert your penis into the partner's vagina?") in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	49% [6%]	57% [15%]	73% [29%]	
		p=.063	*p<.001*	
Study D				
Endpoint [Change from baseline]	46% [2%]	56% [18%]	68% [15%]	
		p=.008	*p<.001*	
Study E				
Endpoint [Change from baseline]	55% [10%]		77% [35%]	85% [35%]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	42% [-8%]			81% [27%]
				p<.001
Study G				
Endpoint [Change from baseline]	45% [-6%]		73% [21%]	76% [21%]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

Table 14: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 3 ("Did your erection last long enough for you to have successful intercourse?") in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	26% [4%]	38% [19%]	58% [32%]	
		p=.040	*p<.001*	
Study D				
Endpoint [Change from baseline]	28% [4%]	42% [24%]	51% [26%]	
		p<.001	*p<.001*	
Study E				
Endpoint [Change from baseline]	43% [15%]		70% [48%]	78% [50%]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	27% [1%]			74% [40%]
				p<.001
Study G				
Endpoint [Change from baseline]	32% [5%]		57% [33%]	62% [29%]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

In addition, there were improvements in EF domain scores, success rates based upon SEP Questions 2 and 3, and patient-reported improvement in erections across patients with ED of all degrees of disease severity while taking CIALIS, compared to patients on placebo.

Therefore, in all 7 primary efficacy and safety studies, CIALIS showed statistically significant improvement in patients' ability to achieve an erection sufficient for vaginal penetration and to maintain the erection long enough for successful intercourse, as measured by the IIEF questionnaire and by SEP diaries.

Efficacy Results in ED Patients with Diabetes Mellitus — CIALIS was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in all 7 primary efficacy studies in the general ED population (N=235) and in one study that specifically assessed CIALIS in ED patients with type 1 or type 2 diabetes (N=216). In this randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 15).

Table 15: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in ED Patients with Diabetes

	Placebo	CIALIS 10 mg	CIALIS 20 mg	
	(N=71)	(N=73)	(N=72)	p-value
EF Domain Score				
Endpoint [Change from baseline]	12.2 [0.1]	19.3 [6.4]	18.7 [7.3]	<.001
Insertion of Penis (SEP2)				
Endpoint [Change from baseline]	30% [-4%]	57% [22%]	54% [23%]	<.001
Maintenance of Erection (SEP3)				
Endpoint [Change from baseline]	20% [2%]	48% [28%]	42% [29%]	<.001

Efficacy Results in ED Patients following Radical Prostatectomy — CIALIS was shown to be effective in treating patients who developed ED following bilateral nerve-sparing radical prostatectomy. In 1 randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial in this population (N=303), CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 16).

Table 16: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in Patients who Developed ED Following Bilateral Nerve-Sparing Radical Prostatectomy

	Placebo	CIALIS 20 mg	
	(N=102)	(N=201)	p-value
EF Domain Score			
Endpoint [Change from baseline]	13.3 [1.1]	17.7 [5.3]	<.001
Insertion of Penis (SEP2)			
Endpoint [Change from baseline]	32% [2%]	54% [22%]	<.001
Maintenance of Erection (SEP3)			
Endpoint [Change from baseline]	19% [4%]	41% [23%]	<.001

Results in Studies to Determine the Optimal Use of CIALIS — Several studies were conducted with the objective of determining the optimal use of CIALIS in the treatment of ED. In one of these studies, the percentage of patients reporting successful erections within 30 minutes of dosing was determined. In this randomized, placebo-controlled, double-blinded trial, 223 patients were randomized to placebo, CIALIS 10, or 20 mg. Using a stopwatch, patients recorded the time following dosing at which a successful erection was obtained. A successful erection was defined as at least 1 erection in 4 attempts that led to successful intercourse. At or prior to 30 minutes, 35% (26/74), 38% (28/74), and 52% (39/75) of patients in the placebo, 10-, and 20-mg groups, respectively, reported successful erections as defined above.

Two studies were conducted to assess the efficacy of CIALIS at a given timepoint after dosing, specifically at 24 hours and at 36 hours after dosing.

In the first of these studies, 348 patients with ED were randomized to placebo or CIALIS 20 mg. Patients were encouraged to make 4 total attempts at intercourse; 2 attempts were to occur at 24 hours after dosing and 2 completely separate attempts were to occur at 36 hours after dosing. The results demonstrated a difference between the placebo group and the CIALIS group at each of the pre-specified timepoints. At the 24-hour timepoint, (more specifically, 22 to 26 hours), 53/144 (37%) patients reported at least 1 successful intercourse in the placebo group versus 84/138 (61%) in the CIALIS 20-mg group. At the 36-hour timepoint (more specifically, 33 to 39 hours), 49/133 (37%) of patients reported at least 1 successful intercourse in the placebo group versus 88/137 (64%) in the CIALIS 20-mg group.

In the second of these studies, a total of 483 patients were evenly randomized to 1 of 6 groups: 3 different dosing groups (placebo, CIALIS 10, or 20 mg) that were instructed to attempt intercourse at 2 different times (24 and 36 hours post-dosing). Patients were encouraged to make 4 separate attempts at their assigned dose and assigned timepoint. In this study, the results demonstrated a statistically significant difference between the placebo group and the CIALIS groups at each of the pre-specified timepoints. At the 24-hour timepoint, the mean, per patient percentage of attempts resulting in successful intercourse were 42, 56, and 67% for the placebo, CIALIS 10-, and 20-mg groups, respectively. At the 36-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 33, 56, and 62% for placebo, CIALIS 10-, and 20-mg groups, respectively.

14.2 CIALIS for Once Daily Use for ED

The efficacy and safety of CIALIS for once daily use in the treatment of erectile dysfunction has been evaluated in 2 clinical trials of 12-weeks duration and 1 clinical trial of 24-weeks duration, involving a total of 853 patients. CIALIS, when taken once daily, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

CIALIS was studied in the general ED population in 2 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12- and 24-weeks duration, respectively. One of these studies was conducted in the United States and one was conducted in centers outside the US. An additional efficacy and safety study was performed in ED patients with diabetes mellitus. CIALIS was taken once daily at doses ranging from 2.5 to 10 mg. Food and alcohol intake were not restricted. Timing of sexual activity was not restricted relative to when patients took Cialis.

Results in General ED Population — The primary US efficacy and safety trial included a total of 287 patients, with a mean age of 59 years (range 25 to 82 years). The population was 86% White, 6% Black, 6% Hispanic, and 2% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>96%) patients reported ED of at least 1-year duration.

The primary efficacy and safety study conducted outside the US included 268 patients, with a mean age of 56 years (range 21 to 78 years). The population was 86% White, 3% Black, 0.4% Hispanic, and 10% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Ninety-three percent of patients reported ED of at least 1-year duration.

In each of these trials, conducted without regard to the timing of dose and sexual intercourse, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 17). When taken as directed, CIALIS was effective at improving erectile function.

In the 6 month double-blind study, the treatment effect of CIALIS did not diminish over time.

Table 17: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two CIALIS for Once Daily Use Studies

	Study H[a]				Study I[b]		
	Placebo	**CIALIS 2.5 mg**	**CIALIS 5 mg**		**Placebo**	**CIALIS 5 mg**	
	(N=94)	**(N=96)**	**(N=97)**	**p-value**	**(N=54)**	**(N=109)**	**p-value**
EF Domain Score							
Endpoint	14.6	19.1	20.8		15.0	22.8	
Change from baseline	1.2	6.1[c]	7.0[c]	<.001	0.9	9.7[c]	<.001
Insertion of Penis (SEP2)							
Endpoint	51%	65%	71%		52%	79%	
Change from baseline	5%	24%[c]	26%[c]	<.001	11%	37%[c]	<.001
Maintenance of Erection (SEP3)							
Endpoint	31%	50%	57%		37%	67%	
Change from baseline	10%	31%[c]	35%[c]	<.001	13%	46%[c]	<.001

[a] Twenty-four-week study conducted in the US.

[b] Twelve-week study conducted outside the US.

[c] Statistically significantly different from placebo.

Efficacy Results in ED Patients with Diabetes Mellitus — CIALIS for once daily use was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in both studies in the general ED population (N=79). A third randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design trial included only ED patients with type 1 or type 2 diabetes (N=298). In this third trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 18).

Table 18: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a CIALIS for Once Daily Use Study in ED Patients with Diabetes

	Placebo (N=100)	CIALIS 2.5 mg (N=100)	CIALIS 5 mg (N=98)	p-value
EF Domain Score				
Endpoint	14.7	18.3	17.2	
Change from baseline	1.3	4.8[a]	4.5[a]	<.001
Insertion of Penis (SEP2)				
Endpoint	43%	62%	61%	
Change from baseline	5%	21%[a]	29%[a]	<.001
Maintenance of Erection (SEP3)				
Endpoint	28%	46%	41%	
Change from baseline	8%	26%[a]	25%[a]	<.001

[a] Statistically significantly different from placebo.

14.3 CIALIS 5 mg for Once Daily Use for Benign Prostatic Hyperplasia (BPH)

The efficacy and safety of CIALIS for once daily use for the treatment of the signs and symptoms of BPH was evaluated in 3 randomized, multinational, double-blinded, placebo-controlled, parallel-design, efficacy and safety studies of 12 weeks duration. Two of these studies were in men with BPH and one study was specific to men with both ED and BPH *[see Clinical Studies (14.4)]*. The first study (Study J) randomized 1058 patients to receive either CIALIS 2.5 mg, 5 mg, 10 mg or 20 mg for once daily use or placebo. The second study (Study K) randomized 325 patients to receive either CIALIS 5 mg for once daily use or placebo. The full study population was 87% White, 2% Black, 11% other races; 15% was of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

The primary efficacy endpoint in the two studies that evaluated the effect of CIALIS for the signs and symptoms of BPH was the International Prostate Symptom Score (IPSS), a four week recall questionnaire that was administered at the beginning and end of a placebo run-in period and subsequently at follow-up visits after randomization. The IPSS assesses the severity of irritative (frequency, urgency, nocturia) and obstructive symptoms (incomplete emptying, stopping and starting, weak stream, and pushing or straining), with scores ranging from 0 to 35; higher numeric scores representing greater severity. Maximum urinary flow rate (Q_{max}), an objective measure of urine flow, was assessed as a secondary efficacy endpoint in Study J and as a safety endpoint in Study K.

The results for BPH patients with moderate to severe symptoms and a mean age of 63.2 years (range 44 to 87) who received either CIALIS 5 mg for once daily use or placebo (N=748) in Studies J and K are shown in Table 19 and Figures 5 and 6, respectively.

In each of these 2 trials, CIALIS 5 mg for once daily use resulted in statistically significant improvement in the total IPSS compared to placebo. Mean total IPSS showed a decrease starting at the first scheduled observation (4 weeks) in Study K and remained decreased through 12 weeks.

Table 19: Mean IPSS Changes in BPH Patients in Two CIALIS for Once Daily Use Studies

	Study J			Study K		
	Placebo (N=205)	CIALIS 5 mg (N=205)	p-value	Placebo (N=164)	CIALIS 5 mg (N=160)	p-value
Total Symptom Score (IPSS)						
Baseline	17.1	17.3		16.6	17.1	
Change from Baseline to Week 12	-2.2	-4.8	<.001	-3.6	-5.6	.004

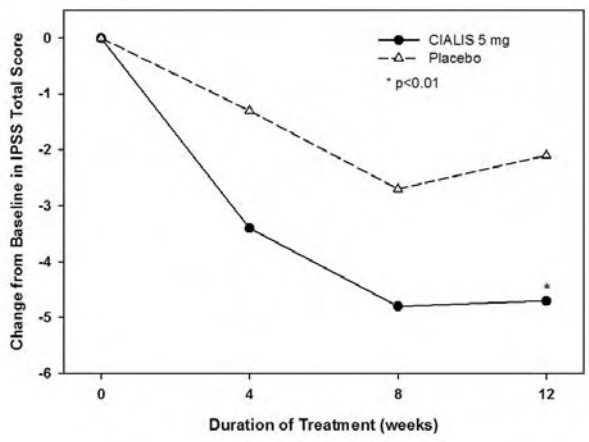


Figure 5: Mean IPSS Changes in BPH Patients by Visit in Study J

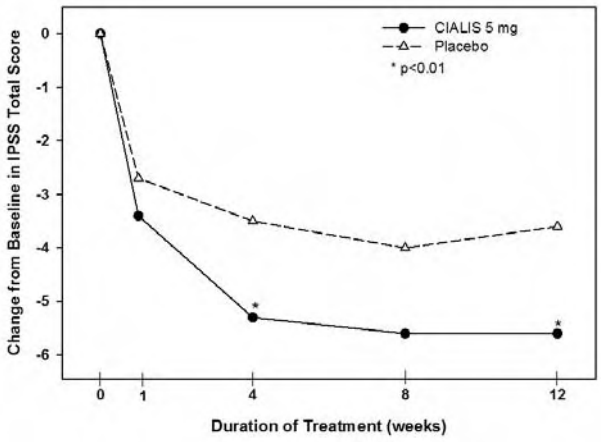


Figure 6: Mean IPSS Changes in BPH Patients by Visit in Study K

In Study J, the effect of CIALIS 5 mg once daily on maximum urinary flow rate (Q_{max}) was evaluated as a secondary efficacy endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

In Study K, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.1 mL/sec); however, these changes were not significantly different between groups.

14.4 CIALIS 5 mg for Once Daily Use for ED and BPH

The efficacy and safety of CIALIS for once daily use for the treatment of ED, and the signs and symptoms of BPH, in patients with both conditions was evaluated in one placebo-controlled, multinational, double-blind, parallel-arm study which randomized 606 patients to receive either CIALIS 2.5 mg, 5 mg, for once daily use or placebo. ED severity ranged from mild to severe and BPH severity ranged from moderate to severe. The full study population had a mean age of 63 years (range 45 to 83) and was 93% White, 4% Black, 3% other races; 16% were of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

In this study, the co-primary endpoints were total IPSS and the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF). One of the key secondary endpoints in this study was Question 3 of the Sexual Encounter Profile diary (SEP3). Timing of sexual activity was not restricted relative to when patients took CIALIS.

The efficacy results for patients with both ED and BPH, who received either CIALIS 5 mg for once daily use or placebo (N=408) are shown in Tables 20 and 21 and Figure 7.

CIALIS 5 mg for once daily use resulted in statistically significant improvements in the total IPSS and in the EF domain of the IIEF questionnaire. CIALIS 5 mg for once daily use also resulted in statistically significant improvement in SEP3. CIALIS 2.5 mg did not result in statistically significant improvement in the total IPSS.

Table 20: Mean IPSS and IIEF EF Domain Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo	CIALIS 5 mg	p-value
Total Symptom Score (IPSS)			
	(N=193)	**(N=206)**	
Baseline	18.2	18.5	
Change from Baseline to Week 12	-3.8	-6.1	<.001
EF Domain Score (IIEF EF)			
	(N=188)	**(N=202)**	
Baseline	15.6	16.5	
Endpoint	17.6	22.9	
Change from Baseline to Week 12	1.9	6.5	<.001

Table 21: Mean SEP Question 3 Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo	CIALIS 5 mg	
	(N=187)	**(N=199)**	**p-value**
Maintenance of Erection (SEP3)			
Baseline	36%	43%	
Endpoint	48%	72%	
Change from Baseline to Week 12	12%	32%	<.001

CIALIS for once daily use resulted in improvement in the IPSS total score at the first scheduled observation (week 2) and throughout the 12 weeks of treatment (*see* Figure 7).

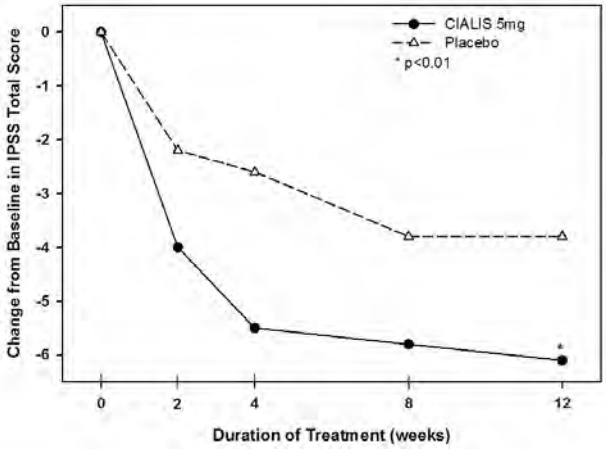


Figure 7: Mean IPSS Changes in ED/BPH Patients by Visit in Study L

In this study, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CIALIS (tadalafil) is supplied as follows:

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow, and supplied in the following package sizes:

2.5 mg tablets debossed with "C 2 1/2"
Blisters of 2 x 15 NDC 0002-4465-34
5 mg tablets debossed with "C 5"
Bottles of 10 NDC 0002-4462-10
Bottles of 30 NDC 0002-4462-30
Blisters of 2 x 15 NDC 0002-4462-34
10 mg tablets debossed with "C 10"
Bottles of 30 NDC 0002-4463-30
20 mg tablets debossed with "C 20"
Bottles of 30 NDC 0002-4464-30

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

"See FDA-approved Patient Labeling (Patient Information)"

17.1 Nitrates

Physicians should discuss with patients the contraindication of CIALIS with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of CIALIS with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*.

17.2 Cardiovascular Considerations

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Physicians should advise patients who experience symptoms upon initiation of sexual activity to refrain from further sexual activity and seek immediate medical attention *[see Warnings and Precautions (5.1)]*.

17.3 Concomitant Use with Drugs Which Lower Blood Pressure

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.4 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should discuss with patients the clinical implications of continuous exposure to tadalafil when prescribing CIALIS for once daily use, especially the potential for interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives and potent inhibitors of cytochrome P450 3A4) and with substantial consumption of alcohol. *[See Dosage and Administration (2.7), Warnings and Precautions (5.6), Drug Interactions (7.1, 7.2), Clinical Pharmacology (12.2), and Clinical Studies (14.2)]*.

17.5 Priapism

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Physicians should advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention.

17.6 Vision

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have

already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors *[see Clinical Studies (6.2)]*.

17.7 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.1, 6.2)]*.

17.8 Alcohol

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Warnings and Precautions (5.9), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.9 Sexually Transmitted Disease

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

17.10 Recommended Administration

Physicians should instruct patients on the appropriate administration of CIALIS to allow optimal use.

For CIALIS for use as needed in men with ED, patients should be instructed to take one tablet at least 30 minutes before anticipated sexual activity. In most patients, the ability to have sexual intercourse is improved for up to 36 hours.

For CIALIS for once daily use in men with ED or ED/BPH, patients should be instructed to take one tablet at approximately the same time every day without regard for the timing of sexual activity. Cialis is effective at improving erectile function over the course of therapy.

For CIALIS for once daily use in men with BPH, patients should be instructed to take one tablet at approximately the same time every day.

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Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

www.cialis.com

A 10.0 NL 6603 AMP

Patient Information

CIALIS® (See-AL-iss)
(tadalafil) tablets

Read this important information before you start taking CIALIS and each time you get a refill. There may be new information. You may also find it helpful to share this information with your partner. This information does not take the place of talking with your healthcare provider. You and your healthcare provider should talk about CIALIS when you start taking it and at regular checkups. If you do not understand the information, or have questions, talk with your healthcare provider or pharmacist.

What Is The Most Important Information I Should Know About CIALIS?

CIALIS can cause your blood pressure to drop suddenly to an unsafe level if it is taken with certain other medicines. You could get dizzy, faint, or have a heart attack or stroke.

Do not take CIALIS if you **take any medicines called "nitrates."** Nitrates are commonly used to treat angina. Angina is a symptom of heart disease and can cause pain in your chest, jaw, or down your arm.

- Medicines called nitrates include nitroglycerin that is found in tablets, sprays, ointments, pastes, or patches. Nitrates can also be found in other medicines such as isosorbide dinitrate or isosorbide mononitrate. Some recreational drugs called "poppers" also contain nitrates, such as amyl nitrite and butyl nitrite.
- Ask your healthcare provider or pharmacist if you are not sure if any of your medicines are nitrates. (See **"Who Should Not Take CIALIS?"**)

Tell all of your healthcare providers that you take CIALIS. If you need emergency medical care for a heart problem, it will be important for your healthcare provider to know when you last took CIALIS.

After taking a single tablet, some of the active ingredient of CIALIS remains in your body for more than 2 days. The active ingredient can remain longer if you have problems with your kidneys or liver, or you are taking certain other medications (see **"Can Other Medicines Affect CIALIS?"**).

Stop sexual activity and get medical help right away if you get symptoms such as chest pain, dizziness, or nausea during sex. Sexual activity can put an extra strain on your heart, especially if your heart is already weak from a heart attack or heart disease.

See also **"What Are The Possible Side Effects Of CIALIS?"**

What Is CIALIS?

CIALIS is a prescription medicine taken by mouth for the treatment of:

- men with erectile dysfunction (ED)
- men with symptoms of benign prostatic hyperplasia (BPH)
- men with both ED and BPH

CIALIS for the Treatment of ED

ED is a condition where the penis does not fill with enough blood to harden and expand when a man is sexually excited, or when he cannot keep an erection. A man who has trouble getting or keeping an erection should see his healthcare provider for help if the condition bothers him. CIALIS helps increase blood flow to the penis and may help men with ED get and keep an erection satisfactory for sexual activity. Once a man has completed sexual activity, blood flow to his penis decreases, and his erection goes away.

Some form of sexual stimulation is needed for an erection to happen with CIALIS.

CIALIS does not:

- cure ED
- increase a man's sexual desire
- protect a man or his partner from sexually transmitted diseases, including HIV. Speak to your healthcare provider about ways to guard against sexually transmitted diseases.
- serve as a male form of birth control

CIALIS is only for men over the age of 18, including men with diabetes or who have undergone prostatectomy.

CIALIS for the Treatment of Symptoms of BPH

BPH is a condition that happens in men, where the prostate gland enlarges which can cause urinary symptoms.

CIALIS for the Treatment of ED and Symptoms of BPH

ED and symptoms of BPH may happen in the same person and at the same time. Men who have both ED and symptoms of BPH may take CIALIS for the treatment of both conditions.

CIALIS is not for women or children.

CIALIS must be used only under a healthcare provider's care.

Who Should Not Take CIALIS?

Do not take CIALIS if you:

- **take any medicines called "nitrates".**
- use recreational drugs called "poppers" like amyl nitrite and butyl nitrite. (See **"What Is The Most Important Information I Should Know About CIALIS?"**)
- **are allergic to CIALIS or ADCIRCA®, or any of its ingredients.** See the end of this leaflet for a complete list of ingredients in CIALIS. Symptoms of an allergic reaction may include:
  - **rash**
  - **hives**
  - swelling of the lips, tongue, or throat
  - difficulty breathing or swallowing

Call your healthcare provider or get help right away if you have any of the symptoms of an allergic reaction listed above.

What Should I Tell My Healthcare Provider Before Taking CIALIS?

CIALIS is not right for everyone. **Only your healthcare provider and you can decide if CIALIS is right for you.** Before taking CIALIS, tell your healthcare provider about all your medical problems, including if you:

- **have heart problems** such as angina, heart failure, irregular heartbeats, or have had a heart attack. Ask your healthcare provider if it is safe for you to have sexual activity. You should not take CIALIS if your healthcare provider has told you not to have sexual activity because of your health problems.
- **have low blood pressure or** have high blood pressure that is not controlled
- **have had a stroke**
- **have liver problems**
- **have kidney problems or require dialysis**
- **have retinitis pigmentosa,** a rare genetic (runs in families) eye disease
- **have ever had severe vision loss, including a condition called NAION**
- **have stomach ulcers**
- **have a bleeding problem**
- **have a deformed penis shape** or Peyronie's disease

- **have had an erection that lasted more than 4 hours**
- **have blood cell problems** such as sickle cell anemia, multiple myeloma, or leukemia

Can Other Medicines Affect CIALIS?

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. CIALIS and other medicines may affect each other. Always check with your healthcare provider before starting or stopping any medicines. Especially tell your healthcare provider if you take any of the following*:

- medicines called nitrates (see **"What Is The Most Important Information I Should Know About CIALIS?"**)
- medicines called alpha blockers. These include Hytrin® (terazosin HCl), Flomax® (tamsulosin HCl), Cardura® (doxazosin mesylate), Minipress® (prazosin HCl), Uroxatral® (alfuzosin HCl), Jalyn® (dutasteride and tamsulosin HCl) or Rapaflo® (silodosin). Alpha-blockers are sometimes prescribed for prostate problems or high blood pressure. If CIALIS is taken with certain alpha blockers, your blood pressure could suddenly drop. You could get dizzy or faint.
- other medicines to treat high blood pressure (hypertension)
- medicines called HIV protease inhibitors, such as ritonavir (Norvir®, Kaletra®)
- some types of oral antifungals such as ketoconazole (Nizoral®), itraconazole (Sporanox®)
- some types of antibiotics such as clarithromycin (Biaxin®), telithromycin (Ketek®), erythromycin (several brand names exist. Please consult your healthcare provider to determine if you are taking this medicine).
- other medicines or treatments for ED.
- CIALIS is also marketed as ADCIRCA for the treatment of pulmonary arterial hypertension. Do not take both CIALIS and ADCIRCA. Do not take sildenafil citrate (Revatio®) with CIALIS.

How Should I Take CIALIS?

- Take CIALIS exactly as your healthcare provider prescribes it. Your healthcare provider will prescribe the dose that is right for you.
- Some men can only take a low dose of CIALIS or may have to take it less often, because of medical conditions or medicines they take.
- Do not change your dose or the way you take CIALIS without talking to your healthcare provider. Your healthcare provider may lower or raise your dose, depending on how your body reacts to CIALIS and your health condition.
- CIALIS may be taken with or without meals.
- If you take too much CIALIS, call your healthcare provider or emergency room right away.

How Should I Take CIALIS for Symptoms of BPH?

For symptoms of BPH, CIALIS is taken once daily.

- **Do not take CIALIS more than one time each day.**
- Take one CIALIS tablet every day at about the same time of day.
- If you miss a dose, you may take it when you remember but do not take more than one dose per day.

How Should I Take CIALIS for ED?

For ED, there are two ways to take CIALIS - either for use as needed OR for use once daily.

CIALIS for use as needed:

- **Do not take CIALIS more than one time each day.**
- Take one CIALIS tablet before you expect to have sexual activity. You may be able to have sexual activity at 30 minutes after taking CIALIS and up to 36 hours after taking it. You and your healthcare

provider should consider this in deciding when you should take CIALIS before sexual activity. Some form of sexual stimulation is needed for an erection to happen with CIALIS.
- Your healthcare provider may change your dose of CIALIS depending on how you respond to the medicine, and on your health condition.

OR

CIALIS for once daily use is a lower dose you take every day.
- **Do not take CIALIS more than one time each day.**
- Take one CIALIS tablet every day at about the same time of day. You may attempt sexual activity at any time between doses.
- If you miss a dose, you may take it when you remember but do not take more than one dose per day.
- Some form of sexual stimulation is needed for an erection to happen with CIALIS.
- Your healthcare provider may change your dose of CIALIS depending on how you respond to the medicine, and on your health condition.

How Should I Take CIALIS for Both ED and the Symptoms of BPH?

For both ED and the symptoms of BPH, CIALIS is taken once daily.
- **Do not take CIALIS more than one time each day.**
- Take one CIALIS tablet every day at about the same time of day. You may attempt sexual activity at any time between doses.
- If you miss a dose, you may take it when you remember but do not take more than one dose per day.
- Some form of sexual stimulation is needed for an erection to happen with CIALIS.

What Should I Avoid While Taking CIALIS?

- Do not use other ED medicines or ED treatments while taking CIALIS.
- Do not drink too much alcohol when taking CIALIS (for example, 5 glasses of wine or 5 shots of whiskey). Drinking too much alcohol can increase your chances of getting a headache or getting dizzy, increasing your heart rate, or lowering your blood pressure.

What Are The Possible Side Effects Of CIALIS?

See **"What Is The Most Important Information I Should Know About CIALIS?"**

The most common side effects with CIALIS are: headache, indigestion, back pain, muscle aches, flushing, and stuffy or runny nose. These side effects usually go away after a few hours. Men who get back pain and muscle aches usually get it 12 to 24 hours after taking CIALIS. Back pain and muscle aches usually go away within 2 days.

Call your healthcare provider if you get any side effect that bothers you or one that does not go away.

Uncommon side effects include:

An erection that won't go away (priapism). If you get an erection that lasts more than 4 hours, get medical help right away. Priapism must be treated as soon as possible or lasting damage can happen to your penis, including the inability to have erections.

Color vision changes, such as seeing a blue tinge (shade) to objects or having difficulty telling the difference between the colors blue and green.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including CIALIS) reported a sudden decrease or loss of vision in one or both eyes. It is not possible to determine whether these events are related directly to these medicines, to other factors such as high blood pressure or diabetes, or to a combination of these. If you experience sudden decrease or loss of vision, stop taking PDE5 inhibitors, including CIALIS, and call a healthcare provider right away.

Sudden loss or decrease in hearing, sometimes with ringing in the ears and dizziness, has been rarely reported in people taking PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the PDE5 inhibitors, to other diseases or medications, to other factors, or to a combination of factors. If you experience these symptoms, stop taking CIALIS and contact a healthcare provider right away.

These are not all the possible side effects of CIALIS. For more information, ask your healthcare provider or pharmacist.

How Should I Store CIALIS?

Store CIALIS at room temperature between 59° and 86°F (15° and 30°C).

Keep CIALIS and all medicines out of the reach of children.

General Information About CIALIS:

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use CIALIS for a condition for which it was not prescribed. Do not give CIALIS to other people, even if they have the same symptoms that you have. It may harm them.

This is a summary of the most important information about CIALIS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CIALIS that is written for health providers. For more information you can also visit www.cialis.com, or call 1-877-CIALIS1 (1-877-242-5471).

What Are The Ingredients In CIALIS?

Active Ingredient: tadalafil

Inactive Ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

This Patient Information has been approved by the U.S. Food and Drug Administration

Rx only

CIALIS® (tadalafil) is a registered trademark of Eli Lilly and Company.

*The brands listed are trademarks of their respective owners and are not trademarks of Eli Lilly and Company. The makers of these brands are not affiliated with and do not endorse Eli Lilly and Company or its products.

Revision Date October 2011

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

www.cialis.com

A 7.0 NL 5226 AMP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 6, 2011
From	Scott Monroe MD
Subject	Division Director Summary Review
NDA	NDA 021368: Efficacy Supplements 20 and 21
Applicant Name	Eli Lilly and Company
Date of Submission	December 3, 2010 (received December 6, 2010)
PDUFA Goal Date	October 6, 2011
Proprietary Name	CIALIS® tablets
Established (USAN) Name	Tadalafil
Dosage Forms/Strengths	Oral tablets: 2.5 mg, 5 mg, 10 mg, and 20 mg
Proposed New Indication(s):	Treatment of (1) signs and symptoms of benign prostatic hyperplasia (BPH) and (2) erectile dysfunction and the signs and symptoms of BPH
Proposed Regimen	One 5 mg tablet daily
Action	***Approve (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Roger Wiederhorn MD (primary Clinical Reviewer)
Statistical Review	Xin Fang PhD
Pharmacology/Toxicology Review	Yangmee Shin PhD
CMC Review/OBP Review	Jeffrey Medwid PhD (CMC)
Microbiology Review	Not required
Clinical Pharmacology Review	E. Dennis Bashaw PharmD
DDMAC	Janice Maniwang PharmD
DSI	Roy Blay PhD
CDTL Review	Mark Hirsch MD (also Clinical Team Leader)
OSE/DMEPA	Yelena Maslov PharmD
OSE/DRISK	Shawn Hutchins MPH, BSN, RN

OND=Office of New Drugs
CMC=Chemistry, Manufacturing and Control
DDMAC=Division of Drug Marketing, Advertising, and Communication
DSI=Division of Scientific Investigations
CDTL=Cross Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DRISK=Division of Risk Management

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objectives of these Efficacy Supplements (S-20 and S-21) for NDA 021368 are to obtain marketing approvals for 2 new indications for Cialis: (1) treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)(S-20); and (2) treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (S-21). Cialis (tadalafil) tablets for oral use was initially approved for marketing in the US in November 2003 for the treatment of ED. The dosing regimen was for use "as needed" (PRN) and was not to exceed one 5, 10, or 20 mg tablet per day. In January 2008, a new dosing regimen for the treatment of ED, consisting of a single daily 2.5 or 5 mg tablet, was approved. In the current Supplements, the Applicant proposes to utilize the once daily dosing regimen for the (1) treatment of symptomatic BPH or (2) treatment of ED in association with symptomatic BPH (ED/BPH). The Applicant proposes 5 mg Cialis once daily as the dosing regimen for both of these new indications.

These Efficacy Supplements (hereafter also referred to as the Applications or the Supplements) contained only limited new clinical pharmacology information and no significant new chemistry, manufacturing or control (CMC) or non-clinical pharmacology/toxicology information. A major component of these Supplements consisted of 2 placebo-controlled Phase 3 clinical trials to support the proposed indication of treatment of the signs and symptoms of BPH and a single placebo-controlled Phase 3 trial to support the proposed indication of treatment of ED and BPH. The Phase 3 clinical trials were designed and conducted in accordance with the recommendations of the Division of Reproductive and Urologic Products (DRUP). Each of the three Phase 3 clinical trials successfully achieved its protocol-specified primary endpoint (or co-primary endpoints); in addition, the safety profile of Cialis in these trials was similar to its profile in men who use the product for the currently approved indication of treatment of ED. No significant preclinical or clinical issues were identified during the review of the Supplements. All reviewers, including the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended that Efficacy Supplements 20 and 21 be approved. I concur with their recommendations for approval of both Supplements.

2. BACKGROUND

2.1 Description of the Product

Cialis (tadalafil) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and the smooth muscle of the corpus cavernosum. This response is mediated by the release of nitric oxide from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. The mechanism for reducing the symptoms of BPH, however, has not been established.

Cialis is available in tablets that contain 2.5, 5, 10, or 20 mg of tadalafil. According to the Applicant, Cialis (tadalafil) for the treatment of ED is approved in more than 100 countries and more than 30 million men have used the product for this indication.

2.2 Currently Available Therapies for the Treatment of BPH

Currently available approved medical therapies for the treatment of the signs and symptoms of BPH include two drug classes: (1) the selective alpha-adrenergic antagonists (alpha-blockers) such as terazosin, tamsulosin, doxazosin, and silodosin and (2) the 5-alpha reductase inhibitors (5-ARIs) finasteride and dutasteride. Although both drug classes are effective therapies, each is associated with unique adverse reactions and/or safety concerns. Treatment with alpha blockers can be associated with postural hypotension, including first-dose syncope and dizziness, rhinitis, asthenia, and ejaculatory dysfunction. Treatment with 5-ARIs can be associated with erectile dysfunction, breast pain, gynecomastia, loss of libido, and a potential increased risk of high grade prostate cancer. In addition to medical therapies, there also are several surgical procedures to alleviate the symptoms of BPH. Although some of these procedures are minimally invasive, none are without side effects or risks. An additional medical therapy for the treatment of symptomatic BPH would therefore be of value and would offer men with symptomatic BPH another therapeutic option.

2.3 Regulatory History

A detailed review of the regulatory history of Cialis for the treatment of (1) symptomatic BPH or (2) ED and symptomatic BPH is provided in Section 2.5 of the primary Clinical Review. There were several meetings and numerous communications between the Applicant and DRUP regarding the design and conduct of the overall development program for Cialis for the treatment of both of these indications. It was agreed by DRUP that a single 12-week, placebo-controlled Phase 2/3 clinical trial (Study LVHG) and a single 12-week, placebo-controlled Phase 3 clinical trial (Study LVHJ), supported by safety data from a one year, open label extension of Study LVHG, could be adequate to support the approval of Cialis for the treatment of the signs and symptoms of BPH. An additional 12-week placebo controlled Phase 3 trial (Study LVHR) that enrolled men with ED and symptoms of BPH could be adequate to support a separate indication for the treatment of ED and the symptoms of BPH when both disorders were present in the same patient.

Division Director's Comment

- *The overall development program for Cialis for the treatment of symptoms of BPH or ED/BPH closely followed the guidance and recommendations provided by DRUP.*

2.4 Comments of Primary Clinical Reviewer and Cross-Discipline Team Leader and Their Recommendations Regarding Approvability

The primary Clinical Reviewer, Roger Wiederhorn MD, stated the following in his review that he signed on September 13, 2011:

> *"It is recommended that sNDA 21-368 SEI-20 and sNDA 21-368 SEI-21 be **APPROVED** at this time. Tadalafil 5 mg was found to be efficacious … in the treatment of signs and symptoms of BPH in men with BPH only and in men with BPH/ED (benign prostatic hypertrophy/erectile dysfunction). Tadalafil 2.5 mg was not found to be efficacious in treating the signs and symptoms of BPH in men with BPH/ED."*
>
> *"A thorough and comprehensive review of sNDA 21-368 SEI-20 and sNDA 21-368 SEI-21 was carried out. These NDA submissions have provided substantial evidence from adequate and well controlled ("pivotal") studies that tadalafil 5 mg once daily will have the effect claimed in labeling. This claim is that, in men with BPH and BPH/ED, tadalafil 5 mg*

once a day is efficacious in treating the signs and symptoms of BPH. In men with BPH/ED, tadalafil 5 mg once a day is also efficacious in treating their ED."

"No discernible differences in the safety profile were detected for the use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH and or BPH/ED as compared to the patient population in the previously approved ED indication for 5 mg tadalafil once daily."

"Tadalafil 5 mg once daily has been shown to be generally safe for its intended use as recommended in the labeling by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to other drugs in its class and to the other indication (ED) for once daily use."

The Cross Discipline Team Leader (Mark Hirsch MD) stated the following in his review that he signed on October 3, 2011:

"I recommend that these efficacy supplements to NDA 21-368 for CIALIS be approved."

"These two efficacy supplements do provide substantial evidence from three, Phase 3, randomized, placebo-controlled studies (LVHG and LVHJ in men with BPH, and LVHR in men with both ED and BPH) that tadalafil is effective and safe for use as a treatment for symptomatic BPH as well as for the treatment of BPH and ED in men with both conditions (BPH/ED)."

"… The safety profile of tadalafil that was demonstrated in the three Phase 3 BPH studies (LVHG, LVHJ, and LVHR), the single Phase 2 study (LVGC), the additional safety studies (LVHK and LVHS), the Phase 1 study in elderly patients (LVHN), the three studies in Asia (LVIA, LVHT and LVHB), and the open-label extension of LVHG is consistent with the known safety profile of tadalafil for the treatment of ED. There were no unexpected or new safety concerns. … The recent postmarketing experience revealed no new findings."

"Overall, the risk benefit assessment is considered favorable for Cialis for treatment of symptomatic BPH and symptomatic BPH and ED."

Division Director's Comment

- *I concur with the recommendations of both Drs. Wiederhorn and Hirsch that these Efficacy Supplements be approved for the treatment of (1) symptomatic BPH and (2) ED in conjunction with symptomatic BPH. The Applicant has provided adequate information for me to conclude that Cialis, when used in accordance with to-be-approved labeling, will be safe and effective for the 2 proposed indications.*

3. CMC

The Applicant did not propose any CMC changes in the current Applications. The drug product (Cialis: 5 mg tablets) to be used for the proposed indications will be the same as that currently marketed for the treatment of ED. The primary CMC Reviewer, Jeffrey Medwid PhD, made the following statement and overall recommendation in the Addendum, signed on September 28, 2011, to his initial Review:

"*From a CMC perspective this supplement is recommended for approval from a CMC point of view based on acceptable review of the PI, container/carton labeling and categorical exclusion*."

Division Director's Comment

- *I concur with Dr. Medwid's recommendation that from a CMC perspective the Applications can be approved.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new toxicology studies were submitted with these Applications. Yangmee Shin PhD, the primary nonclinical Toxicology Reviewer, made the following statement and recommendations in her review that she signed on August 8, 2011:

> *"Previous nonclinical studies submitted in support of the original marketing application of tadalafil are considered sufficient to support the safety of the new indications, given the exposure levels within the range of the approved Cialis® oral tablets.*
>
> ***Approvability**: From a Pharmacology/Toxicology perspective, the previous nonclinical data submitted for the approval of the treatment of ED support the safety of the proposed indications of Cialis®.*
>
> ***Additional nonclinical recommendations:** None."*

Division Director's Comments

- *Dr. Shin requested several revisions to the nonclinical pharmacology/toxicology sections of the proposed Package Insert. All of the requested revisions were made by the Applicant.*
- *I concur with the recommendation of Dr. Shin that from a nonclinical pharmacology/toxicology perspective the previous nonclinical data submitted for the approval of the treatment of ED support the safety of the proposed indications.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

5.1 Pharmacokinetics of Tadalafil

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady state plasma concentrations are attained within 5 days of once per day dosing and exposure is approximately 1.6-fold greater than after a single dose. After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations. The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects.

In a pharmacokinetic study that supported the earlier approval of Cialis for the treatment of ED, healthy elderly male subjects (65 years or over), compared to healthy young subjects (19 to 45 years of age), had a slightly lower clearance of tadalafil, resulting in 25% higher exposure (AUC), but with no effect on C_{max}.

Division Director's Comment

- *Current (and to-be-approved) labeling does not recommend dose adjustments based on age alone.*

5.2 New Clinical Pharmacology Information in Current Submission

The current Applications included information from a new pharmacokinetic trial (LVHN). The findings from Study LVHN indicated that there was no statistically significant difference in the AUC_{0-24} and C_{max} of tadalafil between elderly men (70 to 76 years old) and younger men (48 to 59 years old), both with BPH, following single- and multiple-dose administration of tadalafil 20 mg once daily for 10 days.

Division Director's Comment

- *The results of Study LVHN are somewhat in conflict with results of a previous study reported in the current label for Cialis that showed that healthy elderly male subjects (65 years or over), compared to healthy subjects 19 to 45 years of age), had a lower clearance of tadalafil, that resulted in 25% higher exposures (AUC). A possible explanation for this difference between study findings is that the "younger subjects" in Study LVHN were "younger" in only a relative sense. The "younger" subjects in Study LVHN were between the ages of 48-59 years, a different population than the 19-45 year old subjects referred to in the current label.*

The primary clinical Pharmacology Reviewer, E. Dennis Bashaw PharmD, stated the following in his primary Review that he signed on September 16, 2011:

> *"From a Clinical Pharmacology perspective the sponsor has adequately demonstrated the pharmacokinetics in the target population of BPH. While a separate study was not done in the BPH/ED population, as there would not be expected to be any differences (pharmacokinetically) in the populations, this is acceptable. As for the age issue, while there are conflicting findings across the LVHN study and the approved label with regards to clearance based changes, there does not seem to [be]a significant enough safety concern to raise it to the level of a post-marketing study."*
>
> *"The results of the submitted trials did not reveal any significant changes in the pharmacokinetics of tadalafil. The application is acceptable from a Clinical Pharmacology standpoint provided that appropriate labeling is developed to incorporate the information into the package insert."*

In an Addendum, signed on September 27, 2011, to his primary Review, Dr. Bashaw stated:

> *"Since the execution of this review and its placement in DARRTS (September 16th, 2011), there has been additional communication with the sponsor regarding labeling. As of today September 27th, 2011, the sponsor has agreed to all of the Clinical Pharmacology based labeling recommendations. Based on their agreement, the Division of Clinical Pharmacology-3 considers all of the review issues closed and the application to be acceptable under the provisions of 21CFR320."*

Division Director's Comments

- *Detailed information regarding potential drug-drug interactions and the potential effects of concomitant administrations of Cialis and alpha blockers is provided in the to-be-approved labeling.*
- *I concur with the overall clinical pharmacology assessment of Dr. Bashaw and his recommendation that these Efficacy Supplements are acceptable to support approval.*

6. CLINICAL MICROBIOLOGY

A separate clinical microbiology review was not required because (1) there were no CMC changes in the current submission and (2) the product (Cialis: 5 mg tablets) to be used for the proposed indications will be the same as that currently marketed in the US for the treatment of ED.

7. CLINICAL/STATISTICAL-EFFICACY

The primary sources of efficacy data for these Applications were three double-blind, placebo-controlled, 12-week clinical trials in men with symptomatic BPH (Studies LVHG, LVHJ, and LVHR). The first 2 studies (LVHG and LVHJ) did not require the subjects to have erectile dysfunction and these studies support the first new indication: treatment of signs and symptoms of BPH; the third study (LVHR) required that the subjects also have ED and supports the second new indication: treatment of ED and signs and symptoms of BPH.

7.1 Phase 3 Clinical Trials (LVHG and LVHJ) for Treatment of BPH

7.1.1 Design of Study LVHG and Study LVHJ

Studies LVHG and LVHJ provided the main support for the efficacy of Cialis for the indication of treatment of the signs and symptoms of BPH. The 2 trials were of similar design except for the number of treatment arms (5 and 2 arms in Study LVHG and Study LVHJ, respectively).

Study LVHG was a multinational, Phase 2/3, randomized, double-blind, placebo-controlled, dose-finding trial to evaluate the efficacy, dose response, and safety of treatment with 2.5, 5, 10, or 20 mg Cialis once daily for 12 weeks compared to treatment with placebo in subjects with BPH-lower urinary tract symptoms (BPH-LUTS).

Study LVHJ was a multinational, Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of treatment with Cialis 5 mg once daily for 12 weeks compared to treatment with placebo in subjects with BPH-LUTS.

Both trials included 3 study periods: a screening/wash-out period of 1-4 weeks, a placebo run-in period of 4 weeks, and a treatment period of 12 weeks.

The primary efficacy endpoint in the 2 trials was based on the total International Prostate Symptom Score (IPSS), a 4-week recall questionnaire that was administered at the beginning and end of the placebo run-in period and subsequently at follow-up visits during randomized treatment. The IPSS assesses the severity of irritative (frequency, urgency, nocturia) and obstructive urinary symptoms (incomplete emptying, stopping and starting, weak stream, and pushing or straining), with scores ranging from 0 to 35; higher numeric scores represent greater severity of symptoms.

7.1.2 Baseline Subject Characteristics and Subject Disposition

7.1.2.1 Study LVHG

In Study LVHG, 1,056 subjects were randomized at 94 sites in 10 countries. Baseline characteristics were similar across the 5 treatment groups. The mean age of the subjects was 62 years (range: 45 to 92 years); subjects were predominantly Caucasian (85.6%) or Hispanic (11.7%).

The majority of the subjects completed the 12-week treatment period (placebo: 87.3%; Cialis 5 mg: 85.9%). The most common reasons for early discontinuation among the subjects receiving Cialis 5 mg were adverse event (AE, 5.7%), entry criteria not met (3.3%), and subject decision (3.3%). The most common reasons for early discontinuation among the subjects receiving placebo were subject decision (4.3%), AE (2.4%), and lost to follow-up (2.4%).

7.1.2.2 Study LVHJ

In Study LVHJ, 325 subjects were randomized at 28 sites in 5 countries. Baseline characteristics were similar across the 2 treatment groups. The mean age of the subjects was 64.9 years (range: 44.8 to 87.0 years); subjects were predominantly Caucasian (91.1%).

The majority of randomized subjects completed the 12-week treatment period (placebo: 92.7%; Cialis 5 mg: 91.9%). The most common reasons for early discontinuation among the subjects receiving Cialis 5 mg were entry criteria not met (2.5%), AE (1.2%), physician decision (1.2%), and subject decision (1.2%). The most common reasons for discontinuation among the subjects receiving placebo were subject decision (2.4%), protocol violations (1.8%), lost to follow-up (1.8%), and AE (0.6%).

Division Director's Comment

- *The percentages of subjects treated with Cialis 5 mg once daily who discontinued treatment before 12 weeks for any reason, and specifically because of an AE, in each of Studies LVHG and LVHJ were low and do not raise any safety concerns.*

7.1.3 Primary Efficacy Endpoint and Analysis

The primary objective for Study LVHG and Study LVHJ was to demonstrate the superiority of treatment with Cialis 5 mg once daily at Week 12, compared to placebo, in reducing the signs and symptoms of BPH-LUTS as assessed by the IPSS. In both trials, the primary efficacy endpoint was the change from baseline in the total IPSS (sum of the scores for IPSS Questions 1-7) at Week 12. The primary efficacy analysis population was the intent-to-treat (ITT) population that included all randomized subjects who started study medication.

7.1.3.1 Study LVHG

The mean changes from baseline to Week 12 for the total IPSS in the placebo and Cialis 5 mg treatment groups in Study LVHG are provided in Table 1 and depicted in Figure 1. There was a statistically significant greater decrease in the total IPSS at Week 12 in the Cialis 5 mg group compared to the decrease in the placebo group. The treatment difference was -2.6 with a 95% confidence interval (CI) of -3.7 to -1.5 (p-value < 0.001).

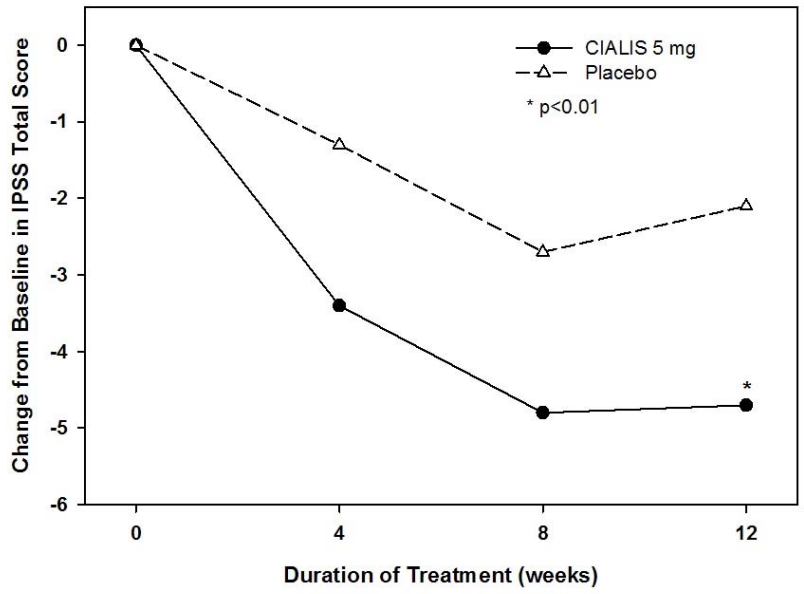
Table 1 Mean Change from Baseline to Week 12 for Total IPSS in Study LVHG (ITT, LOCF)

Endpoint	Placebo N=204	Cialis 5 mg N=205	Difference (95% CI)	P-value
Total IPSS				
Baseline Mean (SD):	17.1 (6.4)	17.3 (6.0)		
Change from baseline: [a]	-2.2	-4.8	-2.6 (-3.7, -1.5)	< 0.001

[a]: Least square mean from the ANCOVA model with fixed effects of treatment, region, and IPSS baseline value as covariate.

Source: Table 5, of FDA Statistical Review signed September 15, 2011.

Figure 1 Mean IPSS Changes in BPH Subjects by Visit (Study LVHG)



Source: Figure 5 from Cialis Package Insert, revised October 2011.

7.1.3.2 Study LVHJ

The mean changes from baseline to Week 12 for the total IPSS in the placebo and Cialis 5 mg treatment groups in Study LVHJ are provided in Table 2 and depicted in Figure 2. The mean changes from baseline in the total IPSS were -3.6 and -5.6 for the placebo and Cialis 5 mg treatment groups, respectively. The treatment difference between the placebo and Cialis groups was -1.9 (95% CI: -3.2 to -0.6; p-value = 0.004).

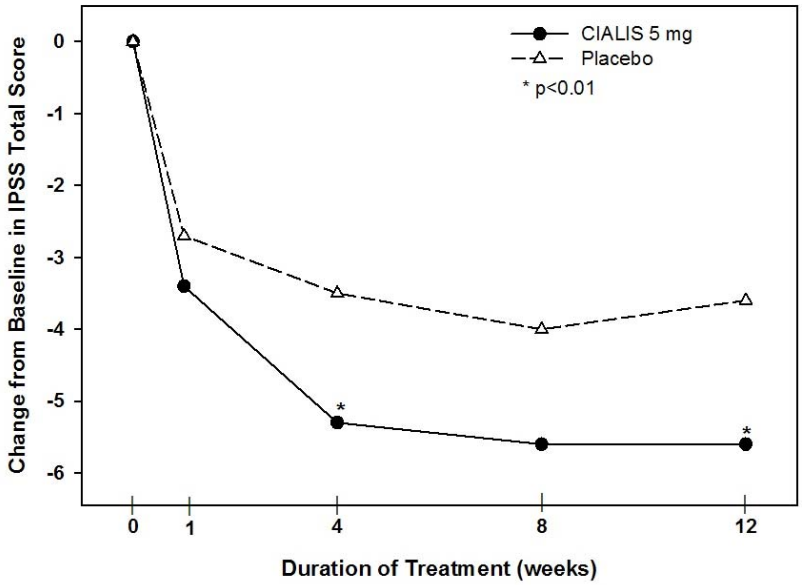
Table 2 Mean Change from Baseline to Week 12 for Total IPSS in Study LVHJ (ITT, LOCF)

Endpoint	Placebo N=164	Cialis 5 mg N=160	Difference (95% CI)	P-value
Total IPSS				
Baseline Mean (SD):	16.6 (6.0)	17.1 (6.1)		
Change from baseline: [a]	-3.6	-5.6	-1.9 (-3.2, -0.6)	0.004

[a]: Least square mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IPSS baseline value as covariate

Source: Table 9 of FDA Statistical Review signed September 15, 2011.

Figure 2 Mean IPSS Changes in BPH Patients by Visit (Study LVHJ)



Source: Figure 6 from Cialis Package Insert, revised October 2011.

7.1.4 Secondary Endpoints

The protocols for Study LVHG and Study LVHJ included several secondary endpoints. These are presented and discussed in the reviews of the primary Clinical Reviewer and the CDTL. Among the secondary efficacy endpoints in Study LVHG was maximum urinary flow rate (Qmax), an objective measure of urine flow. In Study LVHJ, Qmax was assessed as a safety endpoint instead of an efficacy endpoint. In Study LVHG, mean Qmax increased from baseline in both the Cialis 5 mg and placebo treatment groups (Cialis: 1.6 mL/sec; placebo: 1.2 mL/sec). These changes, however, were not significantly different between the 2 treatment groups. In Study LVHJ, the mean Qmax also increased from baseline in both the Cialis 5 mg and placebo treatment groups (Cialis: 1.6 mL/sec, placebo: 1.1 mL/sec). These changes, however, also were not significantly different between the treatment groups.

7.2 Phase 3 Clinical Trial (LVHR) for Treatment of ED and BPH

7.2.1 Design of Study LVHR

Study LVHR provided the main support for the efficacy of Cialis for the indication of treatment of ED and the signs and symptoms of BPH (ED/BPH) in subjects with both conditions.

Study LVHR was a multinational, Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 2.5 or 5 mg Cialis once daily for 12 weeks compared to placebo in subjects with ED and symptomatic BPH.

Study LVHR also included 3 study periods: a screening/wash-out period of 1-4 weeks, a placebo run-in period of 4 weeks, and a treatment period of 12 weeks.

The co-primary endpoints were total IPSS and the Erectile Function (EF) Domain score of the International Index of Erectile Function (IIEF). The IIEF is a 4-week recall questionnaire that was administered at the end of the placebo run-in period and subsequently at the randomized

on-treatment follow-up visits. The IIEF-EF Domain has a 30-point total score, where higher scores reflect better erectile function.

7.2.2 Baseline Subject Characteristics and Subject Disposition

In Study LVHR, 606 subjects were randomized to Cialis 2.5 or 5 mg once daily or placebo at 54 sites in 9 countries. Baseline characteristics were similar across the 3 treatment groups. The mean age of subjects was approximately 63 years (range: 45 to 83 years), with 9.2% being 75 years of age or older. Subjects were predominantly Caucasian (93.2%); 3.8% of subjects were Black or African American. Subjects with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included in the trial.

The majority of subjects randomized to placebo, 2.5 mg, or 5 mg Cialis completed the 12-week treatment period (85.0%, 86.9%, and 88.5%, respectively). The most common reasons for early discontinuation among the subjects receiving Cialis 5 mg were AE (2.9%), entry criteria not met (2.5%), subject decision (1.4%), and lack of efficacy (1.4%). The most common reasons for discontinuation among the subjects receiving placebo were lack of efficacy (4.0%), subject decision (4.0%), protocol violation (3.0%), AE (1.5%), and entry criteria not met (1.5%).

Division Director's Comment

- *The percentages of subjects treated with Cialis 5 mg once daily who discontinued treatment for any reason, and specifically because of an AE, in Study LVHR were low and do not raise any safety concerns.*

7.2.3 Primary Efficacy Endpoints and Analyses

The primary objective for Study LVHR was to demonstrate the superiority of treatment with Cialis (2.5 or 5 mg once daily) at Week 12, compared to placebo, in reducing **both** (1) the symptoms of BPH as assessed by the total IPSS and (2) ED as assessed by the EF Domain score of the IIEF in subjects with both ED and BPH. The 2 co-primary efficacy endpoints were the changes from baseline to Week 12 in the total IPSS and the IIEF-EF Domain score, respectively.

Treatment with Cialis 5 mg once daily was statistically significantly superior to placebo in improving both the total IPSS and the IIEF-EF Domain score at Week 12 as shown in Table 3. The mean changes from baseline for the total IPSS were -3.8 and -6.1 for the placebo and Cialis 5 mg treatment groups, respectively. The difference for the total IPSS between the 2 treatment groups was -2.3 (95% CI: -3.5 to -1.2; p-value < 0.001). The mean changes from baseline for the IIEF-EF Domain scores were 1.9 and 6.5 for the placebo and Cialis 5 mg treatment groups, respectively. The treatment difference for the IIEF-EF Domain score was 4.6 (95% CI: 3.3 to 5.9; p-value < 0.001).

Table 3 Mean Change from Baseline for Co-primary Efficacy Endpoints at Week 12 in Study LVHR (LOCF)

Endpoint		Placebo	5 mg Cialis	Difference (95% CI)	P-value
Total IPSS					
	N:	193	206		
Baseline Mean (SD):		18.2 (5.3)	18.5 (5.8)		
Change from baseline:[a]		-3.8	-6.1	-2.3 (-3.5, -1.2)	<0.001
IIEF-EF Domain Score					
	N:	188	202		
Baseline Mean (SD):		15.6 (6.9)	16.5 (7.2)		
Change from baseline: [b]		1.9	6.5	4.6 (3.3, 5.9)	<0.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and total IPSS baseline value as covariate.
[b]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IIEF-EF baseline value as covariate.

Source: Table 14 of FDA Statistical Review signed September 15, 2011.

Division Director's Comment

- *Treatment with Cialis 2.5 mg once daily compared to treatment with placebo was not statistically significantly superior in improving the symptoms of BPH as assessed by the total IPSS in subjects with both ED and BPH.*

7.2.4 Secondary Endpoints

The protocol for Study LVHR included several secondary endpoints. These are presented and discussed in the reviews of the primary Clinical Reviewer and the CDTL. One of the 2 key secondary endpoints in Study LVHR was Question 3 of the Sexual Encounter Profile diary (SEP3). The SEP is a diary in which subjects recorded each sexual attempt made throughout the trial. SEP Question 3 asks: "Did your erection last long enough for you to have successful intercourse?" The overall percentage of successes maintaining an erection for successful intercourse (SEP3) was derived for each patient. The mean percentage of subjects responding "Yes" to Question 3 of the SEP at baseline and the change from baseline at Week 12 is provided in Table 4.

There was a statistically significantly greater increase from baseline in the percentage of Cialis-treated subjects, compared to the placebo-treated subjects, who responded "yes" to Question 3 of the SEP (see Table 4).

Table 4 Mean Change from Baseline for Question 3 of the Sexual Encounter Profile (SEP3) at Week 12 in Study LVHR (LOCF)

Endpoint	Placebo N=187	5 mg Cialis N=199	Difference (95% C.I.)	P-value
SEP3 (percentage of yes)				
Baseline Mean (SD)	36.3 (38.7)	42.7 (40.0)		
Change from baseline [a]	15.3	33.9	18.7 (11.9, 25.4)	<0.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and SEP3 baseline value as covariate.

Source: Table 16 of FDA statistical review signed September 15, 2011.

7.3 Statistician's Conclusion regarding Primary Efficacy Findings

The primary Statistical Reviewer, Xin Fang PhD, stated the following in his Review that he signed on September 15, 2011:

> *"The data submitted in this application support the efficacy of tadalafil 5 mg once daily for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) in men. Tadalafil 5 mg once daily demonstrated statistically significant improvements in the international prostate symptom score (IPSS) and erectile function (EF) domain score of the international index of erectile function (IIEF), two primary endpoints evaluated to support the above indications. Tadalafil 2.5 mg did not demonstrate statistically significant improvement in the above symptoms.*
>
> *From a statistical perspective, this application provided adequate data to support the efficacy of tadalafil 5 mg once daily in the treatment of signs and symptoms of both BPH and ED in men.*"

7.4 Overall Assessment of Efficacy

The efficacy of Cialis 5 mg once daily for the treatment of the symptoms of BPH was demonstrated in 3 randomized, multinational, double-blind, placebo-controlled trials of 12-weeks duration. Two of the trials (Studies LVHG and LVHJ) enrolled men with symptomatic BPH and one of the trials (Study LVHR) enrolled men with both ED and symptomatic BPH. Treatment with Cialis 5 mg was shown to be statistically superior to treatment with placebo, based on the mean reductions in the total International Prostate Symptom Score (IPSS) from baseline values, in each of the 3 trials. Treatment with Cialis 2.5 mg daily was not statistically better than treatment with placebo. Although there was a small, numerically greater increase in maximum urinary flow rate (Qmax) in subjects receiving Cialis 5 mg once daily compared to those receiving placebo, the difference was not statistically significant.

In the third trial (Study LVHR), treatment with Cialis 5 mg once daily was shown to be statistical significantly better than placebo in improving both ED and the symptoms of BPH. The mean changes from baseline for the erectile function (EF) Domain score of the International Index of Erectile Function (IIEF) were 1.9 and 6.5 in the placebo and Cialis 5 mg treatment groups, respectively. The treatment difference for the EF Domain score of the IIEF (Cialis vs. placebo) was 4.6 (95% CI: 3.3 to 5.9; p-value < 0.001).

8. SAFETY

8.1 Safety Database

8.1.1 Overview of Safety Database

The primary Clinical Review (signed September 14, 2011) and the CDTL Review (signed on October 3, 2011) each included a comprehensive description and analysis of the safety data submitted for these Applications. The main safety components of the Applications included:

- Three 12-week, placebo-controlled Phase 3 trials (LVHG, LVHJ, and LVHR)
- A one year open-label extension of Study LVHG
- Three special safety studies (LVHK, LVHN, and LVHS)
  - A randomized, placebo-controlled, 12-week trial to assess the effects of tadalafil on urodynamics in men with BPH (Study LVHK)
  - A 10-day pharmacokinetic and tolerability study in elderly and young subjects (Study LVHN)
  - A randomized, placebo-controlled, 12-week study to assess the safety of Cialis in men with BPH when used in combination with an alpha-blocker (Study LVHS)

Both reviewers, but particularly the primary Clinical Reviewer, also considered (1) the extensive clinical trial safety database that exists for the approved once daily Cialis dosing regimen for the treatment of ED, (2) the extensive clinical trial safety database that exists for the approved as needed (PRN) Cialis dosing regimen for ED, and (3) the extensive postmarketing safety data for the use of Cialis for treatment of ED.

The following Section focuses on (1) the most significant safety findings from the three Phase 3 placebo-controlled clinical trials and (2) safety issues of particular relevance to the use of Cialis for the treatment of symptomatic BPH or ED and BPH.

8.1.2 Exposure to Cialis in Clinical Trials of Men with BPH

Based on the clinical trials listed above in Section 8.1.1, the following numbers of subjects were treated with Cialis:

- 1,450 subjects were treated with Cialis 5 mg, 10 mg, or 20 mg for at least 3 months, with a total exposure of 624.5 subject-years.
- 363 subjects were treated with Cialis 5 mg, 10 mg, or 20 mg for at least 6 months.
- 296 subjects were treated with Cialis 5 mg, 10 mg, or 20 mg for at least 1 year.

8.2 Deaths and Other Serious Adverse Events

8.2.1 Deaths

A total of 3 deaths were reported (one subject receiving placebo and 2 subjects receiving Cialis) in studies conducted in support of these Applications:

- A 59 year old man receiving placebo in Study LVHK died of a myocardial infarction.
- An 81 year old man receiving Cialis 5 mg in Study LVHJ had a myocardial infarction approximately 2.5 months after his first dose of study drug. Cardiac catheterization demonstrated 75%, 90%, and 90% occlusion of the LAD, circumflex, and right coronary arteries, respectively. He died several days after the myocardial infarction.

- A 67-year male receiving Cialis 2.5 mg in Study LVHR was found dead approximately 2 months after starting treatment. Although an autopsy was not performed and the precise cause of this subject's death was uncertain, the death certificate listed the immediate cause of death as myocardial infarction.

Division Director's Comment

- *These 2 deaths in subjects receiving Cialis with preexisting cardiac risk factors do not raise any new concerns about the safety profile of Cialis.*

8.2.2 Other Serious Adverse Events

In placebo-controlled Phase 3 Studies LVHG, LVHJ, and LVHR, 5 subjects receiving placebo and 4 subjects receiving Cialis 5 mg reported a total of 14 serious adverse events (SAEs) (see Table 5).

Table 5 Serious Adverse Events in the Placebo and Cialis 5 mg Treatment Groups (Studies LVHG, LVHJ, and LVHR)

Preferred Term	Placebo (N=576)	Cialis 5 mg (N=581)
	n (%)	
Subjects with ≥ 1 SAE	5 (0.9)	4 (0.7)
Acute Myocardial Infarction	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)
Endocarditis	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	1 (0.2)
Cartilage Injury	1 (0.2)	0 (0.0)
Cerebrovascular Accident	1 (0.2)	0 (0.0)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Indwelling Catheter Management	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)
Renal Colic	1 (0.2)	0 (0.0)
Rheumatoid Arthritis	1 (0.2)	0 (0.0)
Ureteral Catheterization	1 (0.2)	0 (0.0)
Urinary Retention	1 (0.2)	0 (0.0)

Source: Table 13 of the CDTL Review signed on October 3, 2011.

Division Director's Comments

- *Two cases of myocardial infarction described in Section 8.2.1 are not represented in Table 5 or Table 6 because one of the cases occurred in a Subject in Study LVHK and the other case occurred in a Subject receiving 2.5 mg Cialis.*
- *The types and numbers of serious adverse events reported in the Cialis 5 mg treatment groups in these three Phase 3 trials do not raise any new safety concerns regarding the use of Cialis for the treatment of men with BPH or ED/BPH.*

8.3 Early Discontinuations for Adverse Events

The adverse events leading to early discontinuation and the number of subjects reporting these adverse events in the placebo and Cialis 5 mg treatment groups in the primary placebo-controlled Phase 3 trials are listed in Table 6. The percentage of subjects discontinuing due to an adverse event was greater in the Cialis 5 mg group compared to that in the placebo group (3.6% versus 1.6%). The only AEs leading to early discontinuation from the studies reported by ≥ 1 subject were headache, abdominal pain upper, and myalgia. All AEs leading to early discontinuation were reported with a frequency < 1%.

Table 6 Adverse Events Reported as Reason for Early Discontinuation in the Placebo and Cialis 5 mg Treatment Groups (Studies LVHG, LVHJ, and LVHR)

Preferred Term	Placebo (N=576)	Cialis 5 mg (N=581)
	n (%)	
Subjects Discontinuing due to an AE	9 (1.6)	21 (3.6)
Headache	0 (0.0)	5 (0.9)
Abdominal Pain Upper	2 (0.3)	3 (0.5)
Myalgia	0 (0.0)	2 (0.3)
Acute Myocardial Infarction	0 (0.0)	1 (0.2)
Back Pain	1 (0.2)	1 (0.2)
Dyspepsia	0 (0.0)	1 (0.2)
Muscle Spasms	0 (0.0)	1 (0.2)
Pain	0 (0.0)	1 (0.2)
Pain in Extremity	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	1 (0.2)
Retinal Tear	0 (0.0)	1 (0.2)
Rotator Cuff Syndrome	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)
Abdominal Discomfort	1 (0.2)	0 (0.0)
Blood Creatine Phosphokinase Increased	1 (0.2)	0 (0.0)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Dizziness	1 (0.2)	0 (0.0)
Eye Pain	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)

Source: Table 12 of the CDTL Review signed on October 3, 2011.

8.4 Common Adverse Events

The most common all causality treatment-emergent adverse events that occurred in ≥ 1% of subjects in the Cialis 5 mg group and which were more frequent in the Cialis group in primary Phase 3 Studies LVHG, LVHJ, and LVHR were: headache, dyspepsia, back pain, nasopharyngitis, hypertension, diarrhea, pain in extremity, myalgia, and dizziness (See Table 7).

Table 7 All Causality Adverse Events Reported by ≥ 1% of Subjects Treated with Cialis 5 mg and More Frequent in the Cialis Group (Studies LVHG, LVHJ, and LVHR)

Adverse Event	Placebo (N=576)	Cialis 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Hypertension	0.9%	1.9%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Source: Table 14 of the CDTL Review signed on October 3, 2011.

Division Director's Comments

- *The most common adverse events reported in the primary Phase 3 clinical trials are consistent with those reported previously for Cialis in clinical trials for ED.*
- *The primary Clinical Reviewer's analysis of adverse events coded to "hypertension" revealed that these cases were actually not new-onset hypertension and that the majority of these subjects showed no increase in blood pressure from their elevated baseline blood pressures. Therefore, the Clinical Reviewer concluded that hypertension was not a treatment-emergent adverse event (TEAE) related to Cialis in the controlled Phase 3 clinical trials.*

8.5 Potential Safety Issues of Particular Interest in the Population with BPH

8.5.1 The Effect of Tadalafil on Urodynamics in Men with BPH (Study LVHK)

Based in part on the lack of a statistically significant effect of Cialis compared to placebo in increasing maximum urinary flow rates, DRUP asked the Applicant to conduct a study to investigate the effects of Cialis on urodynamics (i.e., lower urinary tract function) in men with BPH. The objective was to determine if Cialis was actually worsening bladder emptying or creating a "silent obstruction." The results of this investigation, Study LVHK, demonstrated that there was no detrimental effect of treatment with Cialis on bladder emptying or intravesical pressure in subjects with BPH.

8.5.2 Safety of Cialis in Men Taking Both Cialis and an Alpha Blocker for the Treatment of BPH (Study LVHS)

Cialis is intended as a "monotherapy" for BPH; specifically, it is intended to be used alone for the treatment of BPH and not with other treatments for BPH such as alpha adrenergic antagonists (alpha blockers). Nevertheless, it was assumed that some healthcare prescribers might use an alpha blocker in conjunction with Cialis for the treatment of BPH. The Applicant therefore conducted Study LVHS to assess the potential for increased vasodilatory adverse events (e.g., dizziness or hypotension) in subjects with BPH who were taking both Cialis and alpha blockers. Based on the finding from this trial, there appeared to be little risk of an increase in significant vasodilatory adverse events with the combined use of Cialis and an alpha blocker. The efficacy of Cialis, however, was not enhanced by the concomitant use an alpha blocker.

Division Director's Comments

- *The primary Medical Reviewer made the following statement in his review: "LVHS did not result in the identification of new safety concerns related to concomitant administration of tadalafil and alpha blocker therapy. No tadalafil patients reported syncope or an SAE attributable to hypotension. A trend toward increased hemodynamic signs and symptoms in men on nonselective alpha blockers, most notably doxazosin, was noted as described in the existing Cialis USPI (2009)."*
- *Although the likelihood of clinically significant vasodilatory adverse events is low, to-be-approved product labeling will include the following Warning and Precaution: "Cialis is not recommended in combination with alpha blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. Caution is advised when Cialis is used as a treatment for ED in men taking alpha blockers."*

8.5.3 Safety Profile and Pharmacokinetics of Cialis in Elderly Men with BPH (Subgroup Analyses in the Controlled and Uncontrolled Studies and Study LVHN)

Because BPH is a disorder that primarily affects elderly men and treatment of BPH will be a new indication for Cialis, approval of these 2 new indications will likely result in a greater number of elderly men receiving Cialis. Therefore, the primary clinical review team considered it prudent to specifically evaluate the safety profile and pharmacokinetic of Cialis in elderly subjects with BPH, namely, those ≥ 65 and ≥ 75 years of age. The pharmacokinetics of Cialis in this population are described separately in Section 5.2. The CDTL stated the following in his Review signed on October 3, 2011:

"*In regard to the assessment of safety outcomes based on age subgroups (subjects < 65 and ≥ 65 years of age; subjects <75 years and ≥ 75 years of age) in the clinical trials, the data appear to show that across all analysis sets, the AE profiles were similar between age groups, in the pivotal and additional BPH and BPH/ED analysis sets. There were no clinically meaningful differences in the frequencies and types of TEAEs across age groups. The extent of the exposure in elderly patients appears sufficient, when considering both the BPH studies and the ED studies*."

Division Director's Comment

- *These additional safety and pharmacokinetic analyses in elderly subjects with BPH did not raise any new concerns about the safety profile of Cialis.*

Postmarketing Safety Experience

According to the Applicant, as of April 15, 2010, approximately 26.3 million patients worldwide had been exposed to Cialis or tadalafil (excluding use of tadalafil when taken as Adcirca for pulmonary arterial hypertension). Tadalafil has been approved for the treatment of ED in 118 countries and is marketed in 108 countries. Dr. Wiederhorn, the primary Clinical Reviewer, made the following statements based on his review of the Applicant's 13th and 14th Periodic Safety Update Reports (PSUR):

"*It appears that the postmarketing safety profile of the tadalafil daily dosing regimen is consistent with the safety profile shown in clinical trials. No new safety signals for the daily*

dosing regimen were identified in the 13th PSUR. There does not appear to be a worsened AE profile in patients ≥ 65 years of age compared with patients < 65 years of age using the daily dosing regimen in the postmarketing period."

"In both the 13th and 14th PSURs, the information presented did not reveal any new safety signals and no new safety concerns have been identified."

8.6 Overall Assessment of Safety

The safety profile of Cialis in these Applications was adequately assessed based on the data from three placebo-controlled Phase 3 trials, a one-year open label safety extension study, and several additional safety studies that were conducted in men with BPH. These safety data were bolstered by the clinical trial data that originally supported the approval of Cialis for both "as needed" dosing and "once daily" dosing for the treatment of ED, as well as the extensive postmarketing safety database for Cialis.

In the Applicant's overall clinical development program there were 3 deaths (one in the placebo group and 2 in the Cialis treatment groups). None of the deaths could be directly attributed to Cialis. In the placebo-controlled Phase 3 studies, the percentages of subjects reporting serious adverse events were low and similar in the placebo (0.9%) and Cialis (0.7%) groups. The percentages of early discontinuations due to adverse events were low, but there was a small increase in the incidence of discontinuations due to adverse events in Cialis-treated subjects (Cialis: 3.6%; Placebo: 1.6%). In the placebo-controlled studies, the most commonly reported adverse events associated with early termination in the Cialis-treated subjects and the percentages of subjects reporting them were headache (0.9%), abdominal pain (0.5%), and myalgia (0.3%). In these studies, the most commonly reported treatment emergent adverse events in the Cialis-treated subjects were headache (4.1%), dyspepsia (2.4%), back pain (2.4%), nasopharyngitis (2.1%), diarrhea (1.4%), pain in extremity (1.4%), myalgia (1.2%), and dizziness (1.0%). The safety profile for Cialis was not different in subjects ≥ 65 years of age or ≥ 75 years of age, compared to subjects < 65 years of age or < 75 years of age. The recent postmarketing safety data for Cialis revealed no findings that raise new concerns.

Both the primary Clinical Reviewer and the CDTL have concluded that the safety profile of Cialis in subjects with BPH was consistent with the well-established and favorable safety profile of Cialis for the treatment of ED. I concur with their overall assessments. There were no unexpected or new safety concerns based on the information provided in these Applications.

9. ADVISORY COMMITTEE MEETING

These Applications were not discussed at an Advisory Committee Meeting. Cialis is not a new molecular entity and has been approved for the treatment of ED since 2003. The current Applications did not raise any safety or efficacy issues that would warrant discussion at an Advisory Committee Meeting.

10. PEDIATRICS

The Applicant requested a full waiver of the requirement to conduct pediatric studies. DRUP concurred with the Applicant's request. The Pediatric Review Committee (PeRC) reviewed the request for a full waiver on September 14, 2011, and granted a full waiver because the disease/condition of BPH or ED/BPH does not exist in children.

11. OTHER RELEVANT REGULATORY ISSUES

11.1 Financial Disclosure

Financial disclosure information was submitted by all investigators in Phase 3 studies LVHG, LVHJ, and LVHR. Of the 409 investigators who submitted information, 5 were identified as having "accrued equity above suggested limits." The financial disclosure information for these 5 investigators was reviewed and the primary Clinical Reviewer concluded that "*it does not appear that the compensation that the 5 investigators who submitted Form 3435 received affected the outcome of covered studies [12 CFR 54, 2(a)], reflected a proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], or significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]*."

11.2 Division of Good Clinical Practice Compliance

At the request of DRUP, the Division of Good Clinical Practice Compliance conducted inspections at 4 clinical sites. The sites were selected primarily because of their enrollment of relatively large numbers of subjects. Regulatory violations, classified as Voluntary Action Indicated (VAI), were noted at 3 of the 4 sites. The violations were discussed with and considered by DRUP. In the Clinical Inspection Report, Roy Blay PhD of the Division of Good Clinical Practice Compliance stated:

> *"Notwithstanding the observations detailed above, the studies appear to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication*."

12. LABELING

Relevant sections of labeling submitted by the Applicant were reviewed by all of the primary review disciplines as well as by the Division of Drug Advertising, Marketing, and Communication (DDMAC), Division of Medication Errors and Prevention (DMEPA), Division of Drug Risk Assessment (DRISK), and the Study Endpoints and Labeling Development (SEALD) team. All recommendations provided by DDMAC, DMEPA, DRISK, and SEALD were considered by the primary clinical review team and accepted as appropriate.

Acceptable carton and container labeling was submitted by the Applicant on September 1, 2011. DMEPA made the following comments regarding the Applicant's revised blister pack label:

> "*…the revised blister labels still contain days of the week, a statement "last tablet", and clockwise arrows above the tablets organized in a circular manner. Although blister label's design is not ideal, we did not [find] any medication errors related to the product's blisters. Thus, we find the revised blister labels acceptable and have no additional comments to the Applicant at this time*."

On September 30, 2011, the Applicant submitted acceptable Physician (Package Insert) and Patient (Patient Package Insert) labeling.

Division Director's Comments

- *To-be-approved Physician labeling closely follows currently approved labeling and has retained all of the current Warning and Precautions as well as the Contraindication against concomitant use of any form of organic nitrate with Cialis.*

- *A new Warning and Precaution stating the following will be added: "The efficacy of the co-administration of an alpha-blocker and CIALIS for the treatment of BPH has not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure lowering, the combination of CIALIS and alpha-blockers is not recommended for the treatment of BPH"*

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

Cialis (tadalafil) 5 mg tablets will be approved for the new indications of (1) treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) (Supplement 20) and (2) treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (ED/BPH) (Supplement 21).

13.2 Risk/Benefit Assessment

The efficacy of Cialis 5 mg once daily for the treatment of the symptoms of BPH was demonstrated in 3 randomized, multinational, double-blind, placebo-controlled trials of 12-weeks duration. Two of the trials enrolled men with symptomatic BPH and one of the trials (Study LVHR) enrolled men with both ED and symptomatic BPH. In each of the 3 trials, treatment with Cialis 5 mg was shown to be statistically superior to treatment with placebo in improving the symptoms of BPH as assessed by the total International Prostate Symptom Score (IPSS). In Study LVHR, treatment with Cialis 5 mg once daily was also shown to be statistically significantly better than placebo in improving both ED and the symptoms of BPH.

The safety profile of Cialis 5 mg once daily in these Applications was adequately assessed based on the data from three placebo-controlled Phase 3 trials, a one-year open-label safety extension study, and several additional safety studies that were conducted in men with BPH. These safety data were bolstered by the clinical trial data that originally supported the approval of Cialis for both "as needed" dosing and "once daily" dosing for the treatment of ED, as well as by the extensive postmarketing safety database for Cialis. In the placebo-controlled studies submitted in support of these Applications, the most commonly reported adverse events associated with early termination in the Cialis 5 mg treated subjects and the percentages of subjects reporting them were headache (0.9%), abdominal pain (0.5%), and myalgia (0.3%). In these studies, the most commonly reported treatment emergent adverse events in the Cialis 5 mg group were headache (4.1%), dyspepsia (2.4%), back pain (2.4%), nasopharyngitis (2.1%), diarrhea (1.4%), pain in extremity (1.4%), myalgia (1.2%), and dizziness (1.0%). The safety profile for Cialis was not different in subjects $\geq$ 65 years of age or $\geq$ 75 years of age, compared to subjects $<$ 65 years of age or $<$ 75 years of age, respectively. The recent postmarketing safety data for Cialis revealed no findings that raise new concerns.

Both the primary Clinical Reviewer and the CDTL have concluded that the safety profile of Cialis in subjects with BPH was consistent with the well-established and favorable safety profile of Cialis for the treatment of ED. I concur with their overall assessments. There were no unexpected or new safety concerns based on the information provided in these Applications.

In summary, the Applicant has provided substantial evidence, based on three Phase 3 placebo-controlled efficacy and safety trials and several additional supportive safety studies, that Cialis 5 mg once daily will be safe and effective when used in accordance with the to-be-approved labeling for the treatment of (1) symptomatic BPH and (2) ED and symptomatic

BPH when both conditions are present in the same patient. Based on the data submitted in these Applications, the overall risk/benefit profile for Cialis is favorable for the treatment of symptomatic BPH and ED and symptomatic BPH when both are present in the same patient. The risk/benefit profile for the use of Cialis for these 2 new indications appears to be comparable to the well-characterized and favorable risk/benefit profile for Cialis when Cialis is used for the currently approved indication of treatment of ED.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

None.

13.4 Recommendation for other Postmarketing Requirements and Commitments

None other than standard postmarketing pharmacovigilance.

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/s/

SCOTT E MONROE
10/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: sNDA 021368/S-020
Cialis® (tadalafil)

The following officers or employees of FDA participated in the decision to grant this application an Approval and consented to be identified on this list.

Scott Monroe, M.D.
Mark Hirsch, M.D.
Roger Wiederhorn, M.D.
Xin Fang, Ph.D.
Mahboob Sobhan, Ph.D.
Lynnda Reid, Ph.D.
Yangmee Shin, Ph.D.
Myong-Jin Kim, Pharm.D.
Matthew Falter, Pharm.D.
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Shawna Hutchins, MPH, BSN, RN.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	October 3, 2011
From	Mark S. Hirsch, MD
Subject	Cross-Discipline Team Leader Memo
NDA #	21-368 SE8-020 and SE8-021
Applicant	Eli Lilly & Co.
Date of Submission	December 6, 2010
PDUFA Goal Date	October 6, 2011
Proprietary Name / Established (USAN) names	Cialis® tadalafil
Dosage forms / Strength	Oral tablets, 2.5 mg and 5 mg once daily
Proposed Indication(s)	1) Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) 2) Treatment of erectile dysfunction (ED) and the signs and symptoms of BPH
Recommended:	*Approval*

1. Introduction (Executive Summary)

These two efficacy supplements provide substantial evidence from three, Phase 3, randomized, placebo-controlled studies (LVHG and LVHJ in men with BPH, and LVHR in men with both ED and BPH) that tadalafil is effective and safe for use as a treatment for symptomatic BPH as well as for the treatment of BPH and ED in men with both conditions (BPH/ED).

The Phase 3 studies demonstrate a statistically significant and clinically meaningful treatment effect of tadalafil on the symptoms of BPH. It is notable that while tadalafil promotes symptomatic relief in BPH, it does not positively nor negatively affect maximum urinary flow rate. Tadalafil does not interfere with bladder emptying. The transition from other treatments for symptomatic BPH to tadalafil does not lead to adverse consequences. The safety profile of tadalafil that was demonstrated in the three Phase 3 BPH studies (LVHG, LVHJ, and LVHR), the single Phase 2 study (LVGC), the additional safety studies (LVHK and LVHS), the Phase 1 study in elderly patients (LVHN), the three studies in Asia (LVIA, LVHT and LVHB), and the open-label extension of LVHG is consistent with the known safety profile of tadalafil for the treatment of ED. There were no unexpected or new safety concerns. All warnings and precautions for tadalafil as used for ED apply to its use for the new BPH and BPH/ED indications.

The labeling for the new indications is concise and accurate. There are no requests for Phase 4 commitments or requirement. There are no outstanding issues. Therefore, I recommend **approval** of the supplements.

2. Background

2.1 DESCRIPTION OF PRODUCT

Tadalafil (Cialis®) is a selective inhibitor of cyclic guanosine monophosphate (cAMP)-specific phosphodiesterase type 5 (PDE5). It is an approved oral treatment for male erectile dysfunction (ED). It is approved drug for use in the US under NDA 21-368. For ED, Cialis is approved for use in two methods: for as needed (prn) use at doses of 5 mg, 10 mg, and 20 mg, or for once daily use at doses of 2.5 mg and 5 mg. Over 30 million men worldwide have used Cialis for the treatment of ED. The applicant currently proposes utilizing the once daily regimen for the treatment of symptomatic BPH in adult males and for the treatment of symptomatic BPH in association with ED in adult males. The Sponsor proposes the 5 mg dosage strength as a daily dosing regimen for BPH and for BPH/ED. For patients with moderate renal impairment, a daily dose of 2.5 mg is recommended for BPH and BPH/ED.

Through its effect on PDE5 and subsequent increase in cGMP concentrations in the smooth muscle of the corpora cavernosa, tadalafil enhances penile erection. The mechanism of action for relief of symptoms of BPH is not fully known. The Sponsor postulates that tadalafil may similarly relax smooth muscle of the bladder neck and prostate gland, and/or may increase

blood flow to the bladder outlet, resulting in symptomatic improvement of the irritative and obstructive symptoms associated with BPH.

The currently available approved medical treatments for BPH include two drug classes: the selective alpha-adrenergic antagonists ("alpha-blockers", such as terazosin, tamsulosin, and sildosin) and the 5-alpha reductase inhibitors ("5-ARIs" finasteride and dutasteride). There are limitations to both these drug classes. The alpha blockers have been associated with postural hypotension, including first-dose syncope and dizziness, rhinitis, asthenia, and anejaculation. The 5-ARI's have been associated with erectile dysfunction, breast pain and gynecomastia, loss of libido, and a potential risk of high grade prostate cancer. Combinations of an alpha blocker and 5-ARI have also been approved for the treatment of symptomatic BPH. There are several surgical means to alleviate symptomatic BPH, some include minimally invasive techniques, but none are without side effects or risks. Therefore, an addition to the medical armamentarium for the treatment of symptomatic BPH would be welcome.

2.2 REGULATORY HISTORY

On November 21, 2003, Cialis was approved for the treatment of ED. The treatment was approved to be taken on an "as-needed" (or "prn") basis at doses of 5 mg, 10 mg or 20 mg.

On April 25, 2006, Eli Lilly & Company opened IND #73,502 to study tadalafil for the treatment of BPH and the treatment of BPH and ED.

On July 19, 2006, a Type A meeting was held for IND #73,502. The following major agreements were reached:

- Lilly is to develop tadalafil for signs and symptoms of BPH as "monotherapy."
- Lilly is nonetheless to perform a study evaluating the safety of tadalafil in patients taking alpha blockers in order to assess the potential risks should a prescriber choose to use the two products for BPH contrary to the labeled recommendations.
- The planned, large, Phase 2/3, dose-ranging, Study LVHG could be considered a "pivotal" efficacy and safety study.
- In "pivotal" trials, approximately one third of participants will be 65 years of age and older and approximately 10% will be 75 years and older.

On January 7, 2008, Cialis was approved for the once daily treatment of ED at doses of 2.5 mg and 5 mg once daily.

On September 25, 2008, an EOP2 meeting was held for IND #73,502. The following major issues were discussed:

- Sponsor agreed to provide safety data from least 100 men aged 75 years or older.
- Aside from Study LVHN in geriatric subjects, no additional pharmacokinetic and clinical pharmacology (including drug-drug interaction) studies were required for the proposed indications.
- The Division agreed that the urodynamic results from Study LVHK and lack of effect on postvoid urine residual volumes and clinical urological adverse events in Studies

LVGC, LVHG, and LVHK demonstrated no adverse effect of tadalafil on bladder emptying.

- Sponsor agreed to evaluate both the 2.5 g and 5.0 g once daily doses for the BPH/ED indication in a separate Phase 3 study. This study was eventually performed as Study LVHR.
- Sponsor agreed to submit information in support of the validity of the BPH Impact Index (BII), a secondary efficacy endpoint.
- If the onset of action for tadalafil is established at 1 week in Study LVHJ using the modified International Prostate Symptom Score (IPSS) compared to placebo, the results could be included in labeling.
- Sponsor was to provide safety data on patients discontinuing alpha blockers and initiating tadalafil as monotherapy.
- Sponsor again agreed to conduct a study that would investigate the potential adverse events associated with use of tadalafil in combination with alpha-blockers for BPH to assess the risks of such unrecommended use. This study was eventually performed as Study LVHS.
- The Division agreed to the fixed sequence testing procedure in Study LVHJ to control family-wise Type I error in primary and key secondary efficacy endpoints. The Division also agreed to the testing procedure planned for Study LVHR.
- (b) (4)

On April 13, 2010, a Pre-sNDA meeting was held for IND #73,502. The following major issues were discussed:

- The Division requested that safety data be organized in the ISS into 3 groups: 1) All BPH patients 2) BPH patients without ED 3) Patients with both BPH and ED.
- In addition to the special safety topics proposed by Sponsor, The Division requested that Cardiovascular events, myalgias/back pain, seizures, and transient global amnesia be added to the proposed list of special safety topics
- A final study report for the completed 1-year Study of LVHG would be included in the original application as well as an abbreviated study report for the open-label extension of Study LVIA containing at least 6 months of safety data.
- (b) (4)
- (b) (4)

On December 6, 2010, the two efficacy supplements (S-020 and S-021) were submitted.

3. Chemistry, Manufacturing and Controls (CMC)

In the final CMC review dated September 15, 2011, Jeff Medwid and Tom Oliver had the following comment and conclusion:

"*Since these supplements are efficacy supplements, the emphasis of these two supplements will focus on the clinical aspect. As a result, the CMC review will be minimal except for labeling. At the time of this review, several minor labeling issues have yet to be resolved (minor PI and container/carton). When the final labeling is completed and acceptable, we will enter a brief "Addendum" into DARRTS.*

From a CMC perspective, this supplement is recommended for approval from a CMC point of view, pending final labeling and container/carton review and approval"

On September 19, 2011, the Sponsor accepted the single CMC edit to the PI. On September 20, 2011, Drs. Christner and Oliver provided CMC concurrence for the PI. Of note, on September 14, 2011, the Division of Medication Errors Prevention and Analysis provided concurrence with the container/carton labeling. On September 28, 2011, a final CMC memo was entered into DARRTS by Jeff Medwid and Tom Oliver. CMC concluded that all labeling, including container/carton and PI/PII were acceptable from the CMC perspective. CMC also granted the Sponsor's request for a categorical exclusion to submit an environmental assessment for the use of tadalafil. CMC stated that the final calculated predicted concentration of tadalafil that may be discharged into the aquatic environment would be less than 0.11 ppb, which is below the 1 ppb limit allowed in 21 CFR 25.31 (b).

4. Nonclinical Pharmacology/Toxicology

In their final Pharmacology/Toxicology review dated August 8, 2011, Drs. Yangmee Shin and Lynnda Reid had the following comment and recommendation:

"No new toxicology studies were submitted with this application. The only additional nonclinical study included is an interim report evaluating the pharmacodynamic effect of tadalafil in prostate gland oxygenation in a spontaneously hypertensive rat (SHR) model. Tadalafil treatment reduced hypoxia-inducible factor 1α and vasorelaxant andothelin-1 type receptor protein immunopositivity in SHR prostate sections when compared to WKY. Oxygenation was partially normalized after 1 day and was completely restored to WKY after 7 days and 4 weeks. These results suggest that tadalafil treatment may improve prostate gland oxygenation in the SHR although a direct extrapolation to humans is uncertain.

Previous nonclinical studies submitted in support of the original marketing application of tadalafil are considered sufficient to support the safety of the new indications, given the exposure levels within the range of approved Cialis oral tablets.

Recommendation: From a Pharmacology/Toxicology perspective, the previous nonclinical data submitted for the approval of the treatment of ED support the safety of the proposed indications of Cialis."

Drs Shin and Reid had requests for minor labeling revisions which were conveyed to sponsor. Sponsor complied fully with these requests.

5. Clinical Pharmacology/Biopharmaceutics

In their final review dated September 16, 2011, Drs. Dennis Bashaw and Myong-Jin Kim, made the following recommendation:

> *"The results of the submitted trials do not reveal any significant changes in the pharmacokinetics of tadalafil. The application is acceptable from a Clinical Pharmacology standpoint, provided that appropriate labeling is developed to incorporate the information into the package insert."*

Clinical Pharmacology had several minor edits to product labeling; (b) (4) On September 19, 2011, the Sponsor complied with all Clinical Pharmacology requests for labeling revisions.

Results from two Phase 1 studies were submitted, one that compared multiple-dose pharmacokinetics of 20 mg tadalafil in elderly versus young subjects (LVHN), and one that studied safety, efficacy and pharmacokinetics in Asian patients (LVIA).

In regard to mean PK parameters in Study LVHN, the ClinPharm reviewers found a significant degree of overlap between the older and younger subject groups. No significant differences in systemic exposures were observed between groups. This is somewhat in conflict with previous tadalafil study results, showing an increase of approximately 25% in exposure in elderly versus young subjects. The reviewers speculate that the lack of difference between groups in this study may be due to a slightly older age in the "young" treatment group in this study, as well as the older age (70-76 years) of the elderly subjects in this study. Nonetheless, mean PK parameters from this study were consistent with the previous tadalafil studies. The few number of subjects with any degree of renal impairment in this study (n=3) made subgroup analysis for this intrinsic factor impossible. A cross-study evaluation in patients with mid to moderate renal impairment appeared to show no more than a nominal increase in exposure (1.2-fold) in renally impaired subjects compared to subjects with normal renal function. There were two subjects in whom orthostatic hypotension was reported. In one case, the event occurred very early after drug intake and the reviewer stated that it was unlikely to be true orthostatic hypotension due to a drug-related mechanism. In the other case, the event occurred around the time of peak plasma concentration but was reported to last for 11 days, which the reviewer felt to be inconsistent with a drug-related effect. The reviewers also provide BP data showing a decrease in maximum systolic BP in both elderly and young treated subjects, with the maximum decrease being larger in the elderly compared to the younger subjects in this study.

> *CDTL Comment: The independent effect of tadalafil 20 mg on blood pressure in this study is impossible to determine since there was no placebo control. In previous, placebo-controlled studies of PDE5 inhibitors, including tadalafil, blood pressure has decreased significantly in both treatment and placebo groups. In addition, the larger maximum drop in blood pressure in the elderly in this study may be due to a higher baseline BP in elderly*

subjects compared to younger. It is also notable that the dose in this study was 20 mg daily, a dose that is 8-fold and 4-fold greater than the 2.5 mg and 5 mg doses, respectively, that are approved for daily dosing. Finally, it is also relevant that both cases of orthostatic hypotension were mild in this study and no disparate clinical sequelae of orthostatic hypotension were noted in elderly subjects versus young subjects in any clinical studies submitted in these supplemental applications.

Study LVIA was a Phase 2, placebo-controlled, double-blinded, efficacy and safety study in Japanese males, in which limited samples for pK were drawn for analysis. The Sponsor provided descriptive analyses of these data. Clinical pharmacology noted that this was a non-IND study, with extremely limited pK data, and ethnicity had been adequately addressed in previous tadalafil study. Therefore, no formal review of this study was conducted by Clinical Pharmacology.

On September 27, 2011, the Clinical Pharmacology review team finalized a labeling memo which stated:

"*Since the execution of this review and its placement in DARRTS (September 16th, 2011), there has been additional communication with the sponsor regarding labeling. As of today, September 27th, 2011, the sponsor has agreed to all of the Clinical Pharmacology based labeling recommendations. Based on their agreement, the Division of Clinical Pharmacology-3 considers all of the review issues closed and the application to be acceptable under the provisions of 21CFR320.*"

6. Clinical Microbiology

There was no Clinical Microbiology review for these efficacy supplements.

7. Clinical/Statistical- Efficacy

7.1 Clinical Program for Efficacy

The primary source of efficacy data for this NDA was from three, randomized, double-blinded, placebo-controlled, 12-week studies in men with BPH – Studies LVHG, LVHJ and LVHR. The first two studies (LVHG and LVHJ) did not require men to have erectile dysfunction and these support the first new indication (BPH), while the third study (LVHR) targeted men with both BPH and ED. Although there was a pilot Phase 2 study, as well as several non-IND studies in Asian men, these will not be discussed here. The reader is referred to the medical officer's review for details of those studies.

7.2 Studies LVHG and LVHJ (in support of the BPH indication)

Studies LVHG and LVHJ provided the main support for efficacy for the BPH indication. The two studies were of similar design. Therefore, they are discussed together in this section.

Study ***LVHG*** was a multicenter, Phase 2/3, randomized, double-blind, placebo-controlled, parallel-design, dose-finding study to evaluate the efficacy, dose response, and safety of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks versus placebo in men with BPH-LUTS. The study enrolled 1058 subjects ≥45 years old who presented with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Lower urinary tract symptoms were assessed by the International Prostate Symptom Score (IPSS), a validated patient reported outcome instrument consisting of 7 questions related to urinary storage and emptying symptoms.

Study ***LVHJ*** was a multicenter, Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of tadalafil 5 mg once daily for 12 weeks versus placebo in men with BPH-LUTS. The study enrolled 325 subjects with BPH, using the same criteria as in Study LVHG.

Both studies consisted of 3 periods:

- a screening/wash-out period of 1-4 weeks,
- a 4-week, single-bind, placebo run-in period to assess treatment compliance and to establish baseline measures (baseline = Visit 3), and
- a 12-week treatment period, where eligible subjects were randomly assigned to treatment (tadalafil 2.5, 5, 10, 20 mg in LVHG and tadalafil 5 mg in LVHJ), or to placebo. Randomization was in a 1:1:1:1:1 ratio in LVHG and 1:1 ratio in LVHJ. Randomization was stratified by baseline severity (total IPSS <20 or ≥20), geographic region, and history of ED. Subjects were to return on Visit 4 (Week 4), Visit 5 (Week 8), and Visit 6 (Week 12) to assess treatment compliance and to measures of the study endpoints. Visit 6 (Week 12) was the end-of-study visit.

7.2.1 Entry Criteria in Studies LVHG and LVHJ

For both studies, key inclusion criteria were total IPSS≥13 and peak flow rate (Qmax) ≥ 5 mL/sec and ≤15 mL/sec at the start of the placebo lead-in period. Notable exclusion criteria included prostate-specific antigen (PSA) values >10 ng/mL (men with a PSA of 4 to 10 ng/mL were required to have a prostate biopsy negative for malignancy within the preceding 12 months), clinical evidence of urinary tract infection/inflammation at screening , a post-void residual (PVR) volume ≥300 mL at screening, clinical evidence of prostate cancer, and finasteride or dutasteride treatment within 3 and 12 months before the start of the placebo lead-in period, respectively.

7.2.2 Efficacy Assessments and Endpoints in Studies LVHG and LVHJ

For both studies, the *primary endpoint* was the change in total IPSS from baseline to Visit 6 (Week 12) for subjects taking tadalafil 5 mg once-daily versus placebo.

For Study LVHG, the *secondary endpoints* included:

- Evaluating the efficacy of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks compared to placebo in the treatment of BPH-LUTS as assessed by the following measures:
    - Total IPSS for tadalafil 2.5-, 10-, and 20-mg doses
    - IPSS storage and voiding subscores

- IPPS nocturia question
- BPH Impact Index (BII)
- LUTS-General Assessment Questions (GAQ)
- Uroflowmetry parameters, including maximum urinary flow rate (Qmax)
- International Index of Erectile Function (IIEF) Erectile Function (EF) domain score in sexually active men with ED.

In Study LVHJ, the "key" secondary endpoints were pre-defined in a hierarchical testing order as follows:

- IIEF EF Domain score after 12 weeks (in sexually active subjects with ED)
- Total IPSS after 4 weeks of treatment
- BII after 12 weeks of treatment
- Total modified IPSS (mIPSS) after 1 week of treatment
- BII after 4 week of treatment.

7.2.3 Populations and Patient Disposition in Studies LVHG and LVHJ

7.2.3.1 Study Populations

In Study LVHG, the 1056 randomized subjects had similar demographics between the treatment groups. The mean age of subjects was approximately 62 years (range: 45 to 92 years) and were predominantly Caucasian (85.6%). 51% reported experiencing BPH symptoms for >3 years, 33.5% were classified as having severe BPH symptoms by their total IPSS, and 27.8% had used previous therapy for BPH. 67.8% reported a history of ED and 26.9% reported having used previous therapy for ED.

In Study LVHJ, the 325 randomized subjects had similar demographics between the treatment groups. The mean age of subjects was 64.9 years (range: 44.8 to 87.0 years), and were predominantly Caucasian (91.1%). Overall, 20.0% of randomized subjects were at least 75 years of age or older. 35.4% were categorized as having severe BPH symptoms by total IPSS, 38.0% had a Qmax <10 mL/second, and 40% had used previous therapy for BPH. 68.9% reported a history of ED and 22.8% reported having used previous therapy for ED.

7.2.3.2 Subjects Disposition

In Study LVHG, the majority of randomized patients (83.7%) completed the 12-week treatment comparison period. The most common reasons for discontinuation among all tadalafil-treated patients were AEs (4.8%), and subject decision (4.3%). In placebo-treated subjects, 4.3% discontinued due to subject decision, 2.4% discontinued to both AE's, and 2.4% were lost to follow-up.

In Study LVHJ, the majority of randomized patients (92%) completed the 12-week treatment comparison period. The most common reasons for discontinuation among all tadalafil-treated patients were entry criteria not met (2.5%), AEs (1.9%), and subject/physician decision (each 1.9%). In placebo-treated subjects, 2.4% discontinued due to subject decision, 1.8% were lost

to follow-up, 1.8% were discontinued due to protocol violation, and 0.6% discontinued to AE's.

7.2.4 Efficacy Results in Studies LVGH and LVHJ

7.2.4.1 Primary Efficacy Endpoint

For both studies, the *primary efficacy outcome* was the change in IPSS total from baseline to Visit 6 (Week 12) for subjects taking tadalafil 5 mg once-daily versus placebo. These results for Study LVHG are shown Table 1, and for LVHJ in Table 2.

For Study LVHG, 14 ITT subjects (7 in placebo and 7 in tadalafil 5 mg) were excluded from the efficacy analysis for various reasons: one for participating at two sites (using tadalafil 20 mg at site 118 and placebo at site 119), one for a discrepancy IPSS between his case report form and the source file (placebo), and 12 subjects who did not have post-baseline measurement (5 in the placebo group and 7 in the tadalafil 5 mg group).

Table 1. Mean Change from Baseline to Week 12 for Total IPSS in Study LVHG

Endpoint	Placebo N=204	Tadalafil 5 mg N=205	Difference (95% C.I.)	P-value
Total IPSS				
Baseline (SD)	17.1 (6.4)	17.3 (6.0)		
Change from baseline [a]	-2.2	-4.8	-2.6 (-3.7, -1.5)	<.001

[a]: Least square mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IPSS baseline value as covariate

Source: Final Biometrics Review dated September 15, 2011, page 13.

For Study LVHJ, only 1 subject (in tadalafil 5 mg) was excluded from the efficacy analysis.

Table 2. Mean Change from Baseline to Week 12 for Total IPSS in Study LVHJ

Endpoint	Placebo N=164	Tadalafil 5 mg N=160	Difference (95% C.I.)	P-value
Total IPSS				
Baseline (SD)	16.6 (6.0)	17.1 (6.1)		
Change from baseline [a]	-3.6	-5.6	-1.9 (-3.2, -0.6)	0.004

[a]: Least square mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IPSS baseline value as covariate

Source: Final Biometrics Review dated September 15, 2011, page 15.

7.2.4.2 Secondary Efficacy Endpoints

For Study LVHG, the secondary efficacy endpoints included changes from baseline in the total IPSS for each of the other active treatment groups (2.5 mg, 10 mg and 20 mg). For both studies, secondary endpoints included: 1) changes from baseline in the individual domains of the total IPPS (irritative and obstructive), 2) changes from baseline in the IPSS nocturia question, 3) changes from baseline in the IPSS QOL question, 4) changes from baseline in the

BII, and 5) changes from baseline in the IIEF EF domain score. For Study LVHJ, the "key" secondary endpoints were analyzed in a pre-defined hierarchical order.

For Study LVHG, a dose response was observed in the reduction in the total IPSS from baseline to week 12: -2.2 for placebo, -3.8 for tadalafil 2.5 mg, -4.8 for tadalafil 5 mg, -5.1 for tadalafil 10 mg and -5.2 for tadalafil 20 mg. Secondary efficacy outcome results for Study LVHG are shown in Table 3.

Table 3: Secondary Efficacy Outcomes - Study LVHG

	Placebo N=210	Tadalafil 2.5mg N=208	Tadalafil 5mg N=212	Tadalafil 10mg N=216	Tadalafil 20mg N=208
Outcome	n (LS Mean Δ BL)	n (LS Mean Δ BL) p value	n (LS Mean Δ BL) p value	n (LS Mean Δ BL) p value	n (LS Mean Δ BL) pval
Total IPSS	205 (-2.2)	201 (-3.8) .005	205 (-4.8) <.001	207 (-5.1) <.001	199 (-5.2) <.001
BII	205 (-0.8)	201 (-0.9) .583	204 (-1.4) .013	209 (-1.4) .016	199 (-1.5) .007
IPSS Irritative	205 (-1.0)	201 (-1.6) .025	205 (-1.9) <.001	208 (-1.9) <.001	199 (-2.0) <.001
IPSS Obstructive	205 (-1.3)	202 (-2.3) .008	205 (-3.0) <.001	207 (-3.2) <.001	199 (-3.2) <.001
IPSS Nocturia	205 (-0.3)	201 (-0.4) .503	205 (-0.4) .206	208 (-0.4) .452	199 (-0.6) .012
IPSS QoL	205 (-0.5)	202 (-0.8) .029	205 (-0.9) .002	206 (-0.9) <.001	199 (-0.9) <.001
IIEF EF Domain	113 (2.0)	109 (5.4) <.001	113 (6.8) <.001	113 (7.9) <.001	109 (8.2) <.001

Source: Table 2.7.3.3, Summary of Clinical Efficacy, page 38

Results for the top three "key" secondary efficacy outcomes for Study LVHJ are shown in Tables 4, 5, and 6.

For the IIEF-EF domain, the LS mean changes from baseline to endpoint were 6.7 for the tadalafil 5 mg group and 2.0 for the placebo group. The LS mean difference of these changes (4.7) was statistically significant for the tadalafil treatment group compared to placebo ($p<.001$) (95% CI [2.5, 6.9]).

Table 4: IIEF EF Domain Change From Baseline to Endpoint in Sexually Active Subjects with ED in Study LVHJ

Treatment	Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)	Baseline	84	16.8	8.7	
	Endpoint	84	18.1	9.1	
	Change	84	1.3	8.4	2.0
Tadalafil 5 mg (N=161)	Baseline	88	14.3	8.4	
	Endpoint	88	21.8	7.9	
	Change	88	7.5	5.5	6.7

Source: Table LVHJ 11.14, H6D-MC-LVHJ Amended Study Report, page 105.

The LS mean changes from baseline to Week 4 in total IPSS in the primary analysis population for the total IPSS score after 4 weeks were -5.3 for the tadalafil 5 mg group and -3.5 for the placebo group. The LS mean difference of these changes (-1.8) was statistically significant for the tadalafil treatment group compared to placebo (p=.003) (95% CI [-3.0, -0.6]).

Table 5: Total IPSS Change from Baseline to Week 4 in Study LVHJ

Treatment	Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)	Baseline	162	16.6	6.0	
	Endpoint	162	13.2	6.9	
	Change	162	-3.4	5.5	-3.5
Tadalafil 5 mg (N=161)	Baseline	158	17.2	5.9	
	Endpoint	158	11.7	6.3	
	Change	158	-5.5	6.3	-5.3

Source: Table LVHJ 11.15, H6D-MC-LVHJ Amended Study Report, page 106.

For the BPH Impact Index, the LS mean changes from baseline to endpoint were -1.8 for the tadalafil 5 mg group and -1.3 for the placebo group. The LS mean difference of these changes (-0.6) was not statistically significant for the tadalafil group compared to placebo (p=.057) (95% CI [-1.2, 0.0]).

Table 6: BPH Impact Index (BII) Change from Baseline to Endpoint in Study LVHJ

Treatment	Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)	Baseline	163	4.8	3.2	
	Endpoint	163	3.7	3.1	
	Change	163	-1.1	3.1	-1.3
Tadalafil 5 mg (N=161)	Baseline	160	5.1	3.1	
	Endpoint	160	3.2	3.0	
	Endpoint	160	-1.9	3.2	-1.8

Source: Table LVHJ 11.16, H6D-MC-LVHJ Amended Study Report, page 107.

Finally, the modified IPSS mean change from Baseline to Week 1 was -2.6 for placebo and -3.5 for tadalafil 5 mg once daily. This was not statistically significant (p-value = 0.146).

7.2.4.2.1 Effects on Maximum Urinary Flow Rate

With respect to maximum urinary flow rate, in Study LVHG, there were small increases in mean changes from baseline for placebo (1.2 mL/sec), tadalafil 2.5 mg (1.5 mL/sec), 5 mg (1.6 mL/sec), 10 mg (1.7 mL/sec), and 20 mg (2.2 mL/sec), but the differences between groups were not statistically significant.

For Study LVHJ, with respect to maximum urinary flow rate, there were again small increases in mean changes from baseline for placebo (1.1 mL/sec) and for tadalafil 5 mg (1.6 mL/sec), but the difference between groups was not statistically significant (p=0.3).

7.2.4.2.2 Effects on Erectile Function

The previous sections have shown the results from the EF domain (as a secondary endpoint), but these are shown again for clarity.

In Study LVHG, a dose response for this endpoint was observed, showing the estimated least squares means of +2.0 in placebo, +5.4 in tadalafil 2.5 mg, + 6.8 in tadalafil 5 mg, + 7.9 in tadalafil 10 mg, and + 8.2 in tadalafil 20 mg. Table 7 shows the Biometrics analysis for this data. The least squares means of changes from baseline at Week 12 were +2.2 for placebo and +6.9 for tadalafil 5 mg as shown in Table 4. The treatment difference at Week 12 was +4.7 (<0.001) with the 95% CI of +2.9 to +6.5.

Table 7. Mean Change from Baseline to Week 12 for the EF domain of the IIEF in Subjects with ED in Study LVHG

	Placebo N=113	Tadalafil 5 mg N=113	Difference (95% C.I.)	P-value
IIEF-EF domain score				
Baseline Mean (SD)	17.3 (8.0)	15.3 (8.1)		
Change from baseline [a]	2.2	6.9	4.7 (2.9, 6.5)	<.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and IIEF-EF baseline value as covariate

Source: Final Biometrics Review dated September 15, 2011, page 13.

In Study LVHJ, there was a statistically significant difference between treatment groups for the mean change from baseline in the IIEF EF domain score, as shown in the Biometrics analysis in Table 8.

Table 8. Mean Change from Baseline to Week 12 for the EF domain of the IIEF in Subjects with ED in Study LVHJ

	Placebo N=84	Tadalafil 5 mg N=88	Difference (95% C.I.)	P-value
IIEF-EF domain score				
Baseline Mean (SD)	16.8 (8.7)	14.3 (8.4)		
Change from baseline [a]	2.0	6.7	4.7 (2.5, 6.9)	<.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and IIEF-EF baseline value as covariate

Source: Final Biometrics Review dated September 15, 2011, page 15.

7.3 Study LVHR (in support of the BPH/ED indication)

Study LVHR was conducted in support of the BPH/ED indication, intended specifically to support safety and efficacy of Cialis for the treatment of BPH and ED in men with both conditions.

Study ***LVHR*** was a multicenter, Phase 3, randomized, double-blind, placebo-controlled, parallel-design, study to evaluate the efficacy and safety of tadalafil 2.5 mg, and tadalafil 5 mg once daily for 12 weeks versus placebo in men with BPH-LUTS and ED. The study enrolled 606 subjects ≥45 years old who presented with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening and ED for ≥ 3 months . As in Studies LVHG and LVHJ, lower urinary tract symptoms were assessed by the IPSS, and erectile function was assessed by the EF domain of the validated IIEF questionnaire.

As in Studies LVHG and LVHJ, study LVHR consisted of 3 periods:

- a screening/wash-out period of 1-4 weeks,
- a 4-week, single-bind, placebo run-in period to assess treatment compliance and to establish baseline measures (baseline = Visit 3), and
- a 12-week treatment period, where eligible subjects were randomly assigned to treatment (tadalafil 2.5 and 5 mg, or placebo) in a 1:1:1 ratio. Randomization was stratified by baseline severity (total IPSS <20 or ≥20), geographic region, and history of ED. Subjects were to return on Visit 4 (Week 4), Visit 5 (Week 8), and Visit 6 (Week 12) to assess treatment compliance and to measures of the study endpoints. Visit 6 (Week 12) was the end-of-study visit.

7.2.1 Entry Criteria in Study LVHR

Key inclusion and exclusion criteria in Study LVHR were the same as for Studies LVHG and LVHJ except for the requirement in LVHR for a history of ED for at least 3 months.

7.2.2 Efficacy Assessments and Endpoints in Study LVHR

For Study LVHR, there were *co-primary endpoints:* the change in total IPSS from baseline to Visit 6 (Week 12) and the change in EF domain score from baseline to Week 12. Both co-primary endpoints would be tested for both active treatment groups against placebo, each dose group at $p < .027$. Both endpoints would need to be achieved to claim success in the dose group.

For Study LVHR, the *secondary endpoints* were pre-defined in a hierarchical order:

- Evaluating both dose groups against placebo for the Sexual Encounter Profile Question 3 (SEP3). SEP3 is a question from the per-event sexual encounter diary which asks whether the subject's erection lasted long enough for successful intercourse (yes/no).
- Evaluating both dose groups against placebo for the BPH Impact Index (BII).

Additional secondary endpoints included:

- Total IPSS at Visit 4 (Week 2)
- IPSS storage (irritative) and voiding (obstructive) subscores
- IPSS nocturia question
- IPSS QoL question (LUTS-General Assessment Questions [GAQ])
- Other domains of the IIEF (e.g., Intercourse satisfaction, overall satisfaction)
- SEP Question 2
- Several other exploratory outcome measures

Uroflowmetry, included maximum urinary flow rate, was assessed at baseline and at endpoint in Study LVHR as a safety endpoint.

7.2.3 Populations and Patient Disposition in Studies LVHR

7.2.3.1 Study Population

In Study LVHR, the 606 randomized subjects had similar demographics between the treatment groups. The mean age of subjects was approximately 63 years (range: 45 to 83 years) and were predominantly Caucasian (93.2%). 9.2% were 75 years of age or older. 39% were classified as having severe BPH symptoms by their total IPSS, and 33% had used previous therapy for BPH. 92% reported a history of ED for > 1 year duration and 28.5% reported having used previous therapy for ED.

7.2.3.2 Subjects Disposition

In Study LVHR, the majority of randomized patients (86%) completed the 12-week treatment comparison period. The most common reasons for discontinuation among tadalafil 2.5 mg and tadalafil 5 mg treated patients were entry criteria not met (2. 5 mg = 2.0%, 5 mg = 2.9%), adverse event (2. 5 mg = 1.5%, 5 mg = 2.9%), lack of efficacy (2. 5 mg = 0.5%, 5 mg = 1.4%), and lost to follow-up (2. 5 mg = 0.5%, 5 mg = 1.4%). In placebo-treated subjects, 4.0% discontinued due to lack of efficacy, 1.5% due to AEs, and 1.5% due to entry criteria not met.

7.2.4 Efficacy Results in Study LVHR

7.2.4.1 Primary Efficacy Endpoints

In Study LVHR, tadalafil 5 mg statistically significantly improved the total IPSS and the IIEF-EF domain score. The co-primary objectives were met after 12 weeks of tadalafil 5 mg once-

daily dosing. However, treatment with tadalafil 2.5 mg daily was not as favorable. The co-primary objectives were not met after 12-weeks of tadalafil 2.5 mg once-daily dosing due to a failure to achieve a statistically significant improvement in the total IPSS.

For Study LVHR, 18 ITT subjects were excluded from the efficacy analysis for IPSS (7 for placebo, 9 for tadalafil 2.5 mg, and 2 for tadalafil 5 mg); while 30 ITT subjects were excluded from the analysis for IIEF (12 for placebo, 12 for tadalafil 2.5 mg, and 6 for tadalafil 5 mg). Subjects with missing baseline values or no post-baseline values were excluded. Several subjects with discrepancies between their source document and electronic CRF were excluded for IPSS (n=3) and IIEF (n=8).

The least squares mean changes from baseline to Week 12 for the total IPSS were -3.8 and -6.1 for placebo and tadalafil 5 mg, respectively. The treatment difference for the total IPSS was -2.3 with the 95% CI of -3.5 to -1.2. The least squares mean changes from baseline for the IIEF-EF domain score were 1.9 and 6.5 for placebo and tadalafil 5 mg, respectively. The treatment difference for the IIEF-EF domain score was 4.6 with the 95% CI of 3.3 to 5.9.

Table 9. Mean Change from Baseline for Co-primary Efficacy Endpoints for Tadalafil 5 mg at Week 12 in Study LVHR

	Placebo	5 mg Tadalafil	Difference (95% C.I.)	P-value
Total IPSS				
N	193	206		
Baseline Mean (SD)	18.2 (5.3)	18.5 (5.8)		
Change from baseline [a]	-3.8	-6.1	-2.3 (-3.5, -1.2)	<.001
IIEF-EF Domain Score				
N	188	202		
Baseline Mean (SD)	15.6 (6.9)	16.5 (7.2)		
Change from baseline [b]	1.9	6.5	4.6 (3.3, 5.9)	<.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and total IPSS baseline value as covariate.
[b]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IIEF-EF baseline value as covariate.

Source: Final Biometrics Review dated September 15, 2011, page 21.

Tadalafil 2.5 mg did not statistically significantly improve the total IPSS for the patients with both BPH and ED. The p-value for the treatment difference in the total IPSS for tadalafil 2.5 mg was 0.211.

Table 10. Mean Change from Baseline for Primary Efficacy Endpoints for Tadalafil 2.5 mg at Week 12 in Study LVHR

	Placebo	2.5 mg Tadalafil	Difference (95% C.I.)	P-value
Total IPSS				
N	193	189		
Baseline Mean (SD)	18.2 (5.3)	18.2 (5.6)		
Change from baseline [a]	-3.8	-4.5	-0.7 (-1.9, 0.4)	0.211
IIEF-EF Domain Score				
N	188	186		
Baseline Mean (SD)	15.6 (6.9)	16.6 (7.0)		
Change from baseline [b]	1.9	5.3	3.4 (2.1, 4.8)	<.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and total IPSS baseline value as covariate.
[b]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IIEF-EF baseline value as covariate.

Source: Final Biometrics Review dated September 15, 2011, page 22.

The first key secondary endpoint was the change-from-baseline in the percentage of yes/no responses to the SEP3 question. This was analyzed for tadalafil 5 mg only, as tadalafil 2.5 mg failed to meet the IPSS primary endpoint. According to the gatekeeping multiple testing procedures, the test on the SEP3 was performed sequentially at a two-sided alpha of 0.0228. The least squares means were 15.3% and 33.9% for placebo and tadalafil 5 mg, respectively. The treatment difference in the success rate of the SEP3 between tadalafil 5 mg and placebo was 18.7% with the 95% CI of 11.9% to 25.4%.

Table 11. Mean Change from Baseline for Secondary Efficacy Endpoint at Week 12 in Study LVHR

	Placebo N=187	5 mg Tadalafil N=199	Difference (95% C.I.)	P-value
SEP3 (percentage of yes)				
Baseline Mean (SD)	36.3 (38.7)	42.7 (40.0)		
Change from baseline [a]	15.3	33.9	18.7 (11.9, 25.4)	<.001

[a]: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and SEP3 baseline value as covariate.

Source: Final Biometrics Review dated September 15, 2011, page 22.

The Biometrics team calculated the SEP3 results differently than the Sponsor. The post-treatment SEP3 success rate was calculated by the Biometrics team based on the last visit. The Sponsor calculated this rate cumulatively based on the period from the first post-treatment visit to the last visit. In Sponsor's report, the LS mean changes from baseline were 12.0 and 31.7 for placebo and tadalafil 5 mg, respectively. The treatment different was 19.7% with the 95% CI of 14.2 to 25.2. These results are shown in the label. The SEP3 results by either analysis method are comparable.

The results of the BPH Impact Index (BII) are not shown in this section, as the instrument was not shown to have content validity, [redacted] (b) (4)

7.3 Statistical Review

In their final review dated September 15, 2011, the Statistical reviewers Xin Fang and Mahboob Sobhan, stated:

> *"The data submitted in this application support the efficacy of tadalafil 5 mg once daily for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) in men. Tadalafil 5 mg once daily demonstrated statistically significant improvements in the International Prostate Symptom Score (IPSS) and erectile function (EF) domain score of the International Index of Erectile Function (IIEF), two primary endpoints evaluated to support the above indications. Tadalafil 2.5 mg did not demonstrate statistically significant improvement in the above symptoms.*
>
> *From a statistical perspective, this application provided adequate data to support the efficacy of tadalafil 5 mg once daily in the treatment of signs and symptoms of both BPH and ED in men.*
>
> *No major statistical issues were noted with regards to statistical analyses of the efficacy endpoints, except the secondary endpoint BII, which was not considered a valid patient reported outcome (PRO) based instrument. This review excluded pertinent efficacy data from 12 subjects in two of the three studies due to inconsistent IPSS (4 subjects) and IIEF-EF domain scores (8 subjects) between the case report forms (CRFs) and source files. The results of FDA analysis remained consistently similar to the sponsor's results. Handling of missing data in all three studies was addressed appropriately. Adjustment for multiplicity due to multiple dose comparisons was also handled as planned in the protocol".*

The final Biometrics conclusion was:

> *"From a statistical perspective, data from all three studies: LVHG, LVHJ and LVHR supports the efficacy of tadalafil 5 mg once daily in the treatment of men with BPH or men with both BPH and ED, compared with placebo."*

7.4 Overall Assessment of Efficacy

In the medical officer's final review dated September 14, 2011, Dr. Wiederhorn concluded:

> "*These NDA submissions have provided substantial evidence from adequate and well controlled ("pivotal") studies that tadalafil 5 mg once daily will have the effect claimed in labeling. This claim is that, in men with BPH and BPH/ED, tadalafil 5 mg*

once a day is efficacious in treating the signs and symptoms of BPH. In men with BPH/ED, tadalafil 5 mg once a day is also efficacious in treating their ED."

I concur with the medical officer's conclusion regarding overall efficacy.

The three, Phase 3 studies were all of similar design, and all used appropriate eligibility criteria, appropriate study endpoints, and appropriate analysis plans for BPH studies. Details of the design and procedures have been delineated above. Studies LVHG and LVHJ provide support for the BPH indication, and Study LVHR provides support for the BPH/ED indication. The doses studied ranged from 2.5 mg to 20 mg once daily. In summary, the 5 mg once daily dose showed statistically and clinically significant improvements for symptomatic relief of BPH compared to placebo. While there was an improvement in symptomatic relief between 5 mg and 10 mg, it was not enough to justify pursuit of the 10 mg dose, nor the 20 mg dose. Results did not confirm a treatment effect at a dose of 2.5 mg daily. Therefore, the dose for BPH will be 5 mg once daily; and 2.5 mg once daily in patients with moderate or severe renal insufficiency. The only remaining efficacy issues of note are 1) the lack of a statistically significant effect of Cialis on maximum urinary flow rate, and 2) the lack of content validity of the BPH Impact Index (BII). Although the data did not demonstrate a statistically significant effect of Cialis versus placebo on maximum urinary flow rate, there was no demonstrated problem with urodynamic function of the bladder and no increase in bladder pressures or residuals urines. This was demonstrated in a stand-alone, urodynamic safety study LVHK, and throughout the Phase 3 program. The evidence for content validity of the BII was analyzed in great detail by the Clinical review team and by SEALD (b) (4)

8. Safety

The medical officer's review of September 14, 2011 contains a thorough and comprehensive description and analysis of all safety data submitted for these supplements. The main safety components of the submission were:

- A Phase 2, pilot study in BPH patients (Study LVGC)
- Three, randomized, Phase 3, 12-week, placebo-controlled studies LVHG, LVHJ and LVHR.
- A long-term (1 year), open-label extension of Study LVHG
- A Phase 1, pK and tolerability study comparing elderly and young subjects (Study LVHN)
- Two special safety studies, Studies LVHK and LVHS:
    - A randomized, placebo-controlled, 12-week study to assess the effects of tadalafil on urodynamics in men with BPH (Study LVHK).
    - A randomized, placebo-controlled, 12-week study to assess the safety of tadalafil in men with BPH when used in combination with an alpha-blocker (Study LVHS)
- Three, non-IND, (one Phase 2 and two Phase 3) studies in Asian men with BPH.

The medical officer also considered 1) the extensive safety database that exists for the tadalafil once daily regimen for the treatment of ED, 2) the extensive safety database that exists for the p.r.n. (as needed) use of tadalafil for ED, and 3) the vast postmarketing safety data for the use of tadalafil for ED.

This section is intended to summarize the safety results from the Phase 3 BPH efficacy and safety studies, the Phase 3, open-label, BPH extension study, the two special safety studies, and the postmarketing information. This section also discusses safety issues of special interest.

8.1 Overall Exposure

Within the three pivotal Phase 3 studies (Studies LVHG, LVHJ, and LVHR), the 52 week open-label safety extension of LVHG, and the special safety studies LVHK and LVHS:

- 1450 BPH subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 3 months, with a total exposure of 624.5 subject-years.
- 363 BPH were subjects exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months.
- 296 BPH subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year.

An additional 405 subjects were exposed to tadalafil 2.5 mg, with a total exposure of 90.9 subject-years.

8.2 Demographics

The subject population in the "*pivotal BPH analysis set*" (including Studies LVHG and LVHR only) was representative of the general BPH population with regard to demographics and co-morbidities. The mean age in the tadalafil 5-mg and placebo groups was 63.3 years and 63.0 years, respectively; approximately 40% of subjects were older than 65 years of age, while approximately 13% were 75 years of age or older. The predominant race was White in both treatment groups. Mean body mass index (BMI), mean prostate-specific antigen (PSA), mean PVR volume, and Qmax categories (<10 mL/sec, 10-15 mL/sec, or >15 mL/sec) were generally similar between the tadalafil 5-mg and placebo groups. Baseline medical history relevant to cardiovascular disease risk was also well balanced between treatment groups.

In the "*additional BPH analysis set*" (including Studies LVHG, LVHJ, and LVHR), demographics and other baseline characteristics were consistent with those of the pivotal BPH analysis set.

The subject population in the "*pivotal BPH/ED analysis set*" (consisting of Study LVHR alone) was representative of the general BPH/ED population with regard to demographics and co-morbidities. The mean age was 62.6 years; 37.3% of subjects were older than 65 years of age, and 9.2% of subjects were 75 years of age or older. The predominant race was White. Mean BMI, mean PSA, mean PVR volume, and Qmax categories were generally similar across treatment groups. Baseline medical history relevant to cardiovascular disease risk was well balanced across treatment groups.

8.3 Discontinuations due to Adverse Events

In the "additional BPH analysis set" (all subjects in the Phase 3 studies LVHG, LVHJ, and LVHR), the percentage of subjects discontinuing due to an AE was significantly greater in the tadalafil 5-mg group compared to the placebo group (3.6% versus 1.6%, p=.028). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5-mg group and was the only event that was reported by a statistically significantly greater percentage of subjects in the tadalafil group compared to placebo (0.9% versus 0.0%, p=.025). All AEs leading to discontinuation were reported with a frequency <1%, including headache. The only AEs leading to study discontinuation reported by one than 1 subject were headache, abdominal pain upper, and myalgia. Acute MI was reported as an SAE that resulted in death in 1 subject. A narrative for this subject is provided in the next section of this memo.

Table 12: Adverse Events Reported as Reason for Study Discontinuation in the Tadalafil 5 mg and Placebo Groups in Studies LVHG, LVHJ, and LVHR

Preferred Term	Placebo (N=576)	Tadalafil (N=581)
	n (%)	
Subjects Discontinued due to AE	9 (1.6)	21 (3.6)
Headache	0 (0.0)	5 (0.9)
Abdominal Pain Upper	2 (0.3)	3 (0.5)
Myalgia	0 (0.0)	2 (0.3)
Back Pain	1 (0.2)	1 (0.2)
Dyspepsia	0 (0.0)	1 (0.2)
Muscle Spasms	0 (0.0)	1 (0.2)
Pain	0 (0.0)	1 (0.2)
Pain in Extremity	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	1 (0.2)
Retinal Tear	0 (0.0)	1 (0.2)
Rotator Cuff Syndrome	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)
Abdominal Discomfort	1 (0.2)	0 (0.0)
Blood Creatine Phosphokinase Increased	1 (0.2)	0 (0.0)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Dizziness	1 (0.2)	0 (0.0)
Eye Pain	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)

Source: Table ISS.8, Integrated Summary of Safety, page 36. (The episode of syncope occurred in tadalafil 2.5 mg subject LVHG 123-3320.)

Study LVHG included three additional dose groups: tadalafil 2.5 mg, tadalafil 10 mg and tadalafil 20 mg. The SAEs reported in the 2.5 mg , 10 mg and 20 mg dose groups in LVHG were:

2.5 mg (n=4; myalgia, myocardial infarction [while digging tree roots], syncope, ureteric rupture)

10 mg (n= 11; back pain [3], GE reflux [2], myalgia, insomnia, lethargy, muscle spasms, myocardial infarction, peripheral edema, PSA increase [1 each]), and *20 mg* (n=14; back pain [5], myalgia [4], headache [2], dyspepsia, dizziness, esophagitis [1 each]).

In the BPH/ED Study LVHR, a total of 12 subjects discontinued due to AEs (placebo = 3 [1.5%], tadalafil 2.5 mg = 3 [1.5%], and tadalafil 5 mg = 6 [2.9%]). The AEs leading to study discontinuation in the 2.5 mg group were dizziness, myocardial infarction, and nocturia.

In the open-label safety extension of Study LVHG, only 6 AE terms leading to study discontinuation were reported by more than 1 patient: dyspepsia (n=3), stomach discomfort (n=3), bladder neoplasm (n=2), hepatic function abnormal (n=2), muscle tightness (n=2), and visual disturbance (n=2). The remaining AE terms included a variety of co-morbid events commonly reported in patients with BPH (e.g., arrthymia, carpal tunnel syndrome, coronary artery disease, esophagitis, prostate cancer, etc). The reader is referred to the medical officer's review Table 103 for the complete list of SAE terms. In addition, the medical officer's review contains a narrative for each AE. These are provided within the medical officer's review of the individual study in which the AE occurred.

8.4 Deaths

A total of three deaths were reported in studies conducted in support of the new BPH indications:

One was a placebo patient in the special safety study LVHK.

One was an 81 year old male in the tadalafil 5 mg group in BPH Study LVHJ (Subject LVHJ-303-3316). The patient had pre-existing conditions of hyperlipidemia and hypertension (BP 140/90 mm Hg while on lisinopril and study drug). The patient was characterized as having moderate erectile dysfunction. Approximately 2.5 months after receiving the first dose of study drug (tadalafil 5 mg), the subject was hospitalized with chest pain and diagnosed with an acute posterior myocardial infarction (MI) and third degree atrioventricular block; study drug was discontinued. Cardiac catheterization was performed and demonstrated 75%, 90%, and 90% occlusion of the LAD, circumflex and right coronary arteries, respectively. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequent intra-aortic balloon pump. The subject's condition worsened and he died 3 days later.

One was a 67-year male in BPH/ED Study LVHR. The patient's medical history included back pain, sinusitis, and orthopedic surgery on his ankle. On 15-MAY-2009, the patient began study drug. The patient was last seen at visit 6 on 10-JUL-2009 and was on study drug at that time. The patient's last dose of study drug prior to the event was 13-JUL-2009. On (b) (6), the investigator received a telephone call from the patient's wife who informed him that the patient had died. She said she had found him dead in his house on (b) (6) and he had probably been dead for two to three days. There is no witness report to provide medical details at and around the time of

death. Immediate cause of death per medical certification of death document was myocardial infarction, and date of death was documented as (b) (6). It is also noted by the patient's primary care physician that the patient had a cardiac arrhythmia. What role cardiac arrhythmia may have played in the patient's death is uncertain. Other significant conditions that may have contributed to the death included impaired glucose tolerance, sleep apnea, mild mitral valve prolapse, and episodic atrial fibrillation. An autopsy was not performed. The investigator stated that he did not believe that the myocardial infarction was related to drug or protocol.

8.5 Serious Adverse Events (SAEs)

In "the additional BPH analysis set" (Phase 3 Studies LVHG, LVHJ and LVHR), a total of 9 subjects in the placebo and tadalafil 5 mg groups reported a total of 14 SAEs (5 placebo and 4 tadalafil 5 mg).

Table 13: Serious Adverse Events in the Additional BPH Analysis Set (Studies LVHG, LVHJ and LVHR)

	Placebo (N=576)	Tadalafil 5 mg (N=581)
Preferred Term	n (%)	
Subjects with >= 1 SAE	5 (0.9)	4 (0.7)
Acute Myocardial Infarction	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)
Endocarditis	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	1 (0.2)
Cartilage Injury	1 (0.2)	0 (0.0)
Cerebrovascular Accident	1 (0.2)	0 (0.0)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Indwelling Catheter Management	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)
Renal Colic	1 (0.2)	0 (0.0)
Rheumatoid Arthritis	1 (0.2)	0 (0.0)
Ureteral Catheterization	1 (0.2)	0 (0.0)
Urinary Retention	1 (0.2)	0 (0.0)

Source: Table ISS.7, Integrated Summary of Safety, page 34.

Study LVHG included three additional dose groups: tadalafil 2.5 mg, tadalafil 10 mg and tadalafil 20 mg. The SAEs reported in the 2.5 mg, 10 mg and 20 mg dose groups were:

2.5 mg (n=3; myocardial infarction [while digging out tree roots], atrial tachycardia, obstructed kidney stone),
10 mg (n= 2; knee replacement, unstable angina), and
20 mg (n=5; total knee replacement, back pain, heart failure/suspected pulmonary embolism, headache, coronary artery disease).

A total of 4 SAEs were reported in the BPH/ED Study LVHR (placebo n=1, tadalafil 2.5 mg n=2, and tadalafil 5 mg n=1). The two SAES reported in the tadalafil 2.5 mg group in Study LVHR were herniated lumbar disc and acute prostatitis.

In the open-label safety extension of Study LVHG, no SAE term was reported by more than 1 patient. The AE terms included a variety of co-morbid events commonly reported in patients with BPH (e.g., arthritis, knee replacement, non-cardiac chest pain, bladder neoplasm, acute coronary syndrome, etc). The reader is referred to the medical officer's review Table 98 for the complete list of SAE terms. In addition, the medical officer's review contains a narrative for each SAE. These are provided within the medical officer's review of the individual study in which the SAE occurred.

8.5 Common Adverse Events

The most common treatment-emergent adverse events reported in "the additional BPH analysis set" consisting of all subjects in Studies LVHG, LVHJ and LVHR, reported on an all-causality basis, and in greater than 1% of subjects in the tadalafil 5 mg group and greater than placebo were: headache, dyspepsia, back pain, nasopharyngitis, diarrhea, pain in extremity, myalgia and dizziness.

Table 14: Treatment-Emergent Adverse Events Reported by ≥1% of Patients Treated with CIALIS for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Studies LVHG, LVHJ and LVHR

Adverse Event	Placebo (N=576)	Tadalafil 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Hypertension	0.9%	1.9%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Additional, less frequently reported treatment-emergent adverse events (<1%) reported in the "additional BPH analysis set" (LVHG, LVHJ and LVHR): gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Of note, the medical officer's analysis of adverse events coded to "*hypertension*" revealed that these cases were actually not new-onset hypertension, and in fact, the majority showed no increase at all in blood pressure from elevated baseline blood pressures. Therefore, the medical officer stated, and I agree, that hypertension was not a treatment-emergent adverse reaction to tadalafil in the controlled studies.

In Study LVHR, in patients with concomitant BPH and ED, the commonly reported adverse events were similar in type and frequency.

Table 15: Treatment-Emergent Adverse Events Occurring in >= 1% of Tadalafil-Treated Subjects and >Placebo in Study LVHR.

	Placebo (N=220)	Tadalafil 2.5 mg (N=198)	Tadalafil 5 mg (208)
Preferred Term	n (%)		
Subjects with >= 1 TEAE	39 (19.5)	50 (25.3)	57 (27.4)
Headache	6 (3.0)	5 (2.5)	12 (5.8)
Back Pain	5 (1.5)	1 (0.5)	6 (2.9)
Nasopharyngitis	4 (2.0)	6 (3.0)	5 (2.4)
Dyspepsia	0 (0.0)	1 (1.0)	3 (1.4)
Upper Respiratory Tract Infection	0 (0.0)	0 (0.0)	3 (1.4)
Muscle Spasms	0 (0.0)	0 (0.0)	2 (1.0)
Oropharyngeal Pain	0 (0.0)	0 (0.0)	2 (1.0)
Pharyngitis	0 (0.0)	0 (0.0)	2 (1.0)
Vision Blurred	0 (0.0)	0 (0.0)	2 (1.0)
Blood creatine phosphokinase	0 (0.0)	2 (1.0)	0 (0.0)
Tooth infection	0 (0.0)	2 (1.0)	0 (0.0)

Source: Table LVHR 12.3, LVHR Clinical Study Report, page 131

In the open-label extension of Study LVHG, the type and frequency of reports was similar to the type and frequency of reports in the controlled studies LVHG, LVHJ and LVHR.

Table 16: Treatment-Emergent Adverse Events Occurring in >=2% of Tadalafil-Treated Subjects in Open-Label Extension of Study LVHG

Preferred Term	Previous Placebo (N=92)	Total (N=427)
	n (%)	n (%)
Patients with >= 1 TEAE	50 (54.3)	256 (57.6)
Dyspepsia	4 (4.3)	17 (4.0)
Gastroesophageal Reflux Disease	2 (2.2)	17 (4.0)
Back Pain	4 (4.3)	16 (3.7)
Headache	3 (3.3)	13 (3.0)
Sinusitis	0 (0.0)	12 (2.8)
Hypertension	0 (0.0)	11 (2.6)
Cough	1 (1.1)	9 (2.1)

Source: Table LVHG, H6D-MC-LVHG Abbreviated Study Report, page 67.

Of note, the medical officer's analysis of "hypertension" adverse events in the open-label study again revealed that these cases were actually not new-onset hypertension, and in fact, the majority showed no increase at all in blood pressure from elevated baseline blood pressures. Therefore, the medical officer stated that "*hypertension based on line analysis is not a treatment emergent event*."

8.6 Safety Issues of Special Interest

8.6.1 Targeted Clinical Adverse Events

Cialis is known to be associated with several types of adverse reactions, including dyspepsia, back pain/myalgias, headache, nasopharyngitis, and dizziness/modest lowering of the blood pressure. However, there are other adverse events that have been reported in the postmarketing period, where a causal relationship to drug remains unclear, and these include hearing and visual disturbances, seizures, and cardiovascular events. The Sponsor was asked to target both the recognized causal adverse reactions as well as several important, but yet to be determined to be causal, adverse events during the conduct of the BPH program. This section summarizes very briefly the results of the targeted adverse events in the BPH program, which included: bleeding events, cardiovascular events, ear disorders (including sudden hearing loss), eye disorders (including nonarteritic anterior ischemic optic neuropathy [NAION]), adverse events possibly related to hypotension (including headache, asthenia, and fatigue), myalgias/ back pain, seizures, and transient global amnesia. The medical officer conducted a comprehensive review for each of these items and the outcome is shown in great detail in the medical officer's review pages 227-242.

Regarding *Bleeding disorder AEs*: In the additional BPH analysis set (Studies LVHG. LVHJ and LVHR), 6 subjects (1.0%) reported a total of 6 bleeding TEAEs compared to none for placebo. These AEs were epistaxis 3, pancreatitis hemorrhagic 1, hemorrhoidal hemorrhage 1, and rectal hemorrhage 1. None of these events were SAEs or led to study discontinuation. After a case-by-case review, it was not possible to exclude the role of tadalafil in 4 of these events (epistaxis x 2, hemmorhoidal hemorrhage, and rectal hemorrhage). Epistaxis is already listed in the label as an AE reported infrequently in clinical trials where a causal relationship is uncertain. The terms "hemorrhoidal and rectal hemorrhage" will be added to that section as well.

Regarding *Cardiovascular disorder AEs*: In the additional BPH analysis set of all subjects (Studies LVHG, LVHJ, and LVHR), there were no significant differences between treatment groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs. Twenty-nine subjects (2.5%) reported a total of 31 cardiovascular disorder TEAEs. Of note, there were 16 reports of "hypertension" (11 [1.9%] for tadalafil versus 5 [0.9%] for placebo), but a case-by-case reviews reveals few, if any, cases of true new-onset hypertension. In fact, the majority of these reports are baseline high blood pressure without further increase.

Regarding *Ear disorder AEs*: In the additional BPH analysis set (Studies LVHG. LVHJ and LVHR), 5 subjects reported a total of 6 ear disorder TEAEs. No significant differences were observed across treatment groups.

Regarding *Eye disorder AEs*: In the additional BPH analysis set (Studies LVHG, LVHJ and LVHR), seven eye disorder TEAEs (in five patients) were reported, and no significant differences were observed between treatment groups. There were 3 reports (0.5%) of blurred vision in the treatment group versus 1 (0.2%) in the placebo group. It is not possible to

confirm a treatment effect in this situation. Nonetheless, "blurred vision" is currently listed in the label as an AE reported infrequently in clinical trials where a causal relationship is uncertain. This continues to be true for the BPH program.

Regarding *AEs possibly related to hypotension (headache, asthenia, lethargy)*: In the additional BPH analysis set (Studies LVHG. LVHJ and LVHR), no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension using both the expanded and focused list of preferred terms. The focused list included terms most likely to reflect hypotension (headache, dizziness, syncope, orthostatic hypotension), while the expanded list included terms less likely to reflect hypotension (asthenia, fatigue, etc). Fifty-two subjects (4.5%) reported a total of 54 TEAEs possibly related to hypotension using the expanded list of terms. Of note, the medical officer's analysis appears to show that headache is a tadalafil-related event independent of hypotension. Dizziness also appears to be independent of hypotension and was reported by 6 tadalafil patients (1.0%) versus 3 placebo patients (0.5%0. Dizziness will be added to the label in the table of adverse reactions observed in the BPH trials.

Regarding *myalgia/back pain AEs*: In the additional BPH analysis set (Studies LVHG, LVHJ and LVHR), the percentage of subjects reporting at least 1 myalgia/back pain TEAE was significantly greater in the tadalafil 5-mg group compared with the placebo group (5.9% versus 2.4%, p=.004). Forty-eight subjects (4.1%) reported a total of 54 myalgia/back pain TEAEs. Myalgias and back pain will appear in the label as adverse reactions observed in the BPH program.

Regarding *seizures*: No seizure AEs were reported in the BPH program.

Regarding *transient global amnesia AEs*: No transient global amnesia AEs were reported in the additional BPH analysis set (LVHG, LVHJ, and LVHR). However, in the open-label extension of Study LVHG, two subjects (0.5%) reported a total of 2 transient global amnesia AEs. One event was an SAE (transient global amnesia, Subject LVHG-204-1431). Neither of the transient global amnesia TEAEs led to study discontinuation. In Subject LVHG-204-143, the transient global amnesia occurred 4 days after the 12 month study period had ended and after weight lifting. In the second case, LVHG-110-2011 (a non-serious case), the event occurred after 3 months of drug exposure and the patient completed the LVHG study period. Within the clinical pharmacology studies, one placebo subject reported amnesia. The relationship between transient global amnesia and tadalafil in these few cases was unclear.

8.6.2 The Effect of Tadalafil on Urodynamics in Men with BPH (Study LVHK)

Based on the lack of a statistically significant effect of tadalafil versus placebo in maximum urinary flow rate, the Division asked the Sponsor to conduct a study to investigate the effects of tadalafil on urodynamics (lower urinary tract function) in men with BPH. The objective was to determine if tadalafil was actually worsening bladder emptying or creating a 'silent obstruction". The results of this investigation, Study LVHK, demonstrated that there is no detrimental effect of tadalafil on bladder emptying or intravesical pressure in men with BPH.

Study LVHK was a Phase 2, randomized, double-blind, placebo-controlled, parallel-design study to evaluate for potential adverse urodynamic effects of tadalafil 20 mg once daily for 12 weeks in men with BPH-LUTS with or without bladder outlet obstruction. The majority of subjects were categorized as having severe symptomatic BPH (IPSS Total Score ≥20) at baseline (64.0%) and more than half of subjects had symptomatic BPH for >3 years (54.5%).

The primary objective was to compare the effect of tadalafil 20 mg once daily for 12 weeks on detrusor pressure at peak urinary flow rate (pdetQmax) versus placebo Secondary objectives included an examination of the urodynamic effects of tadalafil 20 mg once daily for 12 weeks (compared with placebo) on pressure flow and free flow urodynamic parameters including peak urinary flow rate (Qmax), mean urinary flow rate (Qmean), voided volume (Vcomp), maximum detrusor pressure (maxpdet) during voiding, post-void residual (PVR) volume measurement by catheterization (PVRcath), total bladder capacity, bladder contractility index (BCI), bladder outlet obstruction index (BOOI), bladder voiding efficiency (BVE), presence of involuntary detrusor contractions during bladder filling, and bladder volume at first involuntary detrusor contraction.

Of the 200 randomized subjects, 101 were assigned to placebo and 99 to tadalafil 20 mg. 89 tadalafil and 92 placebo subjects completed the study.

The primary analysis showed neither statistically significant nor clinically adverse effects of tadalafil 20 mg on detrusor pressure at peak urinary flow rate (the mean difference of change from baseline between treatment groups was -4.95 cm H_2O; p=.068) in the primary analysis population. While this result represents a decrease in detrusor pressure in the actively treated tadalafil group versus the placebo group, it was not considered clinically adverse. Furthermore, the negative change was the result of a slight increase from baseline in intravesical pressure for the placebo treatment group with a slight decrease in intravesical pressure for the tadalafil treatment group. Upon review of the individual patient data by external consultants, 3 subjects (2 placebo, 1 tadalafil) were noted to have nonphysiologic changes from baseline to endpoint due to an involuntary detrusor contraction at the initiation of the voiding event. When data from these 3 subjects were removed from the analyses, the mean difference of the change from baseline in $P_{det}Q_{max}$ between active and placebo groups was smaller (-2.18 cm H_2O).

Table 17: Detrusor Pressure at Peak Urinary Flow Rate (pdetQmax) Tadalafil 20 mg versus Placebo in Study LVHK

Treatment Group	Time Point	n	mean	SD
Placebo (N=91)			cm H_2O	
	Baseline	91	54.83	27.36
	Endpoint	91	56.75	26.64
	Change	91	1.92	19.71
Tadalafil 20 mg (N=94)				
	Baseline	94	56.87	29.67
	Endpoint	94	53.92	26.82
	Change	94	-2.95	15.92

Source: Table LJHK, Study LVHK Report, page 78

Secondary analyses on free-flow and pressure-flow urodynamic parameters (both pre-specified analyses, including all subjects in the primary analysis population, and post-hoc analysis excluding subjects with invalid tracings and/or mechanical fill) also showed neither statistically significant nor clinically adverse effects of tadalafil 20 mg. The reader is referred to the medical officer's review Tables 50 and 51 for details.

8.6.3 The Risk of Dizziness in Men with BPH Taking Both Tadalafil and Alpha Blockers for the Treatment of BPH (Study LVHS)

Cialis is intended as a "monotherapy" for BPH; specifically, it is intended to be used alone for the treatment of BPH, not with other treatments for BPH, such as alpha adrenergic antagonists (alpha blockers). However, it was considered reasonable to assume that some prescribers might use tadalafil (off-label) in conjunction with alpha blockers for the treatment of BPH despite the lack of sufficient efficacy investigations and the potential increase in vasodilatory adverse events. Therefore, the Division requested and the Sponsor conducted a study (Study LVHS) to assess the potential risks of increased vasodilatory adverse events in BPH patients taking both tadalafil and alpha blockers. The study showed that the efficacy of tadalafil was not enhanced by the taking of alpha blockers, but that there was little risk of increased vasodilatory adverse events.

Study LVHS was a Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to assess the safety of tadalafil 5 mg once daily for 12 weeks in men with BPH-LUTS on concomitant alpha-blocker therapy. To be enrolled, the subjects had to be using either: alfuzosin, doxazosin, silodosin, tamsulosin or terazosin for 4 weeks prior to Visit 1.

The primary objective of LVHS was to evaluate the proportion of men with symptomatic BPH experiencing treatment-emergent dizziness when adding tadalafil 5 mg once daily to concomitant alpha-blocker therapy compared to adding placebo to concomitant alpha-blocker therapy. Secondary measures (objectives) included AEs (including those possibly related to hypotension), orthostatic vital signs, PVR volume, uroflowmetry, and clinical laboratory tests. A secondary efficacy objective was the change from baseline to endpoint for the International Prostate Symptom Score (IPSS) when adding tadalafil 5 mg once daily to concomitant alpha blocker therapy for 12 weeks in the treatment of men with symptomatic BPH.

Of the 318 subjects randomized, 160 were assigned to placebo and 158 were assigned to tadalafil 5 mg. Clinical dizziness adverse events were captured in this 12 week study and are shown below.

Table 18: Treatment Emergent Dizziness in Study LVHS

	Placebo N=159	Tadalafil 5 mg N=158
Preferred Term	n (%)	n (%)
Subjects with >= 1 TEAE	9 (5.7)	11 (7.0)
Dizziness	8 (5.0)	10 (6.3)
Dizziness Postural	1 (0.6)	1 (0.6)
Procedural Dizziness	0 (0.0)	0 (0.0)

Source: Table LVHS 11.9, LVHS Study Report, page 92 (primary analysis population)

The primary analysis showed no statistically significant difference between treatment groups in the proportion of subjects experiencing treatment-emergent dizziness.

In terms of secondary efficacy analysis, the LS mean change from baseline to endpoint in total IPSS was not significantly different (p= 0.13) for the tadalafil 5 mg treatment group (-2.2) compared with placebo (-1.3). Tadalafil 5 mg once daily, when added to alpha blockers, did not result in statistically significant improvement in storage (irritative) symptoms, voiding (obstructive) symptoms, nocturia symptoms, nor QoL when compared with placebo (all p>.169).

Table 19: Total International Prostate Symptom Score (IPSS) in Study LVHS

Treatment	Time Point	n	Mean	SD
Placebo (N=159)	Baseline	156	13.3	6.6
	Endpoint	156	11.8	6.3
	Change	156	-1.5	5.3
Tadalafil 5 mg (N=158)	Baseline	156	13.9	7.2
	Endpoint	156	11.6	6.7
	Change	156	-2.3	5.7

Source: Table LVHS 11.10, LVHS Study Report, page 94.

8.6.4 Tadalafil in Elderly BPH Patients (Study LVHN and Subgroup Analyses in the Controlled and Uncontrolled Studies)

Since BPH is a new indication for Cialis, and despite the vast safety data available from clinical trials and postmarketing for tadalafil in the treatment of ED, it was considered prudent to evaluate the PK and safety of tadalafil in elderly BPH patients: those ≥ 65 years of age, and perhaps more importantly, those ≥ 75 years of age. This was accomplished in two ways: through a small, Phase 1, PK and tolerability study (LVHN) and through assessment of the clinical safety experience of elderly men in the BPH trials (without encouragement of recruitment of such men) and in the completed ED trials of as-needed and once-daily tadalafil.

Study LVHN was an open-label, Phase 1, clinical pharmacology study conducted to evaluate the pharmacokinetics and hemodynamics of tadalafil 20 mg administered once daily in elderly

men (70 to 76 years of age [n=12]) and young men (42-60 years of age [n=15]) with symptomatic BPH. Tadalafil was administered for 10 consecutive days.

Despite the moderately reduced renal function in elderly subjects in this study (37% reduction in mean baseline Cockcroft-Gault creatinine clearance values in elderly compared to young subjects), tadalafil exposures did not exceed those estimated in young subjects. The Sponsor noted that the lack of an age effect was expected as tadalafil is cleared predominantly via hepatic metabolism by CYP3A. However, there is a role for renal elimination of the tadalafil metabolites (such as IC710) and this resulted in a 47% difference between the highest total IC710 exposure in elderly subjects with mild renal impairment and that in young BPH subjects without renal impairment.

The hemodynamic profile in this study appeared broadly comparable for elderly and young subjects with BPH. Although there appeared to be a larger decrease from baseline (Day 1, predose) in supine and standing systolic and diastolic blood pressure for elderly subjects compared to young subjects with BPH over the first 4 hours post-dose on Days 1 and 10, it is the Sponsor's opinion that this was attributable to a higher baseline blood pressure (Day 1, pre-dose) in the elderly subjects. None of the elderly subjects experienced adverse events associated with orthostatic changes in blood pressure, whereas 2 young subjects experienced orthostatic hypotension. It is also notable that there was no placebo control in this study to assess the independent effect of tadalafil on BP, and the tadalafil dose was 20 mg once daily, 4-fold the dose for the BPH indication

In regard to the assessment of safety outcomes based on age subgroups (subjects ≤65 and >65 years of age; subjects <75 years and ≥ 75 years of age) in the clinical trials, the data appear to show that across all analysis sets, the AE profiles were similar between age groups, in the pivotal and additional BPH and BPH/ED analysis sets. There were no clinically meaningful differences in the frequencies and types of TEAEs across age groups. The extent of the exposure in elderly patients appears sufficient, when considering both the BPH studies and the ED studies. In the BPH studies:

The number of exposed subjects ≥65 years of age:

- 586 were exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission.
- 130 were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months.
- 105 were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year.

The number of subjects ≥75 years of age:

- 160 were exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission.
- 35 were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months.
- 28 were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year.

In the combined BPH, daily ED and as needed (p.r.n.) ED studies, the Sponsor compiled data from 403 subjects ≥ 75 years of age who had been exposed to tadalafil ≥ 5 mg in BPH or daily

ED treatment studies, or to tadalafil ≤ 20 mg in PRN ED treatment studies. Of these subjects, 173 had been exposed for at least 6 months, and 102 had been exposed for at least 1 year.

8.7 Postmarketing Experience

Cialis was approved in November 2003 for the as needed treatment of ED at doses of 5 mg, 10 mg and 20 mg up to once daily. In January 2008, Cialis was approved for the once daily treatment of ED. Tadalafil has also been approved in the U.S. and in 33 countries for the treatment of pulmonary arterial hypertension (PAH). The recommended dose of tadalafil for PAH in approved countries is 40 mg daily.

As of April 15, 2010, approximately 26.3 million patients worldwide had been exposed to tadalafil (excluding use of tadalafil when taken as Adcirca™ for PAH). The medical officer's review describes a comprehensive evaluation of the 13th periodic safety update report (PSUR) to the NDA for the period between April 2010 and October 2010, and a summary analysis of the 14th PSUR for the period between October 2010 and April 2011. In each of these periods, the worldwide exposure was tallied at > 4 million users. The medical officer concludes, and I agree, that in both the 13th and 14th PSURs, the information presented did not reveal any new safety signals and no new safety concerns have been identified. For several adverse event types that are under greater surveillance (hearing and vision abnormalities, cerebrovascular accidents), there remains an inconclusive association to tadalafil, based on the relatively few, and generally incomplete and confounded spontaneous reports that have been submitted. (b) (4)

[redacted]

8.8 Overall Safety

In the medical officer's review, Dr. Wiederhorn had the following conclusion:

> *"No discernible differences in the safety profile were detected for the use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH and or BPH/ED as compared to the patient population in the previously approved ED indication for 5 mg tadalafil once daily.*
>
> *Tadalafil 5 mg once daily has been shown to be generally safe for its intended use as recommended in the labeling by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to other drugs in its class and to the other indication (ED) for once daily use. Treatment emergent adverse events occurring in greater than or equal to 2% in the tadalafil group and greater than placebo group in all randomized subjects in Studies LVHG, LVHJ, and LVHR were: headache, back pain, dyspepsia and nasopharyngitis. Treatment emergent adverse events in subjects taking tadalafil 5 mg once daily for a year occurring in greater than or equal to 2% of subjects*

include dyspepsia, gastroesophageal reflux disease, back pain, headache, sinusitis and cough.

The data provided in the Sponsor's submissions support adequate directions for use, including the data to describe a safe and effective dose. The submissions do allow for labeling that will permit acceptably safe use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH in men with BPH or BPH/ED."

I concur with the medical officer's conclusion regarding overall safety.

The overall exposure and duration of exposure in subjects with BPH was adequate, and was bolstered by significant exposure to the daily dosing regimen for the treatment of ED in clinical trials and in the postmarketing period. The demographics of the target population were appropriate, including BPH subjects ≥ 65 years of age and ≥75 years of age. The assessments of safety were extensive and rigorous, both in the efficacy and safety studies and in the special safety studies. There were two deaths in subjects taking tadalafil, versus one in a placebo subject. No death could be attributed directly to tadalafil. The frequency of reporting of serious AEs was very low, and there appeared to be no discernible repetitive occurrence pattern of SAEs. Most SAE terms were reported by 1 subject each. There is an increased incidence of discontinuations due to AEs in tadalafil-treated versus placebo treated groups (3.6% versus 1.6%), but the rate of discontinuations due to AEs was low, and the AEs appear to be the well-known and recognized AEs associated with tadalafil, including headache, abdominal pain, and myalgia. The commonly reported AEs were reported at low rates (none reaching 5%), and again, included those AEs that are well-known to tadalafil, including headache, dyspepsia, back pain, nasopharyngitis, myalgia and dizziness. While "hypertension" was reported as a clinical AE more frequently in tadalafil compared to placebo groups, a meticulous case-by-case review of each report demonstrated that their were no cases of new-onset hypertension, and in the majority of cases, the AE reflected baseline hypertension with no clinically meaningful increase in blood pressure post-baseline. There were no tadalafil-related effects on electrocardiograms or clinical laboratories. There appeared to be no difference in safety profile between subjects with BPH and subjects with BPH and ED. There appeared to be no difference in clinical AEs between men < 65 years of age and < 75 years of age, compared to subjects ≥ 65 years of age, and ≥ 75 years of age, respectively. Despite a lack of effect on urinary flow rate, no detrimental effects of tadalafil on key urodynamic parameters were observed. There appeared to be no change or unrecognized safety issues in the recent postmarketing safety data despite widespread use (approximately 30 million men with ED in total, and 8 million men in the year corresponding to the safety update). Finally, the risk of switching from another treatment for BPH to Cialis appears to be generally safe, with only a modest risk of urinary retention. It is advised not to use Cialis in conjunction with alpha blockers for the treatment of BPH due to the lack of data to support efficacy of the combination, as well as the small, but recognized risk of increase in vasodilatory adverse reaction.

9. Advisory Committee Meeting

An Advisory Committee was not held for this application. Tadalafil is currently approved in the same dosage strengths (2.5 mg and 5 mg) for once daily use. It is also approved for prn use at doses up to 20 mg once daily. The safety profile for the new indications was no different than that observed for the ED indication. Efficacy analyses showed robust evidence of BPH and BPH/ED treatment effects. Therefore, there were no issues to discuss before an Advisory Committee.

10. Pediatrics

The Sponsor requested a full waiver of the requirement to conduct assessments of Cialis in pediatric patients. The Sponsor stated that studies would be impossible or highly impracticable because the disease/condition does not exist in children. The Division recommended to grant the full waiver. On September 14, 2011, the Pediatric Review Committee (PeRC) conducted a review of the waiver request. On September 20, 2011, the Division received an eMAIL from Mr. George Greely of the Pediatric and Maternal Health Staff (PMHS), stating the following:

> "*The Division presented a full waiver for the indications of treatment of erectile dysfunction and signs and symptoms of benign prostatic hyperplasia (ED/BPH) and treatment of signs and symptoms of benign prostatic hyperplasia (BPH)*
>
> *The PeRC agreed with the Division to grant a full waiver for this product because the disease/condition does not exist in children."*

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)

On July 22, 2011, Roy Blay, Jean Mulinde and Lauren Iacono-Conners of the Office of Scientific Investigations (OSI) provided a final Clinical Inspection Summary. Four clinical investigative sites were inspected. These sites were part of Studies LVHG, LVHJ and LVHR. The overall assessment and recommendations from OSI were as follows:

> "*The clinical investigator sites of Drs. Bidair, Dula, Gaylis and McMurray were inspected in support of this NDA. No significant regulatory violations were noted at Dr. McMurray's site and the final classification for the inspection is No Action Indicated (NAI).*
>
> *Regulatory violations were noted at the sites of Dr. Bidair, Dula and Gaylis and the preliminary classifications for each of these inspections is Voluntary Action Indicated (VAI). Noteworthy were discrepancies observed between the source document questionnaires and the corresponding CRFs at Dr. Bidair's site for Subjects 3707, 3733, 3745 and 3756, and at Dr. Dula's site for Subjects 1101, 1142, 1148, 1151, 1159 and 1173. However, as primary efficacy was determined by the assessment of difference in total IPPS and IIEF domain scores between Visit 3 and Visit 7 in Study*

LVHR, discrepant document would impact primary efficacy data (only) for Subjects 3707 and 3756 from Dr. Bidair's site and Subjects 1151 and 1159 at Dr. Dula's site. At Dr. Gaylis' site, only Subject 1130 (enrolled in Study LVHG) exhibited such a discrepancy. These discrepancies have been discussed with the DRUP reviewing medical officer, Dr. Wiederhorn and the Team Leader, Dr. Hirsch. Dr. Wiederhorn indicated that the discrepancies observed at Dr. Bidair's and Dr. Dula's sites would be unlikely to affect the assessment of the primary efficacy outcome. Similarly, at Dr. Gaylis' site, the exclusion of data from Subjects 1130 for a single discrepant response would be unlikely to affect the primary efficacy outcome.

Notwithstanding the observations detailed above, the studies appear to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication."

In regard to the three sites with discrepancies:

- At Dr. Bidair's site, 6 of the 29 enrolled subjects had minor discrepancies between the hard-copy questionnaire and the electronic CRF, each for single assessments in the trial (Study LVHR). Two subjects (3707 and 3756) had discrepancies at baseline (Visit 3) or at endpoint (Visit 7). Both these subjects were taking the 2.5 mg dose, a dose found to be ineffective in Study LVHR. The analysis was re-conducted by our statistican after exclusion of these subjects, and the conclusions were unchanged. Further, OSI noted that the data from this site was still acceptable for analysis, other than the data from subjects with discrepancies at the primary timepoints.
- At Dr. Dula's site, 7 of the 23 completed subjects had minor discrepancies between the hard-copy questionnaire and the electronic CRF, for assessments in the trial (Study LVHR). Discrepancies were observed for single assessments in 3 subjects, for two assessments in 2 subjects, for four assessments in 1 subjects, and for five assessments in 1 subject. In no circumstance was endpoint data (Visit 7) affected. However, in two patients (Subjects 1151 and 1159), baseline data (Visit 3) was affected. The analysis was re-conducted with data from these 2 subjects excluded and the conclusion was unchanged. Further, OSI noted that the data from this site was still acceptable for analysis, other than the data from subjects with discrepancies at the primary timepoints. Of note, Dr. Dula offered the explanation that the cause of these discrepancies might be simple human error in entering the data into the electronic CRF, where a drop-down, scrolling type electronic menu was used for entering responses.
- At Dr. Gaylis' site, 1 of the 50 enrolled subjects (Subject 1130) had a minor discrepancy between his IPSS hard-copy questionnaire and his eCRF at Visit 8 (total of 8 points versus 12 points) in Study LVHG. This minor difference did not affect the primary timepoints for analysis. There were also a few patients randomized who were technically ineligible based on various minor criteria. Aside from these minor issues, OSI found the data from this site to be acceptable for analysis.

Financial Disclosure

Financial disclosure information was properly submitted by all investigators in the Phase 3 studies LVHG, LVHJ, and LVHR. Financial disclosure information was also submitted for the special safety study LVHS. Of a total of 409 investigators who submitted information, a total of 5 investigators submitted Form 3455 relating to "accrued equity above suggested limits." There was no missing financial disclosure information for investigators in the above listed studies.

The medical officer reviewed the financial disclosure information for these 5 investigators and concluded:

> "*It does not appear that the compensation that the 5 investigators who submitted Form 3435 received affected the outcome of covered studies [12 CFR 54, 2(a)], reflected a proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], or significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]*."

Division of Medication Errors and Prevention (DMEPA)
DMEPA consulted on 1) the container/carton labeling, 2) the Full Prescribing Information (FPI), and 3) the packaging for Cialis with regard to potential medication errors.

In their first completed review, dated July 7, 2011, Yelena Maslov, Zachary Oleszczuk, and Carol Holquist of DMEPA offered 2 recommendations for the regular carton labeling (e.g. remove redundant and distracting logo) and 6 recommendations for the regular container labeling (e.g., remove redundant logo, increase prominence of the dosage form, improve readability of the side panel, add statement "*Do not divide, chew or crush tablets*", based n several reports of patients who divided or chewed Cialis).

DMEPA also had a number of recommendations concerning the blister card label and container (e.g, increase the font size of the established name, increase the prominence of the dosage form, relocate or delete the phrase "for once daily use", add the statement "*Do not divide, chew or crush tablets*", remove the statement "last tablet" and clockwise arrows, increase the difference between the 2.5 mg and 5 mg blister cards, remove one of the two company logos, delete the web address, etc).

All of the DMEPA comments were conveyed to Sponsor on August 15, 2011. Sponsor provided a response to each comment on September 1, 2011.

In their final review, dated September 14, 2011, Yelena Maslov, Zachary Oleszczuk, and Carol Holquist of DMEPA, had the following conclusion:

> "*The revised container labels and carton labeling address all of DMEPA's concerns. However, the revised blister labels still contain days of the week, a statement "last tablet", and clockwise arrows above the tablets organized in a circular manner. Although blister label's design is not ideal, we did not any medication errors related to the product's blisters (sic). Thus, we have find the revised blister labels acceptable*

and have no additional comments to the Applicant at this time. However, we will continue monitoring medication errors involving Cialis."

Division of Drug Advertising, Marketing and Communication (DDMAC)
A consultation regarding the PI and PPI labeling for these Cialis efficacy supplements was requested and completed by DDMAC.

In her final review dated September 2, 2011, Janice Maniwang of DDMAC provided 5 comments on the PI and 2 comments on the PPI for DRUP's consideration. Each of the DDMAC comments were considered individually and discussed within the Clinical review team. In regard to the PI:

1. It was decided to leave the title of Section 5.4 as "*Eye*" to avoid confusion with the heading in Section 12.2 "*Effects on Vision*".
2. DDMAC asked whether any additional tests are needed before starting a patient on Cialis for BPH in order to rule out other urological conditions. No additional tests need be specified in the label.
3. DDMAC asked whether the percentage of patients who required a mild narcotic for back pain/myalgia in the original Phase 3 studies could be quantified. The label currently states a "small" percentage. The label states that in the original studies, < 5% of reports of back pain/myalgia were of moderate or severe severity, and only 0.5% of patients discontinued for back pain/myalgia. The label states that acetaminophen or non steroidal anti-inflammatory were generally effective in relieving the discomfort due to tadalafil-related back pain and maylagia. In addition, the daily doses for the BPH indications (2.5 mg and 5 mg) are generally lower than the prn doses for ED (5 mg, 10 mg and 20 mg), leading to an even smaller risk of severe back pain or myalgia requiring a mild narcotic. Therefore, it was deemed not necessary to add the exact percentage and the text was not changed.

4/5. In the Drug Interactions section, it was decided to leave the word "*tadalafil*" in Section 7.1, rather than replace it with "*Cialis*".

For the PPI:

1. (b) (4)

(b) (4)

2. DDMAC asks whether it would more appropriate to list alpha blockers higher in the PPI, rather than where it is currently listing (under ***Can Other Medicines Affect Cialis?***). The current label states that patients should inform their health care provider if they are taking any of a number of listed alpha blockers, either for the treatment of BPH or for the treatment of hypertension. The label states "*Alpha blockers are sometimes prescribed for prostate problems or high blood pressure. If Cialis is taken with certain alpha blockers, your blood pressure could suddenly drop. You could get dizzy or faint.*" It is notable that this is the same text as for the existing approved Cialis label. It is also notable that Study LVHS, in which men with BPH were co-administered Cialis with alpha blockers revealed no worrisome safety findings. Therefore, it was decided that this text may be kept without change; however, a DRISK consult of the PPI was obtained for greater assurance.

Division of Drug Risk Assessment (DRISK)
DRISK was asked to comment on Patient Package Insert (PPI). In their final review dated September 26, 2011, Shawna Hutchins and LaShawn Griffiths stated:

> "*The PPI is acceptable with our recommended changes*"

DRISK commented that they had conducted a focused review of the PPI for the new BPH and BPH/ED indications. They noted that in the future, all ED drugs PPIs should be brought up to current patient labeling standards. All DRISK recommendations and comments were conveyed to Sponsor on September 26, 2011.

Labeling

Labeling discussions were held with the entire review team on July 20, 2011 and August 3, 2011. A separate Clinical/Biometrics labeling meeting was held on August 8, 2011. The first FDA-revised label was conveyed to Sponsor on August 27, 2011. The Sponsor largely accepted the Division's revisions. Following receipt of the Sponsor's response on September 1, 2011, the Division conveyed additional revisions on September 15, 2011. Again, the Sponsor largely accepted the Division's revisions. Following receipt of the Sponsor's response on September 19, 2011, the Division had several minor edits which were conveyed on September 20, 2011.

On September 22, 2011, the Study Endpoints and Labeling Team (SEALD) completed a review of the label. The purpose of the review is to assure that the label meets the requirements of 21 CFR 201.56 and 201.57 and CDER labeling policies. SEALD concluded:

> "*The following Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved*".

The SEALD review outlined two deficiencies and recommendations for several minor edits. The two deficiencies were:

1. In Highlights, for RECENT MAJOR CHANGES, the heading, and if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval.

2. In Highlights, for REVISION DATE, a placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year" must appear at the end of Highlights.

Based on the SEALD recommendations for edits and the single outstanding item from the DDMAC review, another label was sent to Lilly on September 23, 2011. Finally, on September 26, 2011, a DRISK review of the PPI was received and these additional recommended revisions were conveyed to Sponsor on September 26, 2011. The Sponsor accepted virtually all the DRISK edits and returned the label on September 27, 2011. After some minor additional edits, a final, acceptable label was submitted by Sponsor on September 30, 2011.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action

I recommend that these efficacy supplements to NDA 21-368 for CIALIS be approved.

12.2 Risk Benefit Assessment

In the medical officer's review, Dr. Wiederhorn had the following conclusions:

"A thorough and comprehensive review of sNDA 21-368 SEI-20 and sNDA 21-368 SEI-21was carried out. These NDA submissions have provided substantial evidence from adequate and well controlled ("pivotal") studies that tadalafil 5 mg once daily will have the effect claimed in labeling. This claim is that, in men with BPH and BPH/ED, tadalafil 5 mg once a day is efficacious in treating the signs and symptoms of BPH. In men with BPH/ED, tadalafil 5 mg once a day is also efficacious in treating their ED….

No discernible differences in the safety profile were detected for the use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH and or BPH/ED as compared to the patient population in the previously approved ED indication for 5 mg tadalafil once daily.

Tadalafil 5 mg once daily has been shown to be generally safe for its intended use as recommended in the labeling by all tests reasonably applicable to assessment of safety….

The data provided in the Sponsors submissions support adequate directions for use, including the data to describe a safe and effective dose. The submissions do allow for

labeling that will permit acceptably safe use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH in men with BPH or BPH/ED."

I concur with the medical officer's conclusions regarding risk and benefit.

These two efficacy supplements do provide substantial evidence from three, Phase 3, randomized, placebo-controlled studies (LVHG and LVHJ in men with BPH, and LVHR in men with both ED and BPH) that tadalafil is effective and safe for use as a treatment for symptomatic BPH as well as for the treatment of BPH and ED in men with both conditions (BPH/ED).

The Phase 3 studies demonstrate a statistically significant and clinically meaningful treatment effect of tadalafil on the symptoms of BPH. It is notable that while tadalafil promoted symptomatic relief in BPH, it did not differentiate itself statistically from placebo in regard to increase in maximum urinary flow rate. In this regard, there appears to be no safety concern, as tadalafil does not negatively impact urodynamics nor does it interfere with bladder emptying. The transition from other treatments for symptomatic BPH to tadalafil is reasonably safe. The safety profile of tadalafil that was demonstrated in the three Phase 3 BPH studies (LVHG, LVHJ, and LVHR), the single Phase 2 study (LVGC), the additional safety studies (LVHK and LVHS), the Phase 1 study in elderly patients (LVHN), the three studies in Asia (LVIA, LVHT and LVHB), and the open-label extension of LVHG is consistent with the known safety profile of tadalafil for the treatment of ED. There were no unexpected or new safety concerns. The safety profile was not different nor worse in subjects $\geq$ 65 years of age, or $\geq$ 75 years of age, compared to subjects < 65 years of age or < 75 years of age. The recent postmarketing experience revealed no new findings. All warnings and precautions for tadalafil as used for ED apply to its use for the new BPH and BPH/ED indications.

Overall, the risk benefit assessment is considered favorable for Cialis for treatment of symptomatic BPH and symptomatic BPH and ED.

12.3 Recommendation for Post marketing Requirement

There are no recommendations for postmarketing commitments (PMCs) nor requirements (PMRs).

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/s/

MARK S HIRSCH
10/03/2011

SCOTT E MONROE
10/04/2011
I concur with Dr. Hirsch's overall assessment and his recommendation of Approval of these supplements.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	NDA 21-368-SEI 20 NDA 21-368-SEI 21
Priority or Standard	Standard
Submit Date(s)	December 6, 2010
Received Date(s)	
PDUFA Goal Date	October 6, 2011
Reviewer Name(s)	Roger Wiederhorn, Medical Officer DRUP Mark Hirsch, Team Leader, DRUP
Review Completion Date	
Established Name	tadalafil
(Proposed) Trade Name	Cialis
Therapeutic Class	PDE-5 Inhibitor
Applicant	Eli Lilly
Formulation(s)	Oral
Dosing Regimen	Once Daily
Indication(s)	NDA21-368 SO-20: Signs and Symptoms of benign prostatic hyperplasia (BPH): and NDA21-268 SO-21: Treatment of both ED

	(erectile dysfunction) and Signs and Symptoms of BPH.
Intended Population(s)	Men with BPH and Men with both BPH and ED.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that sNDA 21-368 SEI-20 and sNDA 21-368 SEI-21 be **APPROVED** at this time. Tadalafil 5 mg was found to efficacious in treatment in the treatment of signs and symptoms of BPH in men with BPH only and in men with BPH/ED (benign prostatic hypertrophy/erectile dysfunction). Tadalafil 2.5 mg was not found to be efficacious in treating the signs and symptoms of BPH in men with BPH/ED.

1.2 Risk Benefit Assessment

A thorough and comprehensive review of sNDA 21-368 SEI-20 and sNDA 21-368 SEI-21was carried out. These NDA submissions have provided substantial evidence from adequate and well controlled ("pivotal") studies that tadalafil 5 mg once daily will have the effect claimed in labeling. This claim is that, in men with BPH and BPH/ED, tadalafil 5 mg once a day is efficacious in treating the signs and symptoms of BPH. In men with BPH/ED, tadalafil 5 mg once a day is also efficacious in treating their ED.

Within the three pivotal studies (LVHG, LVHJ, and LVHR) and the 52 week Open-Label Safety Extension of LVHG there were (corrected figures based on 22 June 2011 Amendment):

- 1448 subjects exposed to tadalafil 5 mg, 10 mg, or 20 mg in the BPH and BPH/ED studies, with a total exposure of 624.5 subject years.
- 363 subjects exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 296 subjects exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

No discernible differences in the safety profile were detected for the use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH and or BPH/ED as compared to the patient population in the previously approved ED indication for 5 mg tadalafil once daily.

Tadalafil 5 mg once daily has been shown to be generally safe for its intended use as recommended in the labeling by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to other drugs in its class and to the other indication (ED) for once daily use. Treatment emergent adverse events occurring in greater than or equal to 2% in the tadalafil group and greater than placebo group in all randomized subjects in Studies LVHG, LVHJ, and LVHR were: headache, back pain, dyspepsia and nasopharyngitis. Treatment emergent adverse events in subjects taking tadalafil 5 mg once daily for a year occurring in greater than or equal to 2% of subjects include dyspepsia, gastroesophageal reflux disease, back pain, headache, sinusitis and cough.

The data provided in the Sponsors submissions support adequate directions for use, including the data to describe a safe and effective dose. The submissions do allow for labeling that will permit acceptably safe use of tadalafil 5 mg once daily for the treatment of signs and symptoms of BPH in men with BPH or BPH/ED.

1.3 Recommendations for Postmarket Risk Management Activities

There are no recommendations for postmarket risk management activities.

1.4 Recommendations for Postmarket Studies/Clinical Trials

There are no recommendations for postmarket studies or clinical trials.

2 Introduction and Regulatory Background

2.1 Product Information

Tadalafil (Cialis®) is a selective inhibitor of cyclic guanosine monophosphate (cAMP)-specific phosphodiesterase type 5 (PDE5). It is an oral treatment for male erectile dysfunction (ED). It is an approved drug for use in the USA (NDA 21-368) for ED and as such is not a new molecular entity. The applicant currently proposes utilizing daily doses of tadalafil for the treatment of symptomatic BPH in adult males and for the treatment of symptomatic BPH in association with ED in adult males. The Sponsor proposes the 5 mg dosage strength as a daily dosing regimen for BPH and for BPH/ED. For patients with moderate renal impairment, a daily dose of 2.5 mg is recommended for BPH and BPH/ED.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Treatments for BPH

Medications	Regimen	Advantages	Disadvantages/AEs
Alpha-Adrenergic Antagonists Specific and non-specific for the α1 receptor	Daily oral dosing	Decreases lower urinary tract symptoms (LUTS)	Dizziness, hypotension, ejaculatory dysfunction
5-Alpha Reductase Inhibitors	Daily oral dosing	Decreases LUTS, Reduces the risk of urinary retention and need for BPH related surgery	Less effective in smaller prostates, impotence, libido loss, ejaculatory dysfunction, gynecomastia, may increase incidence of higher grade prostate cancer
Combination Therapy Alpha-Adrenergic Antagonists and 5-Alpha Reductase Inhibitors	Daily oral dosing	Superior results over monotherapy	Impotence, libido loss, ejaculatory dysfunction, gynecomastia, may increase incidence of higher grade prostate cancer
Anticholinergics (not FDA approved for BPH)	Daily oral dosing	When used with alpha blockers there may be additional symptom improvement.	Risk of urinary retention, not studied in men with larger glands, increased PVR or history of urinary retention.
Phytotherapeutics	Multiple food supplements	Efficacy has not been validated by FDA	Data not sufficient and consistent enough to characterize.
Source: Affenberg et al., Established Medical Therapy for Benign Prostatic Hyperplasia, Urol Clin NA: 35(2009), 443-459.			

Surgical	Usually performed when medical therapy is insufficient		
Minimally Invasive Surgical Technique (MIST)	Laser, radio frequency ablation, hyperthermia	Performed in outpatient setting, recovery shorter than TURP	Requires surgical intervention, results and durability less than with TURP
Transurethral Resection of the Prostate (TURP)	Bipolar or monopolar Electrode or vaporization	More effective and longer duration of benefit than MIST	Requires surgical intervention and recovery, impotence, bladder neck contracture
Open Prostatectomy	Multiple techniques	Most effective therapy	Requires surgical intervention and recovery, impotence, blood loss

Table 2: Currently Available Treatment for Erectile Dysfunction

Medications	Regimen	Advantages	Disadvantages/AEs
Phosphodiesterase (PDE5) Type 5 inhibitors	Either daily or as needed oral dosing	Ease of use, first line treatment	Not effective in all patients, nitrate interaction, syncope, dizziness, priapism
Aprostadil intraurethral suppositories	As needed	Less invasive than intracorporeal penile injection	Hypotension after first dose (3%), priapism
Intracavernous Vasoactive Drug Injection	As needed	Highly effective as a non-surgical ED treatment	Requires patient training, priapism
Testosterone	Multiple dosing regimens	Applicable only in patients with subnormal serum testosterone	Efficacy not consistent
Vacuum Constriction Devices		Often effective, low cost, can be use in combination with medications	Low patient acceptability, cumbersome, lack of spontaneity, high negative pressures may injure penis
Surgical			
Penile Prosthesis Implantation	Inflatable, non-inflatable	Inflatable more closely resembles normal flaccidity and erection, permits multiple intercourse episodes	Non-inflatable does not exhibit normal flaccidity, mechanical failure, pump displacement, auto-inflation, infection
Vascular Surgery	Veno-occlusive Arterial	A small patient subset may benefit from venous surgery, A young patient with focal arterial occlusion may benefit from arterial surgery	Difficult to attribute ED to venous lesion alone. Arterial surgery has very limited application

Source: The Management of Erectile Dysfunction: An Update (2007), The American Urological Association

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, tadalafil, is readily available in the United States under NDA 23-368. The tablet strengths are to be manufactured according to the chemistry; manufacturing and controls approved in the Cialis® NDA for the 2.5, 5 mg, 10 mg, and 20 mg tablets.

2.4 Important Safety Issues With Consideration to Related Drugs

The administration of PDE5 inhibitors to patients who are using any form of organic nitrate either regularly or intermittently is contraindicated due to potentiation of the hypotensive effect of nitrates. The daily use of tadalafil will lead to a continuous serum tadalafil concentration and may possibly increase the likelihood of this interaction.

Priapism or prolonged erection may also occur with this class of drugs.

Potentiation of blood pressure lowering effects of alpha-adrenergic blocking agents may also occur with PDE5 inhibitors albeit at the higher previously approved doses. Potentiation of the blood pressure lowering effect of large amounts of alcohol may also occur with PDE5 inhibitors.

There have been reports of non-arteritic ischemic optic neuropathy (NAION) and sudden hearing loss in patients taking PDE5 inhibitors. A direct causal association has not been shown for these events. It is not known whether constant exposure to tadalafil may change the incidence of these reports.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor opened IND 73,502 on April 25, 2006. The IND application was opened to study tadalafil for the treatment of men with signs and symptoms of benign prostatic hyperplasia (BPH)- as in *supplement 20* and for the treatment of men with ED and signs and symptoms of BPH (BPH/ED)-as in *supplement 21.*

During a July 19, 2006, Type A meeting, the following agreements were reached:

- Lilly is to develop tadalafil for signs and symptoms of BPH as "monotherapy."
- Lilly is to perform a study evaluating the safety of tadalafil in patients taking alpha blockers and submit the study results in the NDA.
- Study LVHG may be considered a "pivotal" efficacy and safety study.
- Lilly agreed to add creatinine kinase (CK) to the laboratory tests in the protocol.
- Lilly agreed to amend the protocol for LVHG to exclude patients with systolic BP>160 mmHg and/or diastolic>100 mmHg.
- Lilly agreed to amend the protocol for LVHG to exclude patients with HBA_{1c}>9%.

- In "pivotal" trials, approximately one third of participants will be 65 years of age and older and approximately 10% will be 75 years and older.

  Reviewer's Comment: Greater than one third of the patients in Studies LVHG, LVHJ and LVHR were > than 65 years-old. Patients > 75 years of age were in Study LVHG 6.06 % (N=1056), Study LVHJ 20 % (N=325) and Study LVHR 9.2% (N=606). It was also agreed, at the September 25, 2008, EOP2 meeting, that Sponsor would provide safety data (including potential adverse hemodynamic effects) from least 100 men aged 75 years or older to be derived from the Phase 3 BPH program. Sponsor has adhered to all commitments made at the April 25, 2006, Type A meeting.

An End-of-Phase 2 (EOP2) meeting was held with the Sponsor on September 25, 2008. During the meeting the following items were discussed:

1. Sponsor agreed to provide safety data (including potential adverse hemodynamic effects) from least 100 men aged 75 years or older to be derived from the Phase 3 BPH program.
2. It was agreed that no additional pharmacokinetic and clinical pharmacology (including drug-drug interaction) studies are required for the proposed indications.
3. The Division agreed that the urodynamic results from Study LVHK and lack of effect on postvoid urine residual volume and on urinary tract adverse events in Studies LVGC, LVHG, and LVHK appropriately establish the bladder safety of tadalafil up to 20 mg daily.
4. Sponsor agreed to evaluate both the 2.5 g and 5.0 g once a day tadalafil doses for BPH/ED in a separate co-morbid study.
5. Sponsor agreed that exclusion criteria for Study LVHJ should be modified to exclude patients with a PSA ≥4.0 to ≤10.0 ng/mL unless prostate cancer has been ruled out to the satisfaction of an urologist (all investigators are to be urologists) and that patients with clinically significant microscopic hematuria be excluded.
6. Sponsor agreed that in study LVHJ and LVHS uroflowmetry and measurement of Qmax are to be done at Screening, Baseline, and Endpoint.
7. (b) (4)
8. Sponsor agreed to submit information in support of the validity of the BII.
9. (b) (4)
10. Sponsor is to provide safety data on patients discontinuing alpha blockers and initiating tadalafil as monotherapy.
11. Division agreed that subjects taking alpha blocker and tadalafil in combination could be excluded from Study LVHG.
12. Sponsor agreed to increase the sample size in Study LVHJ to 300 subjects and to include patients using selective and non-selective alpha blockers in assessment of treatment emergent dizziness related to concomitant tadalafil use. Hemodynamic event terms will also be provided. This sub-study within LVHJ was eventually performed as Study LVHS as a stand-alone study with Division agreement that this study would be sufficient to address the Division's safety concerns (10 March 2009 correspondence).

13. Sponsor agreed to collect and analyze data from Studies LVGC, LVHG and LVHK to ascertain in patients discontinuing alpha blockers if there was any worsening of symptoms.
14. The Division agreed in a follow-up e-mail to the fixed sequence testing procedure proposed in Study LVHJ to control family-wise Type I error in primary and key secondary endpoints and with the proposed multiple testing procedure in Studies LVHJ and LVHR.
15. (b) (4)
16. (b) (4)
17. (b) (4)

Reviewer's Comment: Sponsor has complied with all commitments made at the EOP2 meeting.

A Pre-sNDA meeting was held April 13, 2010. During the meeting the following items were discussed:

1. Sponsor agreed to submit datasets from Studies LVHG, LVHJ, LVHR, LVHS, and LVIA in SDTM format.
2. Sponsor agreed to provide references to Phase 1 studies from the approved Cialis NDA that support dosing recommendations in specific populations such as geriatric, hepatic impairment, renal impairment, and race ethnicity.
3. It was agreed that adverse event data from elderly subjects (≥65 years and ≥75 years of age) in Study LVHN be integrated with the adverse event data from elderly patients in Studies LVHS, LVHJ, LVHR, and LVHG as a separate, combined, safety analysis within the ISS.
4. Sponsor agreed that the application is to include an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) to accommodate additional presentations of efficacy and safety data.
5. It was agreed that Study LVIA should be integrated into adverse event data from Asian subjects and the Integrated Summary of Efficacy should include a separate discussion of efficacy in Asians. As a result of limited numbers of Asian subjects in LVHJ, LVHG, LVHR, LVHS, and LVHK, the Division agreed that an integration of efficacy and safety data from Studies LVHT and LVIA would be acceptable in lieu of integrated analyses from study LVIA combined with Asian subjects from Studies LVHJ, LVHG, LVHR, LVHS, and LVHK.
6. In addition to Sponsor's proposed subgroup analysis, the Division requested subgroup analysis by prior alpha blocker therapy (yes/no), by prior PDE5 inhibitor therapy (yes/no), and Asian versus non-Asian.

7. Safety data is to be organized in the ISS in 3 groups: 1) All BPH patients 2) BPH patients without ED 3) Patients with BPH/ED, and is to include a discussion of whether safety was different in LVHR.
8. A separate section in the ISE in which safety data from Study LVIA is integrated with data from Studies LVHJ and LVHG.
9. Cardiovascular events should be added to the proposed list of safety topics and the Special Safety Topics Sections should include a brief discussion of myalgias/back pain, seizures and transient global amnesia.
10. A final study report for the completed 1-year Study of LVHG is to be with the application as well as an abbreviated study report for the open-label extension of Study LVIA containing at least 6 months of safety data.
11. (b) (4)
12. (b) (4)

Reviewer's Comment: Sponsor has adhered to commitments made at the Pre-sNDA meeting.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of good quality and no concerns have been raised about the integrity of the processes that were used by Sponsor to generate this submission.

3.2 Compliance with Good Clinical Practices

The Sponsor appears to have been compliant with good clinical practices.

3.3 Financial Disclosures

Form 0910-0396 (financial disclosure) was submitted by the principal investigators in Studies LVHG, LVHJ, LVHS and LVHR. Of a total of 409 investigators (from all study sites in Studies LVHG, LVHJ, LVHS and LVHR), 5 investigators submitted Form 3455 relating to "accrued equity above suggested limits." There was no missing financial disclosure information for investigators in the above listed studies.

Reviewer's Comment: It does not appear that the compensation that the 5 investigators who submitted Form 3435 received affected the outcome of covered studies [12 CFR 54, 2(a)], reflected a proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], or significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)].

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The active ingredient, tadalafil, is readily available in the United States under NDA 23-368. Manufacturing and controls were approved in the Cialis® NDA for the 5 mg, 10 mg, and 20 mg tablets. On September 4, 2007, ONDQA-DPE concluded that the 2.5 mg strength product is of satisfactory quality and may be approved.

4.2 Clinical Microbiology

There is no microbiology information for this application

4.3 Preclinical Pharmacology/Toxicology

All relevant nonclinical pharmacology, toxicology, and absorption, distribution, metabolism and elimination (ADME) information specific to tadalafil are contained in the original NDA 21-368. On August 8, 2011, PharmTox concluded that the previously submitted nonclinical data support the approval of the proposed dosing regimen of CIALIS.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

PDE5 inhibitors (and tadalafil in particular) cause increased concentration of cyclic guanosine monophosphate (cGMP) and local release of nitric oxide (NO) during sexual stimulation which results in a relaxation of the smooth muscle cells (SMCs). This facilitates inflow of blood into the penile tissues, thereby producing an erection. The effect of PDE5 inhibition on cGMP concentration seen in corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of prostate and bladder and their vascular supply according to the Sponsor. The vascular relaxation results in increased blood perfusion and may reduce BPH symptoms. Relaxation of stromal smooth muscle of prostate and bladder may complement these vascular effects which might further serve to reduce prostatic urethral resistance to micturition.

4.4.2 Pharmacodynamics

The Sponsor conducted a dedicated study, Study LVHS, to assess the pharmacodynamic effect of concomitant use of alpha adrenergic blocking agents and tadalafil in patients with BPH. In addition pharmacodynamics was assessed across clinical studies relevant to the BPH and BPH/ED indications. These results are discussed in detail in the clinical review.

4.4.3 Pharmacokinetics

As part of the NDA review for NDA 21-368 SE 011, it was noted that the Sponsor stated and the Office of Clinical Pharmacology agreed that repeated doses of once daily tadalafil 2.5 and 5 mg resulted in lower Cmax and total systemic exposure than those following single 10 and 20 mg doses of tadalafil. Therefore, it was agreed that the PK, PD interaction studies performed to support the registration of as-needed 10 mg and 20 mg are applicable to once daily administration of the lower doses. Furthermore, the population PK of tadalafil in subjects with ED has been shown to be similar for as needed and once daily regimens.

All drug-drug interaction studies supporting previous indications for tadalafil included doses of at least 10 mg and generally 20 mg. Both the maximum observed drug concentration (Cmax) and area under the curve versus time curve (AUC) from zero to infinity of both of these doses exceed the Cmax and AUC from zero to 24 hours (AUC_{0-24}) of the tadalafil 5 mg dose at steady state. Therefore, any pharmacologic drug-drug interaction related to plasma concentration expected to occur with the 5-mg once-daily dose should have been observed in single-dose studies of higher doses.

To directly support the BPH indication, 1 additional clinical pharmacology study using a 20-mg dose (CSR LVHN) was conducted, Study LVHN. According to the Sponsor, Study LVHN

demonstrated that there was no clinically or statistically significant difference in the AUC0-24 and Cmax of tadalafil between elderly and young subjects with BPH following single- and multiple-dose administration of tadalafil 20 mg once daily for 10 days. Moreover, no clinically relevant differences in tadalafil exposure or in the pharmacodynamics associated with such exposures were observed between patients with BPH and healthy subjects or between elderly and young subjects.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Summary of Clinical Studies for Tadalafil and BPH and BPH/ED

Study Identifier/Type	Objective	Test Product	Subjects Entered/ Number Completed	Treatment Duration
Phase 1 Clinical Pharmacology				
H6D-EW-LVHN/PK	Tadalafil PK evaluation in young/old men with BPH-LUTS: QD administration	Tadalafil 20 mg po QD for 10 Days	27/27 (15 ≤60 years; 12 ≥70 and ≤85 years)	10 days
Phase 2				
H6D-MC-LVGC ("PiLUTS" - Proof of Concept)	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS	Tadalafil 5 mg QD X 6 weeks Escalated to 20 QD for 6 weeks	281 randomized/ 251 completed	12 weeks
Phase 3				
H6D-MC-LVHG Double-blind Period	Evaluate Efficacy, Dose Response and Safety of Tadalafil in men with BPH-LUTS	Tadalafil 2.5, 5, 10, 20 mg and placebo, QD	1058 randomized/ 886 completed	12 weeks
H6D-MC-LVHJ	Evaluate Efficacy and	Tadalafil 5 mg, Placebo, QD	325 randomized/ 300 completed	12 weeks

	Safety of Tadalafil in men with BPH-LUTS			
H6D-MC-LVHR	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS/ED	Tadalafil 2.5, 5 mg, Placebo, QD	606 randomized/ 526 completed	12 weeks
H6D-MC-LVHS (Primarily Safety)	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS on Alpha Blockers	Tadalafil 5 mg, Placebo, QD	318 randomized/ 280 completed	12 weeks
H6D-MC-LVHK (Safety)	Evaluate Urodynamic Effects of Tadalafil QD on Men with BPH-LUTS	Tadalafil 20 mg QD	200 randomized/ 181 completed	12 weeks
H6D-MC-LVHG Open-Label Extension	Evaluate the Safety of Tadalafil 5 mg QD for 1 year in Men with BPH-LUTS	Tadalafil 5 mg QD	428 randomized/ 299 completed	52 weeks
Foreign Non-IND Studies				
H6D-JE-LVIA	Evaluate Efficacy and Safety of Tadalafil 2.5 and 5 mg in Japanese men with BPH	Tadalafil 2.5, 5 mg and Placebo	422 randomized/ 394 completed	12 weeks
H6D-JE-LVIA Open-Label Extension	Evaluate Long-term Efficacy and Safety of Tadalafil 5 mg QD in Japanese men with BPH	Tadalafil 5 mg	394 randomized/ 323 completed	42 weeks
H6D-MC-	Evaluate	Tadalafil 2.5, 5	612 randomized/ 561	12 weeks

LVHB	Efficacy and Safety of Tadalafil QD in Asian men with BPH-LUTS	mg and Placebo	completed	
H6D-MC-LVHT	Evaluate the Efficacy and Safety of Tadalafil and Tamsulosin QD administered in Korean Men with BPH-LUTS	Tadalafil 5 mg Tamsulosin 0.2 mg	151 randomized/ 143 completed	12 weeks

Source: Table 5.1 Tabular Listing of Studies, Module 5.2, pages 5-14.

5.2 Review Strategy

By prior agreement the efficacy data is to be arrayed and analyzed in the following datasets:

Analysis Sets Supporting the BPH Indication

Analyses supporting the BPH indication use data from the placebo and 5-mg tadalafil treatment groups of Studies LVHJ and LVHG. These data define the **pivotal BPH analysis set.**

Additional analyses for BPH conducted using integrated data from subjects without ED and from the placebo and tadalafil 5-mg treatment groups of studies LVHG and LVHJ and Studies LVHG, LVHJ, and LVHR (additional BPH analysis set of all subjects). Finally, in a separate integration, data from the placebo and tadalafil treatment groups of 2 placebo-controlled studies conducted in Asian countries (Studies LVHT and LVIA) were integrated to evaluate the efficacy of tadalafil in Asian countries (non-IND studies conducted in Asian countries analysis set).

Data from the LVHG open-label extension study comprise the primary long-term exposure analysis set as it relates to persistence of effect. In this open-label extension, subjects previously assigned to placebo, 2.5 mg tadalafil, 5 mg tadalafil, 20 mg tadalafil, or 20 mg tadalafil treatment groups in the double-blind treatment period were administered tadalafil 5 mg.

In a separate integration, data from the placebo and tadalafil 5 mg treatment groups of 2 placebo-controlled studies conducted in Asian countries (Studies LVHT and LVIA were integrated to evaluate the efficacy of tadalafil in subjects in Asian countries **(non-IND studies conducted in Asian countries analysis set).**

Data from the LVIA open-label extension study comprise the long-term exposure analysis set as it relates to persistence of effect in non-IND studies conducted in Asian countries. In the LVIA open-label extension, subjects were administered tadalafil 5 mg.

Analysis Sets Supporting the BPH/ED Indication

Analyses supporting the BPH/ED indication use the **pivotal BPH/ED analysis set** from placebo, 2.5 mg, and 5 mg tadalafil treatment groups of Study LVHR. Study LVHR enrolled subjects presenting with BPH-LUTS and ED.

Additional analyses for the BPH/ED indication are conducted using integrated data from subjects with ED from the placebo and tadalafil treatment groups of Studies LVHG and LVHR, and integrated data from subjects with ED from the placebo and tadalafil 5 mg treatment groups of Studies LVHG, LVHJ and LVHR (**additional BPH/ED analysis set of all subjects with ED).**

Table 4: Clinical Summary of Efficacy Analysis

Analysis Set	Content	Efficacy Outcomes	
		Primary	Secondary
BPH Indication (Tadalafil 5 mg)			
Pivotal BPH	Pivotal BPH Studies LVHG and LVHJ (Integrated 12-week double-blind treatment period data)	Total IPSS	BII
Long-Term BPH	Long-Term Extension (Data from 52-week, open-label extension of Study LVHG)	Total IPSS	BII
Additional BPH All Subjects	Integrated Pivotal BPH and BPH/ED Studies (LVHG, LVHJ, and LVHR) (Integrated 12-week double-blind treatment period data)	Total IPSS	BII
Additional BPH Subjects Without ED	Subjects Without Erectile Dysfunction Integrated Pivotal BPH Studies LVHG and LVHJ (Integrated 12-week double-blind treatment period data)	Total IPSS	BII
Non-IND studies conducted in Asian countries	Non-IND Studies Conducted in Asian Countries Studies LVIA and LVHT (Integrated 12-week double-blind treatment period data)	Total IPSS	NA
Non-IND Long-Term	Long-Term Extension (Data from 42-week, open-label extension of Study LVIA)	Total IPSS	NA
BPH/ED Indication (Tadalafil 2.5 and 5 mg)			
Pivotal BPH/ED	Pivotal BPH/ED Study LVHR (12-week double-blind treatment period data)	Total IPSS, IIEF EF	BII, SEP Q3
Additional BPH/ED Subjects With ED	Subjects With Erectile Dysfunction Integrated Studies LVHG and LVHR (Tadalafil 2.5 mg versus placebo; integrated 12-week double-blind treatment period data); Integrated Pivotal BPH and BPH/ED Studies LVHG, LVHJ, and LVHR (Tadalafil 5 mg versus placebo; integrated 12-week double-blind treatment period data)	Total IPSS, IIEF EF	BII[b]

Clinical Summary of Efficacy Analysis Sets (Concluded)

Abbreviations: BPH = benign prostatic hyperplasia; BII = BPH impact index; ED = erectile dysfunction; IIEF EF = international index of erectile function - erectile function domain; IND = investigational new drug; IPSS = international prostate symptom score; NA = not applicable; SEP Q3 = Sexual Encounter Profile Question #3.

[a] Designation of primary and secondary measures relate to the presentation in this Clinical Summary of Efficacy and not necessarily that of the individual study or studies.

[b] The Sexual Encounter Profile diary was not collected in Studies LVHG and LVHJ.

Source: Copy of Table 2.7.3.2, Clinical Summary of Efficacy, current submission, page 27.

By prior agreement safety data will be analyzed in the following datasets:

BPH Indication

For the BPH indication, the primary safety analysis set contains integrated data from the 12-week, double-blind, placebo-controlled Studies LVHG and LVHJ (the BPH "pivotal" studies), and is to be referred to as the **pivotal BPH analysis set**. Long term safety data is presented in the 1 year open-label extension period of Study LVHG. Data form BPH safety studies LVHK and LVHS and from the clinical pharmacology Study LVHN are presented separately.

As requested by the Division, the Pre-NDA Meeting, 24 August 2010, the following additional BPH analysis sets are summarized in this submission:

- **Additional BPH analysis of all subjects**: Contains integrated data from the 12 week, double-blind, placebo-controlled periods of LVHG, LVHJ, and LVHR (includes the two BPH pivotal studies and the single "BPH/ED" pivotal study).
- **Additional BPH analysis set of subjects without ED**: Contains integrated data from the placebo-controlled Studies LVHG and LVHJ for subjects who did not report ED.
- Additional age group analysis set containing integrated data from all doses in Studies LVHG, LVHJ, LVHK, and LVHR. Due to differences in dose, duration, and study design, Study LVHN is displayed separately.
- Additional age group analysis set containing integrated data from the placebo-controlled Studies LVHG, LVHJ and LVHR.
- **Non-IND studies conducted in Asian countries** (LVIA and LVHT): Contains integrated data from placebo-controlled Studies LVIA and LVHT and from the open-label extension period of Study LVIA. The results to Study LVHB were not integrated with the other non-IND Asian studies; as agreed upon with the Division, the LVHB CSR is included separately with this submission.

BPH/ED Indication

For the BPH/ED indication, the primary safety analysis set contains data from the 12-week, double-blind, placebo-controlled Study LVHR and is referred to as the **pivotal BPH/ED analysis set.**

As requested by the Division at the pre-NDA meeting, 24 August 2010, the **additional BPH/ED analysis set of subjects with ED** contains integrated data from placebo-controlled Studies LVHG, LVHJ, and LVHR for subjects who reported ED and supports the BPH/ED indication.

Table 5: Safety Data Analysis Sets

Analysis Sets	Content	Treatment Group
Analysis Sets Supporting the BPH Indication		
Pivotal BPH analysis set	Integrated data from Studies LVHG and LVHJ	Placebo and tadalafil 5 mg
Pivotal long-term analysis set	Data from 1-year OLE period of Study LVHG	Tadalafil 5 mg
Additional BPH analysis set of all subjects	Integrated data from Studies LVHG, LVHJ, and LVHR (all subjects)	Placebo and tadalafil 5 mg
Additional BPH analysis set of subjects without ED	Integrated data from Studies LVHG and LVHJ (subjects who did not report ED)	Placebo and tadalafil 5 mg
Additional BPH age-group analysis sets	1) Integrated data from Studies LVHG, LVHJ, and LVHR 2) Integrated data from Studies LVHG, LVHJ, LVHR, and LVHK; Study LVHN[a]	1) Placebo and tadalafil 5 mg 2) Placebo and tadalafil 2.5, 5, 10, and 20 mg
Non-IND studies conducted in Asian countries	1) Integrated data from Studies LVIA and LVHT 2) Data from the 42-week OLE period of Study LVIA	1) Placebo and tadalafil 5 mg 2) Tadalafil 5 mg
Analysis Sets Supporting the BPH/ED Indication		
Pivotal BPH/ED analysis set	Study LVHR	Placebo and tadalafil 2.5 and 5 mg
Additional BPH/ED analysis set of subjects with ED	Integrated data from Studies LVHG, LVHJ, and LVHR (subjects who reported ED)	Placebo and tadalafil 2.5 and 5 mg

Abbreviations: BPH = benign prostatic hyperplasia; ED = erectile dysfunction; IND = Investigational New Drug; OLE = open-label extension.

[a] For the age-group analysis, Study LVHN was not integrated with the other studies due to differences in dose, duration, and study design, and results are displayed separately. Study LVHS was not included in this analysis set due to confounding study design (co-administration of alpha-blocker therapy).

Source: Copy Table 2.7.4.2, Clinical Summary of Safety current submission, page 16.

Safety was analyzed encompassing all the data sets.

In addition there are special safety topics that were evaluated in the following studies:

- LVHK: urodynamic effects of tadalafil
- LVHS: safety of tadalafil once daily for 12 weeks in men with BPH-LUTS on concomitant alpha-blocker therapy
- LVHN: evaluate the pharmacokinetics and hemodynamics of tadalafil 20 mg administered once daily in elderly (70 to 85 years of age [12]) and young (below and including 60 years of age[15]) subjects with BPH-LUTS

Adverse events relating to the following Special Safety topics were evaluated:

- Bleeding Events
- Cardiovascular Events
- Ear Disorders
- Eye Disorders
- Treatment-Emergent Event Possibly Related to Hypotension, Including Headache, Asthenia, and Fatigue
- Myalgias and Back Pain
- Seizures
- Transient Global Amnesia

Safety in Special Groups and Situations were analyzed under the following headings:

- Ethnicity
- Diabetes
- Renal Impairment
- Hepatic Impairment
- Extrinsic and Intrinsic Factors

Additional safety analysis was done in the following situations:

- Co-administration and prior use of alpha-blocker therapy
- AEs by prior PDE5 Inhibitor Therapy

For this application, particular attention was directed to ascertain any differences in the safety profile relative to tadalafil exposure in patients with BPH or BPH/ED and by age.

5.3 Discussion of Individual Studies/Clinical Trials

Study LVHG: A Randomized, Double-Blind, Placebo Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia

Study LVHG was a pivotal, Phase 2b/3, randomized, double-blind, placebo-controlled, parallel-design, dose-finding study to evaluate the efficacy, dose response, and safety of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks versus placebo in men with BPH-LUTS. The study enrolled subjects ≥45 years old who presented with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Lower urinary tract symptoms were assessed by the IPSS, consisted of 7 questions regarding urinary storage and voiding symptoms. The first subject was enrolled 15 August 2006 and the last subject completed the study 17 October 2007.

Key inclusion criteria were total IPSS≥13 and peak flow rate (Qmax) ≥ and ≤15 mL/sec at the start of the placebo lead-in period. Notable exclusion criteria included prostate-specific antigen (PSA) values >10 ng/mL (men with a PSA of 4 to 10 ng/mL were required to have a prostate biopsy negative for malignancy within the preceding 12 months), clinical evidence of urinary tract infection/inflammation at screening , a post-void residual (PVR) volume ≥300 mL at screening, clinical evidence of prostate cancer, and finasteride or dutasteride treatment within 3 and 12 months before the start of the placebo lead-in period, respectively. Subjects were excluded if they had evidence of New York Heart Association [NYHA] ≥Class III congestive heart failure within 6 months of screening. There were no specific blood pressure enrollment high and low limits. Subjects with a history of significant renal insufficiency defined as renal dialysis or having an estimated creatinine clearance <50 mL/min at screening as calculated by the Cockcroft-Gault formula, were also excluded from study participation.

The study consisted of 3 periods:

1. Screening/Wash-Out Period: Subjects were to sign an informed consent document (ICD) at Visit 1 prior to participating in any study procedures. The first period consisted of 1 to 4 weeks of screening (and if needed, a 4-week wash out of BPH treatments listed in inclusion criterion [4]) to assess symptoms and uroflowmetry in the absence of therapy. Those not taking prohibited BPH treatments were allowed to begin the next study period after screening results were reviewed.

2. Placebo Run-In Period: After the screening/wash-out period, subjects were to return for Visit 2 to assess whether eligibility criteria were met before proceeding to the placebo run-in period. Visit 2 inclusion criteria included an IPSS ≥13 and urinary peak flow rate (Q_{max}) ≥4 to ≤15 mL/second (from a prevoid total bladder volume [assessed by ultrasound] ≥150 to ≤550 mL and a minimum voided volume of 125 mL). Eligible subjects were to begin a 4-week, single-blind, placebo run-in period to assess treatment compliance and to establish baseline measures at its conclusion.

3. Treatment Period: At Visit 3 (randomization), eligible subjects were to be randomly assigned to treatment (tadalafil 2.5, 5, 10, 20 mg, or placebo) in a 1:1:1:1:1 ratio. The treatment period lasted 12 weeks. Subjects were to return on Visit 4 (Week 4), Visit 5 (Week 8), and Visit 6 (Week 12) to assess treatment compliance and measures of the study endpoints. Visit 6 (Week 12) was the end-of-study visit (study termination).

Randomization was stratified by baseline LUTS severity (total IPSS <20 or ≥20), geographic region (US/Canada, Latin America [Mexico], Europe [France, Germany, Greece, Italy, Spain, and Sweden], and Australia), and history of ED. Randomization was on a 1:1:1:1:1 ratio. 1056 subjects were randomized. 886 subjects completed the study (701 tadalafil and 185 placebo). 540 randomized patients were from the United States.

The 1056 subjects randomized for treatment had similar demographics between the treatment groups. The mean age of subjects was approximately 62 years (range: 45 to 92 years) and were predominantly Caucasian (85.6%). Two hundred ninety-four subjects (27.8%) had used previous therapy for BPH and 348 subjects (33.0%) had used previous therapy for ED. Five hundred forty-one subjects reported experiencing LUTS for >3 years and 354 subjects (33.5%) were classified as having severe LUTS (by International Prostate Symptom Score [IPSS]). At baseline, 67.8% of subjects reported a history of ED and 26.9% of subjects reported having used previous therapy for ED. Of those subjects with a history of ED at baseline, 84.8% reported ED duration of ≥1 year. The majority of subjects reported moderate severity (54.5%). There were 80.6% of subjects reporting that they were sexually active with a female partner and 55.0% reported that they were sexually active and had ED.

The majority of randomized patients (83.7%) completed the 12-week treatment comparison period. The most common reasons for discontinuation among all tadalafil-treated patients were AEs (41;4.8%) and subject decision (36;4.3%). In placebo-treated subjects, 9 (4.3%)

discontinued due to subject decision and 5 (2.4%) discontinued to both AE's and lost to followup.

Reviewer's Comment: Number of discontinuation with 2.5mg daily was the same as with placebo. Overall subject discontinuation increased with increasing tadalafil dose.

Table 6: Subject Disposition Study LVHG

1058 Subjects Randomized					
1056 Subjects Received Study Drug					
	Placebo (n=211)	Tadalafil 2.5 mg (n=208)	Tadalafil 5 mg (n=212)	Tadalafil 10 mg (n=216)	Tadalafil 20 mg (n=209)
Subjects discontinued	26	26	30	41	47
Adverse event	5	4	12	11	14
Entry criteria not met	2	6	7	8	4
Lack of efficacy	1	1	2	1	2
Lost to followup	5	3	0	4	6
Protocol violation	1	0	1	6	4
Physician decision	0	1	1	0	1
Sponsor decision	3	4	0	5	0
Subject decision	9	7	7	6	16

Source: Figure LVHG 10.1, H6D-MC-LVHG Study Report, page 72.

The primary objective of Study LVHG was to evaluate the efficacy of tadalafil 5 mg once daily for 12 weeks compared to placebo in improving total IPSS in men with BPH-LUTS.

The secondary efficacy objectives included:

- Examining whether a dose-response relationship exists for placebo and tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks in the treatment of BPH-LUTS.
- Evaluating the efficacy of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks compared to placebo in the treatment of BPH-LUTS as assessed by the following measures:
    - Total IPSS (for tadalafil 2.5-, 10-, and 20-mg doses);
    - IPSS storage and voiding subscores and nocturia question;
    - BII;
    - LUTS-General Assessment Questions (GAQ);
    - Uroflowmetry parameters, including Qmax, mean flow rate (Qmean), and voided volume (Vcomp); and
    - IIEF EF Domain score in sexually active men with ED.

The analysis of efficacy data is conducted using the following general considerations:

- Primary and secondary efficacy outcomes are analyzed on intent –to- treat basis.

- Subjects included in the efficacy analysis are referred to as the Primary Analysis Population.
- Analysis of covariance (ANCOVA) is the primary analysis methods used to evaluate continuous efficacy data. Treatment differences are examined based on Type III sums of squares and associated two-sided p-values.
- Both last-observation-carried-forward (LOCF) and mixed model repeated measures (MMRM) methods are used to handle missing data in the statistical models. For analyses of change from baseline to Weeks 4 and 8 post baseline, no imputation for missing data is applied.
- Missing responses to any individual IPSS or BII question are not imputed for analysis. If a subject had a missing response to any IPSS question(s) at a specific visit, the total IPSS and any subscore containing said question(s) are missing at that visit. If a subject had missing responses to any individual BII question at a specific visit, the BII score is missing at that visit.
- If the score of a component question of the IIEF EF Domain score is missing at a specific visit, the missing score is imputed with the mean of non missing scores at that visit, rounded to the nearest integer. If 2 or more component questions for the IIEF EF Domain score are missing at a visit, the IEFF EF Domain score is treated as missing for that visit.

In Study LVHG, across the treatment groups, 90.0% to 95.0% of subjects were ≥70.0% compliant with study drug treatment. Subjects were considered to be compliant for enrollment purposes with minimum dosing requirements if they administered ≥70% of prescribed doses between Visit 2 and Visit 3, which were confirmed by documentation that the subject returned ≤30% of prescribed doses at the Visit 3 study drug reconciliation. Compliance was assessed for the treatment period of Visit 3 through Visit 6.

The primary efficacy outcome was the change in IPSS total from baseline to Visit 6 (Week 12) for subjects taking tadalafil 5 mg once-daily versus placebo. These results are a shown in the table below:

Table 7: IPSS (International Prostate Symptom Score) Test Results (Tadalafil 5-mg versus Placebo) All Randomized Subjects in the Primary Efficacy Analysis Population (Study LVHG)

Parameter at Time Point	Placebo (N=210)	Tadalafil 5 mg (N=212)
Change from Baseline		
n	205	205
Mean (SD)	-2.25(6.17)	-4.92(5.67)
Treatment p-value	<0.01	
Endpoint		
n	205	205
Mean(SD)	14.83(7.69)	12.38(7.23)
Baseline		
n	205	205
Mean(SD)	17.08(6.36)	17.30(5.97)

Source: Table LVHG.11.10, H6D-MC-LVHG Study Report, page 92.
The results of the secondary efficacy endpoints are shown below:

Table 8: Efficacy Outcomes All Randomized Subjects in the Primary Analysis Population Study LVHG

	Placebo N=210	Tadalafil 2.5mg N=208		Tadalafil 5mg N=212		Tadalafil 10mg N=216		Tadalafil 20mg N=208	
Outcome	n LS Mean (Δ BL)	Treatment Difference LS Mean	p-value	Treatment Difference LS Mean	p-value	Treatment Difference LS Mean	p-value	Treatment Difference LS Mean	p-value
Total IPSS	205 -2.23	-1.58	.005	-2.60	<.001	-2.90	<.001	-2.94	<.001
BII	205 -0.83	-0.13	.583	-0.57	.013	-0.55	.016	-0.62	.007
IPSS Storage	205 -0.98	0.57	.025	-0.90	<.001	-0.96	<.001	-1.07	<.001
IPSS Voiding	205 -1.31	-0.97	.008	-1.69	<.001	-1.89	<.001	-1.87	<.001
IPSS Nocturia	205 -0.30	-0.07	.503	-0.13	.206	-0.08	.452	-0.26	.012
IPSS QoL	205 -0.52	-0.26	.029	-0.37	.002	-0.43	<.001	-0.40	<.001
IEFF EF Domain	113 2.04	3.36	<.001	4.75	<.001	7.87	<.001	6.15	<.001

Source: Table 2.7.3.3, Summary of Clinical Efficacy, Current Submission, page 38

Reviewer's Comment: Tadalafil 5 mg once daily favorably alters in a significant manner the primary efficacy endpoint. A dose effect is noted up to 10 mg a day dosing, but the increase in

IPSS in the 10 mg versus 5 mg once daily dosing is small. The same is true for the IPSS storage, and voiding domains. The BII was marginally significantly statistically improved and nocturia domain was not significantly statistically improved. The IIEF EF domain was favorably changed in a statistically significant manner showing dose effect across all doses except tadalafil 20 mg.

With respect to peak flow rate, there were small improvements in the median changes from baseline for tadalafil 2.5 mg (1.10 mL/second), 5 mg (1.15 mL/second), 10 mg (1.30 mL/second, and 20 mg (1.65 mL/second) when compared to placebo but the differences observed were not statistically significant. There were numeric improvements in mean change from baseline to endpoint observed in all treatment groups.

There were 581 subjects with a history of ED who indicated they were sexually active with a female partner, thus being eligible to complete the IIEF questionnaire; of those subjects, 557 completed at least 1 post-randomization IIEF questionnaire. Non-parametric permutation tests comparing tadalafil (2.5, 5, 10, and 20 mg) once-daily versus placebo were performed for the IIEF EF Domain. Median change from baseline for tadalafil 2.5 mg (3.00; p=0.0013), 5 mg (4.00; p<0.001), 10 mg (5.00; p<0.001), and 20 mg (6.00; p<0.001) was significantly different compared with placebo (1.00).

Table 9: LVHG IIEF Erectile Function Domain ANCOVA of Change from Baseline to End of Therapy (Subjects with History of ED)

Treatment Group	Time Point	n	Mean	p-value
Placebo (N=114)	Baseline	113	17.26	
	Endpoint	113	18.04	
	Change	113	0.78	
Tadalafil 2.5 mg	Baseline	109	17.42	<.001
	Endpoint	109	21.39	
	Change	109	3.97	
Tadalafil 5 mg	Baseline	113	15.29	<.001
	Endpoint	113	21.85	
	Change	113	6.56	
Tadalafil 10 mg	Baseline	113	17.22	<.001
	Endpoint	113	23.86	
	Change	113	6.64	
Tadalafil 20 mg	Baseline	109	16.28	<.001
	Endpoint	109	23.72	
	Change	109	7.44	

Source: Adapted from Table LVHG 11.19, H6D-MC-LVHG Study Report, page 113

Reviewer's Comment: Efficacy for ED in this patient population is demonstrated.

Safety

Drug exposure was evaluated for 1056 randomized subjects (2 subjects were discontinued from the 1058 subjects randomized for treatment prior to receipt of drug). The tadalafil and placebo groups had similar durations of exposure and mean doses per week. Mean duration of therapy for each tadalafil treatment group ranged from 80-84 days. Mean number of doses received for each tadalafil treatment group per week ranged from 6.4 to 6.6 doses.

There were no deaths reported during the study. A total of 279 (33.0%) of all tadalafil-treated subjects reported experiencing at least 1 TEAE compared to 45 (21.2%) placebo-treated patients. The incidence of subjects with 1 or more TEAE increased with increasing tadalafil dose. Forty-one subjects (4.8%) in the combined tadalafil treatment group and 5 subjects (2.4%) in the placebo treatment group discontinued due to an adverse event. Discontinuations due to an AE were more frequent among subjects in the tadalafil treatment groups of ≥5mg once -daily dosing compared to placebo. There was no difference in number of SAEs between placebo and tadalafil dose groups.

Table 10: Overview of Adverse Events Study LVHG

Adverse Events	Placebo (N=212)	IC 2.5 mg (N=209)	IC 5 mg (N=212)	IC 10 mg (N=216)	IC 20 mg (N=209)	Tadalafil (N=846)
	n (%)					
Deaths	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SAEs	6(2.8)	3(1.4)	1(0.5)	2(0.9)	5(2.4)	11(1.3)
Discontinuation AE	5(2.4)	1(1.9)	12(5.7)	11(5.1)	14(6.7)	41(4.8)
TEAE	18(8.5)	56(26.8)	65(30.7)	75(34.7)	83(39.7)	279(33.0)

IC=tadalafil Source: Table LVHG 12.2, H6D-MC-LVHG Study Report, page 132.

Table 11: Treatment-Emergent Adverse Events by Decreasing Frequency of Occurrence in Greater than 2% of Subjects in any Tadalafil Group in Study LVHG

	Placebo (N=212)	IC 2.5 mg (N=209)	IC 5 mg (N=212)	IC 10 mg (N=216)	IC 20 mg (N=209)	Tadalafil (N=846)
	n (%)					
Subjects with ≥ TEAE	45 (21.2)	56 (26.8)	65 (30.7)	75 (34.7)	83 (39.7)	279(33.0)
Headache	6 (2.8)	5 (2.4)	6(2.8)	11 (5.1)	7 (3.3)	29 (3.4)
Dyspepsia	0 (0.0)	2 (1.0)	10 (4.7)	6 (2.8)	10 (4.8)	28 (3.3)
Back Pain	1 (0.5)	3 (1.4)	2 (0.9)	10 (4.6)	12 (5.7)	27 (3.2)
Myalgia	0 (0.0)	3 (1.4)	3 (1.4)	6 (2.8)	6 (2.9)	18 (2.1)
Nasopharyngitis	2 (0.9)	7 (3.3)	4 (1.9)	2 (0.9)	5 (2.4)	18 (2.1)
Diarrhea	3 (1.4)	2 (1.0)	6 (2.8)	3 (1.4)	2 (1.0)	6 (2.8)
GE Reflux	0 (0.0)	2 (1.0)	2 (0.9)	6 (2.8)	3 (1.4)	13 (1.2)
Pain in Extremity	0 (0.0	3 (1.4)	5 (2.4)	2 (0.9)	3 (1.4)	13 (1.5)
Influenza	1 (0.5)	4 (1.9)	4 (1.9)	1 (0.5)	2 (1.0	11 (1.3)
Bronchitis	1 (0.5)	3 (1.4)	1 (0.5)	5 (2.3)	0 (0.0)	9 (1.1)
Muscle Spasms	0 (0.0)	2 (1.0)	0 (0.0)	2 (0.9	5 (2.4)	9 (1.1)

Source: Table LVHG 12.3, H6D-MC-LVHG Study Report, page 134.

Narratives of SAEs in patients taking study drug:

Subject LVHG 1011166: The subject is a 93 year-old US Caucasian male. Relevant medical history was not provided. Concomitant medications included a multivitamin and acetylsalicylic acid for prophylaxis. Approximately two weeks after starting the study medication (tadalafil 2.5 mg daily), while performing heavy manual labor including digging out tree roots, experienced a myocardial infarction. The study medication was stopped. Additional information was requested, but is not in the report.

Subject LVHG 1071726: The subject is a 73 year-old US Caucasian male. Relevant medical history includes hypertension, hypercholesterolemia, gastroesophageal reflux disease, sinus congestion, knee arthritis, knee joint pain and back pain. Concomitant medications include atenolol, multivitamins, glucosamine with chondroitin sulfate, lisinopril, lovastatin, Nasarel, omeprazole, and vitamin C. The patient on the third day of dosing (tadalafil 2.5 mg daily) at Visit 4 reported being diagnosed with "atrial tachycardia" (His ECG at Visit 1 revealed sinus bradycardia). The patient was hospitalized on the third day of dosing for atrial tachycardia. No laboratory data was reported. The event ended 20 days later. The patient received only three daily doses of study drug. The patient withdrew from the study upon the advice of his primary care physician.

Subject LVHG 110 2027: The subject is a 61 year-old US Caucasian male who was randomized to tadalafil 5 mg daily. His relevant medical history included coronary artery disease, hypertension and diabetes mellitus. Concomitant medications were pantoprazole,

metformin/rosiglitazone, clopidogrel, acetylsalicylic acid, fenofibrate, and benazepril/hydrochlorthiazide. On 9 January 2007, the patient received the blinded study medication. On 26 January, 2007, approximately 11 weeks after initiation of therapy, the patient experienced severe abdominal pain radiating into his back. The patient was admitted to the hospital on (b) (6) with the diagnosis of pancreatitis and cholecystitis (confirmed (b) (6) (b) (6)). He never recovered from his abdominal discomfort. A hepatobiliary (HIDA) scan was performed on (b) (6), and on (b) (6), the patient underwent a cholecystectomy. On (b) (6) he underwent endoscopic retrograde cholangiopancreatography (ERCP) and repair of a cystic duct stump leak. On (b) (6), after the abdominal drain was removed, the patient became febrile to 104.6 degrees F. and was hospitalized to receive i.v. antibiotic therapy for a liver bed abscess which was reported resolved (b) (6). The patient was discharged from hospital on home antibiotic therapy (b) (6). On an unspecified date, the study medication was permanently discontinued.

Reviewer's Comment: This SAE occurred in association with acute cholecystitis which I cannot attribute to study drug.

Subject LVHG 1233320: The subject is a 62 year-old US Caucasian male randomized to 2.5 mg tadalafil daily and started treatment on 25 June 2007. A review of medical history per the patient's hospitalizations noted a history of former tobacco usage 30 years ago, benign prostatic hypertrophy, sinusitis, and gastroesophageal reflux disease. There were no concomitant medications. On (b) (6), he was seen in the emergency room for a kidney stone and released with pain medication and no antibiotics. It was noted that the patient had a 2mm right ureteropelvic junction calculus with obstruction and right calyceal rupture with acute renal insufficiency. On (b) (6) after receiving the first dose of blinded study drug, the patient noted increased right upper quadrant pain and fever. His primary care physician hospitalized him and began intravenous Levaquin therapy. His creatinine was elevated at 2.1. Blood cultures obtained at hospital admission showed no growth. An abdominal-pelvic CT confirmed the presence of a 2 mm right uretero-vesical junction calculus without evidence of hydronephrosis. A left simple renal cyst was noted. The patient underwent holmium laser lithotripsy of the calculus and a right ureteral stent insertion. A small bladder tumor overlying the left ureteral orifice was noted and resected. At discharge (b) (6), his creatinine was 1.3. The study drug was permanently discontinued 9 August 2007. Additional information obtained 4 September 2007, was that all medical issues had resolved. The tumor histology report is not included in the report.

Subject LVHG 1334313: The subject is a 72 year-old US Caucasian male randomized to receive 20 mg of tadalafil daily. His reported medical history includes elevated cholesterol and hypertension. He also has a history of osteoarthritis in both knees with pain since 1995. His concomitant medications include hydrochlorthiazide/losartan and clonidine for hypertension, simvastatin, and celecoxib (discontinued 24 July 2007) and naproxen. On 30 June 2007 the patient began treatment with the study drug. On (b) (6) the patient was hospitalized for a left total knee replacement for worsening arthritis. He continued to use the study drug.

Subject LVHG 1415106: The subject is a 65 year-old US Caucasian male randomized to receive 10 mg of tadalafil daily. He had a history of arthritis for many years but had never taken medication for it. He began study drug on 22 February 2007. At Visit 10 (14 November 2007), he informed site staff that he had had a right knee replacement for worsened arthritis and repair of a torn left meniscus. The patient completed the study.

Subject LVHG 3152555: The patient is a 61 year-old Greek Caucasian male randomized to receive 20 mg of tadalafil daily. Past medical history includes hypertension and bilateral cataract surgery. There is no past medical history of back pain. Concomitant medications include Azopt and Xalcom as eye medications and irbesartan and hydrochlorthiazide. On 22 March 2007, the patient was first administered the study drug. On 3 May 2007, 43 days after starting the study drug, the patient experienced severe backache. The patient was treated only with 500 mg paracetamol 500 mg three times a day on 12 May 2007 and 13 May 2007. The investigator noted that the event improved when the study drug was stopped on 14 May 2007. It was also reported that the pain reappeared when the study drug was restarted on an unspecified date. These events resulted in permanent discontinuation of the patient from the study drug on 14 May 2007.

Subject LVHG 3465654: The subject is a 66 year-old Swedish Caucasian male randomized to receive 20 mg of tadalafil daily. The patient's medical history included a common cold and that he was a marathon runner. There were no reported medical risk factors. On 23 May 2007, the patient received the blinded study drug for the treatment of BPH. The last dose of study drug prior to the acute event was 23 August 2007. On 7 October 2007, is noted that the patient had a 9 week history of dizziness, dyspnea, dyspepsia, and flatus with worsening of this symptoms over the last five weeks. An ECG at Visit 6 revealed bradycardia, atrial fibrillation and atrial flutter. The blood pressure was 125/80. On (b) (6) the patient was hospitalized with heart failure and suspected pulmonary embolism. Chest x ray and CT scans did not document a pulmonary embolism. An echocardiogram showed left ventricle hypertrophy and pulmonary hypertension. Fibrinogen and d-dimer lab tests are not included in the report. Liver enzymes were normal, CK was 245 (normal 19-199). No deep venous problems were reported. The ECG and stress ECG showed an atrioventricular interval block plus II block Wenckebach. Holter monitoring showed bradycardia with sleep. The patient was suspected to have sarcoidosis and amyloidosis in relation to heart failure. This was ruled out with a negative biopsy. The events of heart failure with suspected pulmonary embolism were still ongoing and had not improved after study drug discontinuation (Patient completed the study. Treatment stop and last visit date 10 September 2007. At that visit 28 doses of study medication were returned.). This report includes updates through 7 February 2008.

Subject LVHG 2041420: The subject is a 67 year-old male with essentially a negative medical history aside from smoking 1 cigarette a day. He was randomized to tadalafil 10 mg a day. Approximately 12 weeks after receiving the first dose of study drug, he was hospitalized with unstable angina. He underwent an angioplasty. The findings at angioplasty were proximal "roughening" of 20% of the right coronary artery, the left anterior descending(LAD) artery was 80% narrowed proximally and there was 60-75 narrowing at the origin of the first diagonal and 60-75% narrowing of the proximal septal vessel. "Roughening" was noted in the distal LAD in

the circumflex. Angioplasty without stent was performed on the LAD. The patient went on to complete the study.

Subject LVHG 4006007: The subject is a 56 year-old German Caucasian male. His relevant medical history includes BPH for 6 years and ED. His tadalafil 20 mg daily treatment started 10 April 2007. The patient at that time was taking tamsulosin. He had previously been taking tadalafil from 5 December 2006 until 28 December 2006. From the third day of treatment "the patient experienced pain in the whole body, anginose pain [my interpretation=chest pain] and since 11 May 2006, headache." On 11 May 2007, an NMRI was performed due to headache and right arm weakness which revealed an "insult to the pons" estimated to have occurred 4 weeks prior. An orthopedic exam did not reveal "any organic reasons" for the right arm weakness and paralysis. On 13 April 2007, tachycardia and chest pain was not verified with a cardiologist examination. ECG and echocardiography "were without pathological findings." CK was elevated 3 May 2007 (339 [normal< 198]) but was modestly elevated 27 February 2007. The blood pressure was not elevated at the time of the acute event. The patient was permanently discontinued.

Subject LVHG 4096925: The subject is a 68 year-old German Caucasian male with BPH for 4 years and known 1 vessel coronary artery disease (CAD). Past medical history includes type II diabetes mellitus, arterial hypertension, tinnitus, arteriosclerosis and obesity. His concomitant medications include: felodipine/ramipril, moxonidine, hydrochlorthiazide, and metformin. He was randomized to tadalafil 20 mg once daily. Three months after receiving the first dose of study drug (exposure day 62, 20 June 2007)), he was hospitalized for the placement of a coronary stent for a 75% stenosis of the "proximal ramus circumflexis (RCX)." There was also 30% stenosis in the right medial coronary artery (RCA). The indication for the intervention was a positive thallium scan. The drug was permanently discontinued. The last drug administration was 18 June 2007. The event was considered recovered on 20 June 2007.

> *Reviewer's Comment: Worsening of arthritis and the need for knee replacement therapy occurred in 2 placebo subjects (1384837 and 1415102). One placebo patient experienced rheumatoid pain (6001081). One placebo patient required coronary artery angioplasty or stent insertion (3091952). A single placebo patient (4066610) had renal colic and urinary retention leading to TURP. One placebo patient sustained a CVA (4006007). The SAEs are similar in type between placebo and active drug and the overall incidence of SAEs is not increased in the tadalafil group versus placebo. I see no discernible safety signal.*

Table 12: Adverse Events Leading to Discontinuation Study LVHG

	Placebo (N=212)	IC 2.5 mg (N=209)	IC 5 mg (N=212)	IC 10 mg (N=216)	IC 20 mg (N=209)	Tadalafil (N=846)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subject with >= 1AE Discontinuing	5 (2.4) 4	4 (1.9)	12 (5.7)	11 (5.1)	14 (6.7)	41 (4.8)
Back Pain	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	5 (2.4)	8 (0.9)
Myalgia	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	4 (1.9)	7 (0.8)
Headache	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)	2 (1.0)	5 (0.6)
Abdominal Pain	2 (0.9	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.2)
Dyspepsia	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.2)
GE Reflux	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.2)
Dizziness	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Muscle Spasms	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Myocardial Infarction	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Edema Peripheral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Esophagitis	0 (0.0	0 (0.0)	0 (0.0	0 (0.0)	1 (0.5)	1 (0.1)
Pain	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Pain in Extremity	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Pancreatitis	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
PSA Increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Retinal Tear	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Rotator Cuff Syndr.	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Syncope	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ureteric Rupture	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Coronary Art. Stenosis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Pain	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

IC=tadalafil Source: Table LVHG, H6D-MC-LVHG Study Report, page 139.

Reviewer's Comment: It is of note that the number of subjects discontinuing with an AE was the same for 2.5 mg and 5 mg daily as for placebo, then increases with increasing dose of tadalafil. It is also noted that the difference in the above AEs leading to discontinuation is driven by the categories of back pain, myalgia, headache and dyspepsia which are known adverse events with tadalafil.

The discontinuation narratives for Patient 1011166 (myocardial infarction), Patient 1233320 (ureteric rupture), and Patient 11002027 (pancreatitis) can be found in the narratives for LVHG SAEs. I have chosen to add selected AE discontinuation narratives as shown below:

LVHG Patient 1243419: The patient is a 67 year-old US Caucasian male with a medical history of BPH, hypertension and dyslipidemia. He was on multiple medications including allopurinol, aspirin, folic and nicotinic acid, clopidogrel, rosuvastatin and lisinopril. During the placebo lead-in phase of study period II he experienced a syncopal episode and was hospitalized for 23 hours. A CAT and NMRI scans of were within normal limits. The patient was not receiving tadalafil at the time of the adverse event.

LVHG Patient 6001002: The patient is a 70 year-old Australian Caucasian male who was randomized to receive 2.5 mg of tadalafil daily. The patient's medical history includes asthma, bronchiectasis, hypertension, and retinal degeneration. His concomitant medications include verapamil, candesartan, doxycycline, esomeprazole, budesonide w/formoterol (Symbicort 400 mcg and 12 mcg/day), and nedocromil sodium. The patient started treatment on 17 May 2007. On 29 May 2007, the patient had 1 episode of fainting at 5 am. There is no narrative detail of this event. The blood pressures at Visits 1, 2, and 3 were 142/82, 125/90, and 124/90 mm Hg respectively. There is no blood pressure data at the time of the acute event. The outcome is not documented. Treatment stopped 30 July 2007 and 35 doses of study drug were returned at that time.

The Sponsor has analyzed adverse events related to the cardiovascular system and reported "8 subjects reporting 8 events (5 terms; MI: 1 event [tadalafil 2.5 mg]; coronary arterial stent insertion: 1 event [tadalafil 20 mg]; unstable angina: 1 event [tadalafil 10 mg]; chest pain: 3 events [tadalafil 5 mg]; musculoskeletal chest pain: 2 events [1: placebo and 1: tadalafil 10 mg])." The narratives for Subjects 101-1166, 204-1420 and 409-6925 have been discussed in SAEs and discontinuation. Subjects 1091913 and 1142403 appeared to have musculoskeletal chest pain.

LVHG Subject 101-1169, a 56-year-old subject receiving tadalafil 5 mg, experienced chest pain and headache with an onset 3 days after randomization lasting 7 days. There was no change in ECG (unchanged from abnormal at Visit 1 to abnormal at the last visit). The ECG at Visit 1 was left axis deviation, abnormal conduction, and right bundle-branch block. At the subject's last visit, the ECG reading was left axis deviation, abnormal conduction, right bundle-branch block, and early R wave progression. Blood pressure at Visit 3 was 116/80 mm Hg and 112/60 mm Hg at Visit 4 (first time assessed after onset of the event). Historical diagnoses for this subject included arthroscopic knee surgery and hernia repair. Preexisting conditions for this subject included hypercholesterolemia and ED. The subject was discontinued from the study due to a non-cardiac-related AE (headache).

The Sponsor has also analyzed AEs by special safety topics and has presented additional narratives which are discussed below.

Sponsor has also identified "3 subjects (1 subject each: tadalafil 2.5, 5, and 20 mg) had a total of 3 event terms identified reflecting tachyarrhythmia in the Study LVHG safety database (tachycardia and atrial tachycardia)." Subject 1071726 was discussed previously under discontinuations.

LVGH Subject 411-7100, a 55-year-old subject receiving tadalafil 5 mg, experienced a notable TEAE of tachycardia (and dyspnea) 38 days after randomization lasting 15 days. The ECG at Visit 1 reported sinus tachycardia. The subject did not report a history of cardiovascular disease. The subject's blood pressure at Visits 3, 4, 5, and 6 were 155/95, 150/90, 153/91 and 158/90 mm Hg, respectively. Heart rates at Visits 3, 4, 5, and 6 were 65, 68, 58, and 57 beats per minute (bpm), respectively. At the end of the study, the subject had a normal cardiovascular status. Historical diagnoses included inguinal hernia. No preexisting conditions were reported. The subject completed the study.

2 subjects reported 2 cerebrovascular accidents. Subject 4006007 has been discussed under SAEs.

LVHG Subject 600-1084, a 70-year-old subject receiving placebo, reported to the investigator that while he was out of his country visiting the Philippines, he was hospitalized for the a cerebrovascular accident (minor stroke); the event occurred 28 days after randomization. The subject was discharged from the hospital after 2 days. After experiencing this event, the investigator stated the subject needed a walking stick for shaky legs. No historical diagnoses were reported. Preexisting conditions included hypertension, high cholesterol, and fungal infection on the right hand. The subject completed the study.

Two subjects receiving tadalafil 2.5 mg experienced syncope. Subject 600-1002 has been discussed in discontinuation narratives.

LVHG Subject 1102007: This subject experienced syncope for a duration of 1 day at 61 days after randomization. The subject had been taking ramipril for blood pressure starting in 2006. Thirty- three days after randomization, the ramipril was stopped on the advice of the PCP secondary to coughing. The ramipril was restarted 35 days after randomization secondary to blood pressure elevation that the patient reported to the PCP. 60 days following randomization following a blood donation, the patient experienced weakness and the next day had a syncopal episode that lasted for approximately 1 minute following sexual intercourse. The subject was hospitalized and stopped taking ramipril. He was released on the same day "after test results showed normal ranges." He resumed ramipril treatment and did not experience any further fainting episodes. His blood pressure at Visit 1 was 136/76 and at Visit 6 (the visit after the syncope) it was 140/72. The patient had a history of angina and ED. The subject completed the study.

> *Reviewer's Comment: This episode of syncope's significance is confounded by the recent blood donation antedating the event and possibly leading to hypovolemia.*

One 53 year-old subject (LVHG 3061637) receiving tadalafil 5 mg experienced hypotension with an onset 50 days after randomization and ocular hypertension with an onset 57 days after randomization. The duration of these events was not disclosed. The ECG reading at Visit 1 was poor precordial R-wave progression. At Visit 1, his blood pressure was 134/83 mm Hg and heart rate was 58 bpm. No ECG information was available for Visit

6. At Visit 6, his blood pressure was 108/68 mm Hg and heart rate was 73 bpm. Historical diagnoses for this subject included abscess, nephrolithiasis, sarcoidosis, and toe operation. Preexisting conditions for this subject included insomnia, back pain, and ED. The subject completed the study.

The Sponsor has identified five subjects who experienced dizziness (113-2306, 201-1121, 346-5654, 522-3278, and 600-1092).

LVHG Subject 113-2306, a 66-year-old subject receiving placebo, experienced dizziness with an onset 33 days after randomization. At Visit 3, his blood pressure was 128/84 mm Hg; at Visit 4 it was 128/76 mm Hg. No ECG information was available for this subject. At Visit 1 and Visit 4, his liver enzymes were elevated (Visit 1: aspartate transaminase [AST 43]; gamma glutamyl transferase [GGT 121] and Visit 4: AST [48], GGT [147]). The subject was taking the cardiovascular medication, lisinopril, for approximately 9 years. Historical diagnoses for this subject included calculus bladder. Preexisting conditions for this subject included hypertension, hyperlipidemia, GERD, paraesthesia, gout, and pain. The subject was discontinued from the study due to the AE.

LVHG Subject 201-1121, a 65-year-old subject receiving tadalafil 20 mg, experienced dizziness with an onset 5 days after randomization, information from the site showed the event occurred after attempting to lie down or get up from bed. The dizziness event lasted for 2 days. There were no significant changes in the subject's blood pressure during the study. The ECG reading at Visit 1 was abnormal (occasional ventricular repolarization identified) and no endpoint ECG was available. No historical diagnoses for this subject were reported. The subject had a preexisting condition of sleep apnea of which was treated with oxygen/continuous positive airway pressure (CPAP) machine. The subject was discontinued from the study due to the AE.

LVHG Subject 346-5654, a 65-year-old subject receiving tadalafil 20 mg, experienced dizziness with an onset 37 days after randomization. At Visit 6, the subject was suffering from bradycardia and his ECG revealed atrial fibrillation and atrial flutter. The subject was hospitalized 113 days after randomization for heart failure with suspected pulmonary embolism. Computed tomography showed no evidence of embolism. There was no final resolution of relatedness, but the subject sustained bradycardia and exercise dyspnea. There were no historical diagnoses for this subject related to these events; however, the subject was a marathon runner. The subject completed the study. This subject was also discussed under SAEs relating to cardiac arrhythmia.

LVHG Subject 522-3278, a 51-year-old subject receiving tadalafil 5 mg experienced headache and dizziness. The onset of both symptoms occurred 2 days after randomization and lasted 5 days. At Visit 3, his blood pressure was 120/85 mm Hg and heart rate was 80 bpm. At the final visit, his blood pressure, heart rate, and ECG information were not available. Historical diagnoses for this subject included cholecystectomy and hernia repair. The subject was discontinued from the study due to the AE of headache.

Subject 600-1092, a 50-year-old subject receiving tadalafil 20 mg, experienced an onset of dizziness 2 days after randomization; the duration of this event was unknown. At Visit 3, his

blood pressure was 130/86 mm Hg and heart rate was 60 bpm. At Visit 4 (the first visit after the event), his blood pressure was 138/90 mm Hg and heart rate was 60 bpm. An ECG was only available at Visit 1 and was considered abnormal. Historical diagnoses for this subject included fractured pelvis, sacrum, and skull and 60% of his body was burned with skin grafts. Concomitant medication for this subject included Telfast 60 mg, taken for his preexisting condition of pruritis. The subject completed the study.

> *Review's Comment: All episodes of dizziness in tadalafil patients occurred in the 20 mg dose group and 1 such episode occurred in association with heart failure and possible pulmonary embolism.*

A total of 12 subjects reported at least 1 eye-related adverse event (placebo: 3 subjects, tadalafil 5 mg: 5 subjects, tadalafil 10 mg: 1 subject , tadalafil 20 mg: 3 subjects). Among the eye events, there were 8 subjects reporting 8 AEs. Two subjects reported blurred vision (placebo, tadalafil 5 mg), one subject reported retinal tear (tadalafil 5 mg), one subject reported ocular hyperemia (tadalafil 20 mg), one subject reported choroidal neovascularization (tadalafil 5 mg), one subject reported eye pain (placebo), one subject reported ocular hypertension (tadalafil 5 mg), and one subject reported glaucoma (tadalafil 10 mg). No subjects reported NAION.

LVHG Subject 102-1212, a 53-year-old subject receiving tadalafil 5 mg, experienced blurred vision 5 days after randomization for duration of 85 days. His blood pressure at Visit 3 was 114/66 mm Hg and at Visit 4 was 106/80 mm Hg (first visit after the onset of event). There were no ECG changes between Visits 1 and 6. Historical diagnoses for this subject included alopecia areata, cholecystectomy, tonsillectomy, and vasectomy. The subject had preexisting conditions of dyspepsia and arthritis. The subject completed the study.

LVHG Subject 344-5458, a 70-year-old subject receiving placebo, experienced blurred vision 21 days after randomization for duration of 23 days. Blood pressure, heart rate (range 56-64 bpm), and ECG were normal at every visit. Historical diagnoses for this subject included intervertebral disc protrusion. No preexisting conditions were reported for this subject. The subject completed the study.

LVHG Subject 106-1605, a 62-year-old subject receiving tadalafil 5 mg, experienced retinal tear 6 days and 37 days after randomization. The first retinal tear occurred approximately 10 hours after the subject had taken tadalafil when the subject reported seeing black floaters and light flashes in his left eye. He was referred to a retinal specialist by his ophthalmologist for a retinal tear. The retinal specialist found 2 tears and believed there was too much bleeding to operate on the subject, so a freezing technique was performed. The subject's eye healed well following this procedure. The investigator believed that the event may be linked to the age of the subject. Historical diagnoses included nephrolithiasis, vasectomy, vasectomy reversal, and ED. Preexisting conditions included depression, bladder obstruction, osteoarthritis, seasonal allergy, phlebolith, epididymal cyst, and anxiety. The subject had previously used tadalafil for the treatment of ED due to the use of sertraline HCI. Concomitant medications included multi-vitamin, beta carotene, CoQ 10, vitamin C, vitamin E, folic acid, garlic, glucosamine

chondroitin, Omega 3 fish oil, selenium, and fluticasone propionate. The subject was discontinued from the study due to this event.

LVHG Subject 110-2005, a 55-year-old subject receiving tadalafil 20 mg, experienced ocular hyperemia (red eyes) 2 days after randomization. The event resolved without treatment. His blood pressure was unchanged and there was no change in ECG between Visits 1 and 6. Historical diagnoses for this subject included atrial fibrillation and hypertension. The subject had preexisting conditions of hypermetropia, ED, insomnia, and myopia. Concomitant medications included sotalol as prophylaxis. The subject completed the study.

LVHG Subject 112-2204, a 71-year-old subject receiving tadalafil 5 mg, experienced choroidal neovascularization 52 days after randomization. His blood pressure exhibited small changes throughout the study and there was no change in abnormal ECG between Visits 1 and 6. Historical diagnoses for this subject included basal cell carcinoma and inguinal hernia. The subject had preexisting conditions of glaucoma, allergic sinusitis, hypercholesterolemia, iodine allergy, hypermetropia, myopia, headache, constipation, hemorrhoids, bladder obstruction, ED, and arthralgia. The subject took the following concomitant medications during the study: timolol, diphenhydramine, vitamin E, vitamin C, bimatoprost, acetylsalicylic acid, pravastatin, zinc, ranibizumab ophthalmic, and famotidine. The subject completed the study.

LVHG Subject 119-2900, a 51-year-old subject receiving placebo experienced eye pain with an onset on the same day the subject was randomized for the study. No historical diagnoses were reported for this subject. The subject had pre-existing conditions of seasonal allergy. The subject discontinued due to this AE.

LVHG Subject 124-3408, a 66-year-old subject receiving tadalafil 10 mg, experienced glaucoma with an onset 34 days after randomization and was treated with Travatan. No eye-related historical diagnoses or preexisting conditions were reported for this subject. The subject had a preexisting condition of seasonal allergy. Additional concomitant medications included Voltaren for osteoarthritis and Lipitor for hypercholesterolemia. The subject completed the study. No further information was available from the study site.

LVHG Subject 306-1637, a 53-year-old subject receiving tadalafil 5 mg, experienced hypotension with an onset 50 days after randomization and ocular hypertension with an onset 59 days after randomization. The duration of these events was not disclosed. The subject reported no visual disturbance and had an ocular pressure of 26/27 mm Hg. For prevention purposes, the subject was administering latanoprost ophthalmic solution at 1 drop per day for each eye. This subject had a family history of ocular hypertension and was being monitored for it by an ophthalmologist. According to the study site, the event resolved and the subject's ocular tension was normal at 18/19 mm Hg. For further information on this subject, please refer to Section 12.3.4.1.4 (hypotensive events). The subject completed the study.

Within the hepatobiliary disorders and investigations' SOCs, 5 subjects (placebo: 3,

tadalafil 5 mg: 2) reported 5 events related to hepatobiliary safety. In light of the excess cases in the placebo group this group will not be discussed further. One case of pancreatitis (Subject 1102027) has been previously discussed in SAEs.

Four patients had the AEs of elevated or abnormal hepatic enzymes.

LVHG Subject 118-2837 is a 52-year-old subject with known hepatitis C receiving tadalafil 5 mg, experienced "hepatic enzymes increased" identified at Visit 6 (Visit 1: AST 31 U/L, alanine transaminase [ALT] 29 U/L, GGT 28 U/L; Visit 3: AST 26 U/L, ALT 24 U/L, GGT 35 U/L; Visit 6: AST 181 U/L, ALT 254 U/L, GGT 105 U/L). Bilirubin values were normal. Historical diagnoses for this subject included appendicitis and tonsillitis. Historical diagnoses for this subject included appendicitis and tonsillitis. The subject had preexisting conditions of back pain, osteoarthritis, scoliosis, lumbar spinal stenosis, anxiety, hepatitis C, and ED. The subject completed the study.

LVHG Subject 1203003 is a placebo patient.

LVHG Subject 1405001 is a placebo patient.

LVHG Subject 1384837 is a placebo patient.

Two subjects had adverse events related to urinary tract invasive procedures. Subject 123-3320 has been discussed previously received tadalafil 2.5 mg was hospitalized with the SAEs of acute renal failure, left urethral orifice bladder tumor, right obstructing kidney stone, and right-sided calyceal rupture. Procedures completed on the subject during the study involved lithotripsy, urethral stent insertion and transurethral bladder tumor resection. Placebo Subject 4066610 experienced urinary retention and underwent a transurethral resection of the prostate.

> *Reviewer's Comment: The analysis of notable adverse events and special safety topics has not identified any new safety concerns or signals.*

Clinical Laboratory

There were small decreases in the hemoglobin at endpoint in the 20 mg tadalafil dose group and in the lymphocyte count at endpoint in the 10 mg tadalafil dose group. There were small decreases in ALT, AST, GGT, bilirubin, alkaline phosphatase and creatine phosphokinase versus placebo at endpoint. There were no statistical significant decreases in urea nitrogen, calcium, inorganic phosphorus, sodium, potassium, chloride, total protein, albumin, nonfasting glucose, uric acid, cholesterol, creatinine or creatinine clearance from baseline to endpoint for any tadalafil treatment group compared with placebo.

Seven subjects met either the criteria of any value for AST or ALT more than 3- to 5- fold the upper limit of normal (ULN) or bilirubin more than 1.5 fold the ULN (placebo : 2 subjects,

tadalafil 5 mg 3 subjects, and tadalafil 10 mg: 2 subjects). The placebo patients will not be discussed. 5 mg tadalafil Subject 1182737 has been discussed above.

LVHG Subject 1021204 is a 65-year-old subject receiving tadalafil 10 mg, experienced peripheral edema 49 days after randomization. The subject's ALT was slightly elevated at Visit 1 (57 U/L), further increased at Visit 3 (151 U/L), and returned to near baseline at Visit 5 (59 U/L). The AST was normal at Visit 1 (24 U/L), abnormally increased at Visit 3 (78 U/L), and returned to normal at Visit 5 (33 U/L). Total bilirubin was normal throughout the study. Historical diagnosis included cataract, drug hypersensitivity (Biaxin), sepsis, eye operation, and cholecystitis infective. Preexisting conditions included solitary kidney, hypertension, gout, hyperlipidemia, and carpal tunnel syndrome. Concomitant medications included acetylsalicylic acid, atenolol, colchicine, losartan, doxazosin, lisinopril, multi-vitamin, Oxycocet, pravastatin, prednisone, tamsulosin, torsemide, colesevelam HCl, and ezetimibe. The subject was discontinued due the event of peripheral edema.

LVHG Subject 1273709 is a 57-year-old subject receiving tadalafil 5 mg, had normal hepatic enzymes at Visits 1 and 3, but hepatic enzyme elevation at Visit 6 (Visit 1: AST 23 U/L, ALT 33 U/L; Visit 3: AST 25 U/L, ALT 42 U/L; and Visit 6: AST 53 U/L, ALT 131 U/L. Total bilirubin was normal at Visits 1 and 3 then decreased to <0.2 µmol/L at Visit 6; GGT values were normal. Historical diagnoses for this subject included coronary artery bypass. The subject had preexisting conditions of hyperlipidemia, gout, and ED. The subject was taking multiple concomitant medications of indomethacin, pantoprazole, nicotinic acid, pravastatin, and zinc. The subject completed the study. The study site did not respond to request for further information on this subject.

LVHG Subject 3001067 is a 59-year-old subject receiving tadalafil 5 mg, had abnormal hepatic enzymes at Visit 3 prior to receiving study drug; hepatic enzymes decreased at Visit 6 (Visit 1: AST not available, ALT not available, GGT 117 ⌈mol/L; Visit 3: AST 142 U/L, ALT 185 U/L, GGT 160 ⌈mol/L; and Visit 6: AST 44 U/L, ALT 65 U/L, GGT 71 ⌈mol/L). Total bilirubin was normal. Historical diagnoses for this subject included nephrectomy and splenectomy. The subject had a preexisting condition of hypertension. The subject was taking concomitant medications of amlodipine, urapidil, and valsartan. The subject completed the study.

LVHG Subject 4056536 a 69-year-old subject receiving tadalafil 10 mg, had elevated hepatic enzymes throughout the study with minimal changes (Visit 1: AST 81 U/L, ALT 145 U/L, GGT 65 U/L; Visit 3: AST 61 U/L, ALT 70 U/L, GGT 57 U/L; and Visit 6: AST not available, ALT 82 U/L, GGT 73 U/L). Total bilirubin was normal. No historical diagnoses were reported for this subject. The subject had preexisting conditions of hypertension, hypercholesterolemia, and fungal infection. The subject was taking concomitant medications of Inegy, acetylsalicylic acid, nystatin, and enalapril. The subject completed the study. The study site did not respond to request for further information on this subject.

Changes from baseline to end of therapy for PSA values in all tadalafil treated patients were minimal. In the tadalafil 5 mg treatment group, the change from 1.79 to 1.86 ng/mL reached statistical significance. There were less than 15 subjects with PSA values more than twice

baseline values across all treatment groups (placebo: 3, tadalafil 2.5 mg: 2, tadalafil 5 mg: 6, tadalafil 10 mg: 0, tadalafil 20 mg: 3).

Vital Signs

Overall, there were no statistically significant mean changes from baseline to endpoint in tadalafil treatment groups when compared to placebo for heart rate, SBP, or DBP.

Table 13: Summary of Potentially Significant Changes in Blood Pressure during Treatment in Phase 3 Study LVHG

Variable		Placebo	IC 2.5 mg	IC 5 mg	IC 10 mg	IC 20 mg
		N=210	N=208	N=212	N=216	N=208
SYSTOLIC		n (%)				
Systolic BP <95 mm HG		0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.49)
Maximal Change SBP						
	Increase ≥ 20 mmHg	31(14.76)	15(7.21)	29(13.68)	28(12.96)	23(11.06)
	Decrease ≥ 20 mmHg	25(11.90)	27(12.98)	30(14.15)	18(8.33)	26(12.50)
Maximal Decrease in SBP						
	≤ 30 mm Hg	201(95.71)	199(95.67)	199(93.87)	208(96.30)	194(93.27)
	> 30 mm Hg	3(1.43)	4(1.92)	2(2.83)	2(0.93)	4(1.92)
	Not available	6(2.86)	5(2.40)	7(3.30)	6(2.78)	10(4.81)
DIASTOLIC		n (%)				
Diastolic BP <45 mm HG		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maximal Change DBP						
	Increase ≥ 10 mmHg	53(25.24)	44(21.15)	38(17.92)	42(19.44)	46(22.12)
	Decrease ≥ 10 mmHg	47(22.38)	57(27.40)	65(30.66)	59(27.31)	54(25.96)
Maximal Decrease in DBP						
	≤ 20 mm Hg	198(94.29)	199(95.67)	198(93.40)	206(95.37)	191(91.83)
	> 20 mm Hg	6(2.86)	4(1.92)	7(3.30)	4(1.85)	7(3.37)
	Not available	6 (2.86)	5 (2.40)	7 (3.30)	6 (2.78)	10 (4.81)

Source: Tables LVHG 14.107 and 14.108, H6D-MC-LVHG Study Report, pages 1088-1089.
IC=tadalafil

Only 1 subject experienced SBP< 85 mmHg (tadalafil 20 mg). There were no subjects that experienced a DBP <45 mmHg. For maximal DBP changes, a similar percentage of subjects in

the tadalafil treated groups had a decrease ≥ 10 mmHg compared to placebo. The same is observed for the ≥ 20 mmHg compared to placebo category. For maximal SBP changes, a similar percentage of subjects in the tadalafil treatment groups (range 8.33% to 14.15%) had a decrease ≥20 mm Hg compared to the placebo (11.9). A similar percentage of subjects in the tadalafil-treated groups (range 0.93% to 2.83%) had maximal decrease in SBP >30 mm Hg compared to placebo.

This reviewer accessed DATASET-VITALS.XPT and identified 4 tadalafil subjects and one placebo subject identified with hypertension as an adverse event.

(b) (4)

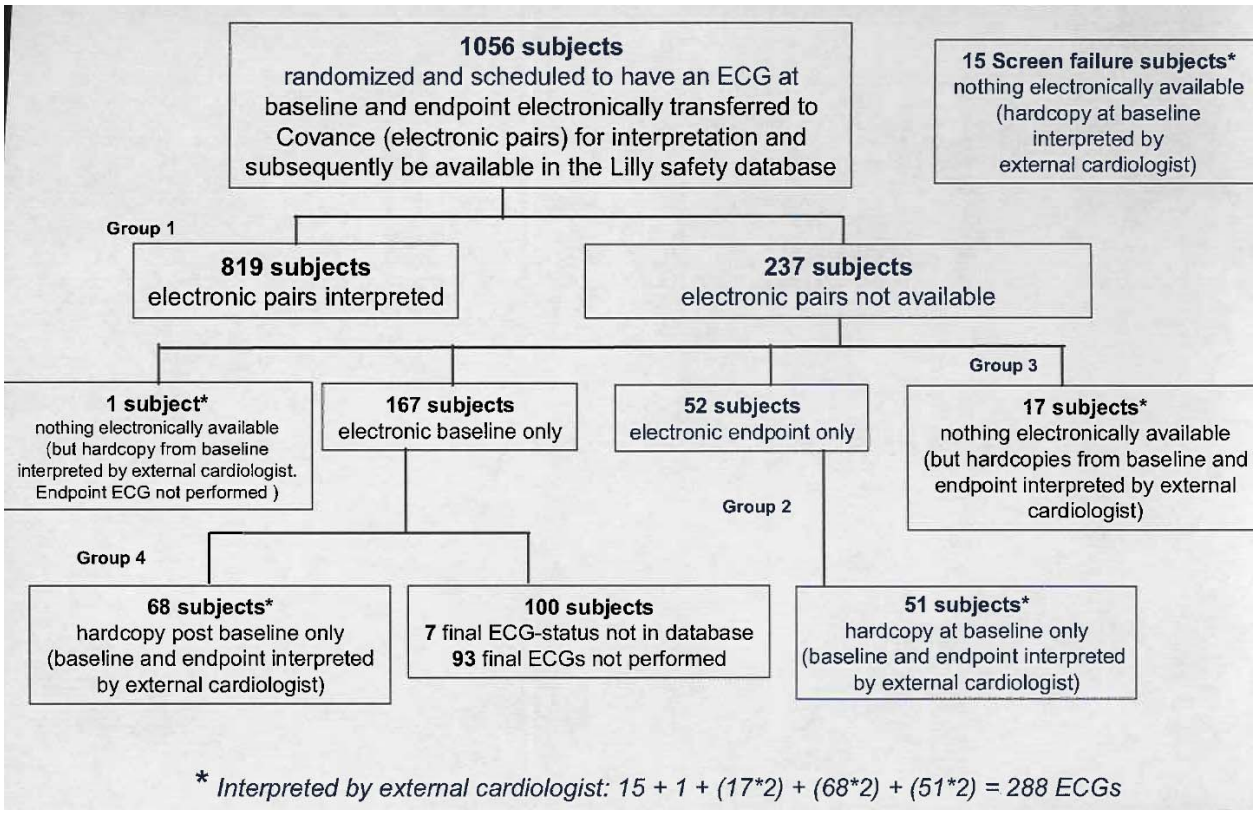
Reviewer's Comment: Four of the five subjects had systolic BP in excess of 140 mmHg at Visit 1 and one patient had a diastolic blood pressure of 90 mmHg at Visit 1. At Visit 6, the only patient with an increased systolic blood pressure > 140 mmHg was the placebo patient. The highest diastolic blood pressure at Visit 6 was 85 mmHg in a patient who had a diastolic blood pressure at Visit 1 of 90 mmHg. Overall, with the exception of the placebo subject, the blood pressures in these patients actually improved while on tadalafil.

Electrocardiograms

Electrocardiograms were performed at Visit 1 and the final visit, Visit 6. The ECG pairs (Visit 1 and Visit 6) were interpreted by a cardiologist employed by (b) (4)

In addition to the primary analysis, there were 17 subjects who had no ECGs from either baseline or endpoint electronically transferred to (b) (4) Hardcopies of these 18 paired ECGs were interpreted by external cardiologist. One subject with baseline ECG hardcopy only who had no endpoint ECG performed was interpreted as well. The cardiologist also interpreted paired ECGs from 68 subjects where baseline ECGs were electronically available and endpoint was available as hardcopy. For 100 subjects with electronic ECGs at baseline only, final ECG was not performed at the study site in 93 subjects and 7 subjects had final ECG status undisclosed in the database. Interpretation by external cardiologist was initiated before the completion of the study; some ECGs were eventually identified as screen failures. These constitute 15 single baseline ECGs and are included in the overall evaluation by the external cardiologist.

Figure 1: Diagram for Handling Electrocardiogram interpretation Study LVHG



Source: Scanned Copy Figure LVHG 12.1, H6D-MC-LVHG Study Report page 157

In the Sponsor's opinion, there were no statistically significant mean changes from baseline to endpoint in tadalafil treatment groups in the ECG parameters. Few ECG changes, suggestive of an MI, were not clinically verified, and overall, there was no evidence that daily treatment with tadalafil for 12 weeks increased the risk of MI in this population of men with BPH-LUTS.

The consultant cardiologist stated "Forty-seven patients had any abnormality on an electrocardiogram according to the Lilly interpretive standards….There were seven patients with paired observations that had treatment emergent electrocardiographic events…" 6 of these events were judged to be clinically insignificant and will not be discussed. One event was significant and a brief narrative is below.

LVHG Patient 2213 at visit 1 the electrocardiogram shows sinus rhythm with left axis deviation and a possible septal myocardial infarction age indeterminate. Visit 6 electrocardiogram showed left axis deviation, possible septal infarction age indeterminate, and new inferior Q waves indicative of a new inferior myocardial infarction. This is clinically significant in the opinion of the consultant cardiologist.

ECG analyses of heart rate, PR interval, QRS interval, QTC interval, QT interval, and RR interval were not statistically different compared with placebo. Changes did not indicate any dose-like impact of tadalafil.

Proportionally, more subjects taking tadalafil 5 mg had nonspecific T-wave abnormalities compared to the other treatment groups (placebo: 3.7%, tadalafil 2.5 mg: 4.4%, tadalafil 5 mg: 10.0%, tadalafil 10 mg: 1.9%, and tadalafil 20 mg: 4.2%); clinical meaning of this is uncertain in the Sponsor's opinion. The incidence of rhythm abnormalities in tadalafil subjects as compared to placebo is similar. The most frequently reported ST segment abnormality was "nonspecific ST abnormality" and did not appear to be different between placebo and tadalafil groups. There was no increase in myocardial ischemic abnormalities between tadalafil versus placebo groups.

With respect to ECG myocardial infarction abnormalities, the incidence was low and not different across groups.

Table 15: Myocardial Infarction ECG Abnormalities Double-Blind Period Study LVHG

Myocardial Infarction Abnormalities	Placebo N=210	IC 2.5 mg N=208	IC 5 mg N=212	IC 10 mg N=216	IC 20 mg N=209
No infarct present	178 181 (98.34)	176 177 (99.44)	165 168 (99.21)	169 172 (98.26)	153 155 (98.71)
Cannot R/O Infarction Inferior Septal	 0 181 (0.00) 0 181 (0.00)	 0 177 (0.00) 0 177 (0.00)	 1 168 (0.60) 0 168 (0.00)	 1 172 (0.58) 1 172 (0.58)	 0 155 (0.00) 0 155 (0.00)
Age Undetermined MI	1 181 (0.55)	1 177 (0.56)	0 168 (0.00)	0 172 (0.00)	0 155(0.00)
Inferior Infarct	0 181 (0.00)	1 177 (0.56)	0 168 (0.00)	0 172 (0.00)	0 155 (0.00)
Unable to Evaluate	2 181 (1.10)	1 177 (0.00)	2 168 (1.19)	1 172 (0.58)	2 155 (1.29)

IC=tadalafil
Source: Table LVHG 14.126, H6D-MC-LVHG Study Report, page 1122

With respect to potential myocardial infarction identified in ECGs and not reported as an adverse event, the incidence was not different between placebo and tadalafil treatment groups. 6 subjects were identified by (b) (4) and/or the external cardiologist with 7 ECG-evident MI or cannot rule out MI events (placebo: 1 subject, tadalafil 2.5 mg: 1 subject/2 events, tadalafil 5 mg: 1 subject, and tadalafil 10 mg: 2 subjects, tadalafil 20 mg: 0 subjects). Of these subjects, subject 525-3595 (tadalafil 2.5 mg) was determined to have had a treatment emergent MI of age indeterminate. All but one of the above patients completed the study. 1 subject discontinued due to lack of compliance. In 4 of 5 cases the sites did not respond to requests for further information. The Sponsor states that "without further clinical correlation, it is not possible to establish a final diagnosis."

LVHG Subject 525-3592, a 57-year-old subject receiving tadalafil 2.5 mg, had an MI (age undetermined) and an inferior MI identified in ECG reports; the event was without clinical

verification and was not registered as a TEAE or SAE. These findings were based on an ECG at Visit 6 only, which was electronically transferred to the ECG vendor (b) (4). However, when both Visit 1 and Visit 6 ECGs were compared by an external cardiologist, no changes were observed. Blood pressure at Visit 1 was 120/80 mm Hg and heart rate was 80 bpm. Blood pressure at Visit 6 was 130/90 mm Hg and heart rate was 72 bpm. Laboratory values of ALT, AST, and creatine kinase were all within normal range throughout the study. Concomitant medication included metoprolol. Except for hypertension, no cardiovascular or other relevant historical or preexisting diagnoses were reported. The subject completed the study. The study site did not respond to requests for further information on this subject.

LVHG Subject 105-1503, a 68-year-old subject receiving tadalafil 5 mg, had an inferior MI (cannot rule out MI) identified in ECG reports; the event was not registered as a TEAE or SAE. At Visit 1, he had an abnormal ECG assessment, an abnormal myocardial ischemia which resulted in inferior T-wave abnormality and probable ischemia. At Visit 1, his blood pressure was 132/76 mm Hg and heart rate was 66 bpm. At Visit 6, he had an abnormal ECG assessment with left axis deviation, Wolff-Parkinson-White conduction, and cannot rule out inferior MI. According to the investigator, the subject had no clinical signs or symptoms of an MI and the subject's PCP did not feel that the subject had an MI. His blood pressure at Visit 6 was 131/77 mm Hg and heart rate was 62 bpm. Following the Visit 6 ECG assessment, the study site requested the subject return for a repeat ECG, but the subject refused. Laboratory values of ALT, AST, and creatine kinase were all within normal range throughout the study. Concomitant medications included atenolol (since 1980), duloxetine, Excedrin, lovastatin, metformin, primidone, clopidogrel, triamterene (since 1980), and Vicodin. Historical diagnoses included transient ischemic attack (TIA) and vasectomy. The subject had no history of previous MI. Preexisting diagnoses included essential tremor, hypertension, ED, neuropathy in feet, diabetes, migraine, exostosis, Peyronie's disease, elevated cholesterol, and cardiac arrhythmia. The subject completed the study.

LVHG Subject 125-3519, a 68-year-old subject receiving tadalafil 10 mg, had an inferior MI (cannot rule out MI) identified in ECG reports; the event was not registered as a TEAE or SAE. On the subject's ECG at Visit 1, his heart rate was 57 bpm. His blood pressure at Visit 1 was 137/86 mm Hg with a sitting heart rate of 83 bpm. At Visit 6, he had an abnormal ECG assessment, which identified an MI that could not be ruled out with a QRS interval of 120. His blood pressure at Visit 6 was 128/78 mm Hg and heart rate was 69 bpm. Laboratory values of ALT, AST, and creatine kinase were all within normal range throughout the study. Concomitant medications included nifedipine, eprosartan, aspirin, acetaminophen, and Inegy (simvastatin and ezetimibe). Historical diagnoses included angioplasty, MI in 1992, hydrocele and inguinal hernia repair, rotator cuff repair, and cataract operation. Preexisting diagnoses included hypertension, hypercholesterolemia, hypogonadism, hemorrhoids, osteoarthritis, seasonal allergies, and aortic aneurysm. The subject completed the study. The study site did not respond to requests for further information on this subject.

LVHG Subject 331-4102, a 52-year-old subject receiving tadalafil 10 mg, had an ECG at his last visit that revealed a possible septal MI; this event was not registered as a TEAE or SAE. Sinus tachycardia was noted on the ECG assessment at Visit 1. His blood pressure at Visit 1 was

130/85 mm Hg and heart rate was 87 bpm. At the last visit, the ECG reading was abnormal and revealed a left atrial enlargement, poor precordial R-wave progression, and MI that could not be ruled out. His blood pressure at Visit 6 was 140/95 mm Hg with a heart rate of 90 bpm. Laboratory values of AST and creatine kinase were all within normal range throughout the study. The ALT was identified as abnormal (59 U/L; range 6-43 U/L) before randomization. Alanine transaminase returned to within normal range after randomization. No concomitant medications or historical diagnoses were reported for this subject. Preexisting conditions included ED. The subject discontinued at Visit 5 (approximately 70 days after randomization) due to low compliance (protocol violation). The study site did not respond to requests for further information on this subject.

> *Reviewer's Comment: In the absence of follow-up ECGs and clinical follow-up the diagnosis of MI in the above four cases cannot be established.*

With respect to ECGs evaluated only by the external cardiologist only 1 tadalafil treated (10 mg) subjects had a treatment emergent ECG assessment of MI at Visit 6 without documented correlation.

LVHG Subject 112-2213, a 53-year-old subject receiving tadalafil 10 mg, had an MI identified in ECG reports; the event was not clinically verified and was not registered as a TEAE, SAE, or AE leading to discontinuation. The finding was identified by an external cardiologist who reviewed ECGs not electronically transferred to the (b) (4) ECG vendor. At Visit 1, the ECG showed sinus rhythm (SR) with left axis deviation and possible septal MI (age indeterminate). The Visit 6 ECG showed left axis deviation, possible septal infarction (age indeterminate), and new inferior Q waves indicative of a new inferior MI, which was considered clinically significant by the external cardiologist. Blood pressure at Visit 1 was 118/82 mm Hg and heart rate was 60 bpm. Blood pressure at Visit 6 was 118/74 mm Hg and heart rate was 60 bpm. Laboratory values of ALT, AST, and creatine kinase were all within normal range throughout the study. Concomitant medication included ibuprofen. No cardiovascular or other relevant historical or preexisting diagnoses were reported. The subject completed the study. The study site did not respond to requests for further information.

Reviewer's Overall Conclusions: Efficacy for BPH is demonstrated in all dose groups with the 5 mg tadalafil dose superior to the 2.5 mg tadalafil dose. There is little improvement in efficacy with the dose above 5 mg of tadalafil. The safety profile is similar to other patient populations using tadalafil and is acceptable.

Study LVHG Open Label Extension: An Open-Label Extension to Evaluate the Long-Term Safety of Tadalafil Once-a-Day Dosing in Men with Signs and Symptoms of Benign Prostatic Hyperplasia

The long-term safety and persistence of efficacy of tadalafil 5-mg once-daily dosing was assessed as the primary objective with a 52-week, open-label extension period of Study LVHG. Subjects from the US and Canada who completed the double-blind treatment period of Study LVHG were given the option to continue into the open-label extension. Subjects with PSA at entry to the open-label extension ≥2 times higher than PSA at randomization of the double-blind treatment period were not eligible for the open-label extension. The double-blind period together with the open-label extension provided 64 weeks of assessments.

The secondary objectives were:

- Total IPSS defined as the sum of scores for IPSS Questions 1-7;
- IPSS storage irritative (Questions 2, 4 and 7) and voiding (Questions 1, 3 5, and 6) subscore and nocturia question (Question 7);
- BII;
- IPSS Quality of Life (QoL) Index.
- To examine the effect of tadalafil 5 mg once-daily as assessed by the IIEF EF Domain score in sexually active men with ED.

Subjects who entered the open-label extension had a mean age of approximately 63 years at Visit 1, similar to previous treatment groups (range of approximately 62 to 64 years). A majority of subjects were <65 years of age (60%); 7.7% were ≥75 years of age. Most subjects were Caucasian (91.6%). For those entering the open-label extension, physical characteristics (height, weight, and BMI) at Visit 1 were similar for all subjects by previous treatment group.

For those entering the open-label extension, over half of the subjects reported having LUTS for >3 years (60%). There were 159 subjects (37.3%) who reported having severe LUTS (IPSS total score ≥20) at baseline (Visit 3). There were 127 subjects (29.74%) who reported taking previous therapy for BPH-LUTS. There were 69.3% of subjects enrolled in the open-label extension who reported ED at Visit 1, of whom 90.5% reported having ED for ≥1 year.

Of the 428 subjects who entered the open-label extension, 427 subjects received at least one dose of study drug. There were 128 subjects (29.9%) who discontinued the open-label extension early. The most common reasons for early discontinuation were due to subject decision (59 subjects, 13.79%), AEs (22 subjects, 5.14%), subject lost to follow-up (16 subjects, 3.74%), and perceived lack of efficacy (15 subjects, 3.50%).

Table 16: Summary of Reasons for Study Discontinuation Study LVHG Open-Label Extension Period.

	Previous Double-Blind Therapy					
	Placebo N=92	IC 2.5 mg N=97	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=428
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Enrolled	92(100.00)	97(100.00)	83(100.00)	85(100.00)	71(100.00)	428(100.00)
Received Study Drug	92(100.00)	96 (98.97)	83(100.00)	85(100.00)	71(100.00)	427(99.77)
Complete	65(70.65)	66(68.04)	59(71.08)	62(72.94)	47(66.20)	299(69.86)
Discontinued	27(29.35)	30(30.93)	24(28.92)	23(27.06)	24(33.80)	128(29.91)
Reason for Discontinuation						
Abnormal PSA Visit 10	1(1.09)	0 (0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.23)
Abnormal PSA Visit 6	0(0.00)	0(0.00)	0(0.00)	1(1.18)	0(0.00)	1(0.23)
Adverse Event	6(6.52)	4(4.12)	4(4.82)	5(5.88)	3(4.23)	22(5.14)
Lack of Efficacy	3(3.26)	3(3.09)	1(1.20)	3(3.53)	5(7.04)	15(3.50)
Lost to Follow up	2(2.17)	4(4.12)	2(2.41)	3(3.53)	5(7.04)	16(3.74)
Physician Decision	0(0.00)	1(1.03)	1(1.20)	0(0.00)	0(0.00)	2(0.47)
Protocol Violation	2(2.17)	3(3.09)	0(0.00)	1(1.18)	2(2.82)	8(1.87)
Sponsor Decision	0(0.00)	2(2.06)	1(1.20)	0(0.00)	1(1.41)	4(0.93)
Subject Decision	13(14.13)	13(13.40)	15(18.07)	10(11.76)	8(11.27)	59(13.79)

IC=tadalafil, Source: Table LVHG 6.1, H6D-MC-LVHG Abbreviated Study Report, page 39.

Reviewer's Comment: I could not discern any significant trend in the disposition data. There were 4 patients who used or were administered nitrates while enrolled in the OLE (Open-Label Extension). Three were not recorded as protocol violations (1132315, 1233315, and 2058001) and one was (112-2210). There did not appear to be any untoward outcome related to this type of protocol violation.

The baseline visit for safety and efficacy measurements was Visit 3 (Week 0, randomization) of the double-blind, placebo-controlled period. The post baseline visits of the open-label extension began at Visit 7 (Week 12) and continued through Visit 12 (Week 64). Endpoint was the last measurement collected after Visit 7 and prior to study discontinuation. Change from baseline

was calculated as the endpoint value minus the baseline value, provided both baseline and endpoint values existed for a subject. If either value was missing, change from baseline was regarded as missing for that subject. Additional comparisons of change were calculated from the endpoint value minus data collected at Visit 6 (end of the double-blind treatment period).

Analysis of long-term tadalafil effectiveness for this open-label extension period was primarily descriptive in nature. Summary statistics for IPSS total, IPSS sub-scores, BII, and IIEF were provided at Visits 2 (Week -4), 3 (Week 0, randomization), and 6 (Week 12) of the placebo-controlled period, and at Visits 8 (Week 16), 9 (Week 24), 10 (Week 38), 11 (Week 51), and 12 (Week 64) of the open-label extension period. Efficacy parameters were also summarized as change from baseline to endpoint in the open-label extension period, and as change from Visit 6 to endpoint.

Safety was assessed by evaluating all reported adverse events, changes in clinical laboratory values (serum chemistry and hematology, urinalysis), PSA, PVR, vital signs, and ECGs.

Efficacy

The overall mean change in IPSS total from baseline to endpoint was -5.0 ± 6.7. The range of mean changes by previous treatment group was -4.1 to -5.7. The overall mean change from Visit 6 to endpoint was -0.9 ± 5.7. When evaluated by previous treatment group, subjects who changed from placebo to tadalafil 5 mg and from tadalafil 2.5 mg to tadalafil 5 mg had a mean reduction of -2.2 ± 5.3 and -2.5 ± 5.1 in IPSS total, respectively. From Visit 6 to endpoint, there was no clinically meaningful change in IPSS total score for subjects who remained on tadalafil 5 mg (0.2 ± 5.4) or decreased dose from tadalafil 10 mg to tadalafil 5 mg (-0.2 ± 5.8). Subjects who decreased from tadalafil 20 mg increased in mean IPSS total score (0.8 ± 6.4). It was also noted that in subjects who increased the tadalafil dose from 2.5 mg to 5 mg once-daily or started on 5 mg tadalafil once daily from placebo statistically significant improvements in IPSS total scores were noted.

> *Reviewer's Comment: As Table 15 shows efficacy is maintained at 64 weeks as measured by the IPSS total score.*

Table 17: IPSS from Baseline to Endpoint LVHG Open-Label Extension

IPSS Total		Previous Double-Blind Therapy					
		Placebo N=91	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Visit 3	Week 0	n=91	n=95	n=83	n=85	n=71	n=425
IPSS Mean (SD)		17.5(5.7)	17.6(6.0)	18(6.2)	19(5.5)	17.7(6.2)	18.0(5.9)
Visit 6	Week 12	n=92	n=96	n=83	n=85	n=71	n=427
IPSS Mean (SD)		15.6(6.4)	14.5(6.4)	12.7(7.1)	13.6(7.3)	12.4(6.4)	13.9(6.8)
Endpoint	Week 64	n=89	n=95	n=82	n=81	n=69	n=416
IPSS Mean (SD)		13.4(7.1)	11.9(6.6)	13.0(7.8)	13.2(6.7)	13.1(7.5)	12.9(7.1)
Change From Visit 3 to Endpoint							
		n=89	n=95	n=82	n=81	n=69	n=416
IPSS Mean (SD)		-4.1(6.8)	-5.7(5.4)	-5.0(7.2)	-5.7(6.4)	-4.6(7.7)	-5.0(6.7)
Change From Visit 6 to Endpoint							
		n=89	n=95	n=82	n=81	n=69	n=416
IPSS Mean (SD)		-2.2(5.3)	-2.5(5.1)	0.2(5.4)	-0.2(5.8)	0.8(6.4)	-0.9(5.7)

IC=tadalafil Source: Table LVHG 11.7 H6D-MC-LVHG Abbreviated Study Report, page 642

Table 18: IEFF EF Domain Scores Open-Label Extension Period Sexually Active Patients with History of ED

International Index of Erectile Function EF Domain Score		Previous Double-Blind Therapy					
		Placebo N=51	IC 2.5 mg N=53	IC 5 mg N=47	IC 10 mg N=43	IC 20 mg N=41	Total N=235
Visit 3	Week 0	n=51	n=53	n=47	n=42	n=41	n=234
IIEF EF Mean (SD)		16.3(8.8)	16.3(9.0)	15.8(8.7)	15.9(8.5)	16.0(8.9)	16.1(8.7)
Visit 6	Week 12	n=51	n=52	n=47	n=42	n=41	n=233
IIEF EF Mean (SD)		16.6(8.9)	20.8(7.9)	21.1(9.2)	22.7(8.1)	23.3(8.4)	20.7(8.8)
Visit 8	Week 16	n=47	n=53	n=43	n=42	n=38	n=223
IIEF EF Mean (SD)		23.2(8.2)	22.4(7.4)	24.0(6.7)	21.7(8.2)	23.9(7.1)	23.0(7.5)
Endpoint	Week 64	n=40	n=39	n=32	n=31	n=28	n=170
IIEF EF Mean (SD)		24.6(6.3)	24.4(7.0)	22.1(9.5)	22.5(7.8)	25.6(5.7)	23.9(7.6)

Source: Table LVHG 11.21, H6D-MC-LVHG Abbreviated Study Report, page 669

Reviewer's Comment: In patients with ED and BPH, the efficacy of tadalafil for the treatment of ED is maintained at 64 weeks.

Safety Results

The total exposure was 347.4 subject-years. The median duration of therapy was approximately 365 days (interquartile range of 148 days) and the mean duration of therapy approximately 297 days. There were 372 subjects (87%) with at least 91 days of exposure in the open-label extension period and 233 subjects with at least 365 days of exposure in the open-label extension period (55%). 92 of the 427 subjects enrolled in the open-label extension period had previously been placebo subjects.

Table 19: Adverse Events Overview Study LVHG Open-Label Period

	Previous Double-Blind Therapy					
	Placebo N=92	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Adverse Events(AE)	n (%)	n(%)	n(%)	n(%)	n(%)	n(%)
Deaths	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Serious AEs	5 (5.4)	3 (3.1)	6 (7.2)	4 (4.7)	2 (2.8)	20 (4.7)
Discontinuations Due to AE	6 (6.5	4 (4.2)	4 (4.8)	5 (5.9)	3 (4.2)	22 (5.2)
Treatment Emergent AEs	50 (54.3)	52 (54.2)	47 (56.6)	49 (57.6)	48 (67.6)	246 (57.6)

Source: Table LVHG 8.4, H6D-MC-LVHG Abbreviated Study Report, page 64.

There were no deaths reported during the open-label extension period.

A total of 20 patients reported 23 SAEs.

Table 20: Serious Adverse Events Open-Label Extension of Study LVHG

	Previous Double-Blind Therapy					
	Placebo N=92	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Preferred Term	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Patients with ≥ 1 SAE	5 (5.4)	3 (3.1)	6 (7.2)	4 (4.7)	2 (2.8)	20 (4.7)
Arthritis	0(0.0)	0(0.0)	1 (1.2)	1(1.2)	0(0.0)	2(0.5)
Knee Arthroplasty	1(1.1)	0(0.0)	1 (1.2)	0(0.0)	0(0.0)	2(0.5)
Non-Cardiac Chest Pain	0(0.0)	0(0.0)	1 (1.2)	1(1.2)	0(0.0)	2(0.5)
Acute Coronary Syndrome	0(0.0)	0(0.0)	1 (1.2)	0(0.0)	0(0.0)	1(0.2)
Atrial Flutter	0(0.0)	0(0.0)	1 (1.2)	0(0.0)	0(0.0)	1(0.2)
Basedow's Disease*	0(0.0)	0(0.0)	0(0.0)	1(1.2)	0(0.0)	1(0.2)
Bladder Neoplasm	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Cardiac Arrest	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Cardiac Congestive Failure	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Coronary Artery Disease	0(0.0)	0(0.0)	0(0.0)	1(1.2)	0(0.0)	1(0.2)
Coronary Artery Stenosis	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Fibular Fracture	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
GE Reflux Disease	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1(0.2)
Global Amnesia	0(0.0)	0(0.0)	1 (1.2)	0(0.0)	0(0.0)	1(0.2)
Hip Arthroplasty	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Infection	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Meniscus Lesion	0(0.0)	0(0.0)	0(0.0)	1(1.2)	0(0.0)	1(0.2)
Osteoarthritis	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Pneumonia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1(0.2)
Sinus Polyp	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)

*(Basedow's disease: autoimmune disease attacking thyroid resulting in hyperthyroidism)
Source: Table LVHG 8.2, H6D-MC-LVHG Abbreviated Study Report, page 60

Four patients reported SAEs related to cardiovascular disorders:

LVHG Subject 138 4801 is a 72-year-old with a history of atrial fibrillation who received tadalafil 5 mg in the double-blind phase, had atrial flutter and ventricular arrhythmia reported at Visit 12. The subject was successfully treated with electrophysiology ablation and reverted into sinus rhythm. ECG assessment at Visit 1, Visit 6, and Visit 12 presented 1st degree AV-block.

One of the ECGs in hospital also revealed an inferior infarct age undetermined per the physician who interpreted the ECG. It is noted that the ECG obtained on Visit 1 (from the OLE data set under EGASMLBL) states "myocardial infarction." After expert cardiologist review, the interpretation for the ECG at Visit 1 (under EGRDESC) is "no infarct present." The same sequence of interpretive events is repeated through Visit 12. The patient had a past history of fluctuating blood pressure and hypercholesterolemia. Additionally, his ALT laboratory values were marginally elevated at Visits 1, 3, and 8; at Visit 12, the subject had elevated alanine transaminase (ALT) levels reported as "ALT increased." The last dose of study drug was 3 February 2008. OLE enrollment date was 31 January 2007.The subject completed the study.

Reviewer's Comment: The ECG changes interpreted as "an inferior infarct age undetermined" were present at Visit 1. The patient had a past history of atrial fibrillation.

LVHG Subject 1233315 is a 62-year-old with coronary artery disease (CAD), sinus bradycardia, and hypertension who received tadalafil 10 mg in the double-blind phase, experienced a worsening of CAD and was hospitalized 7 months after dispensing before Visit 10. The subject was successfully treated with a stent insertion. The subject discontinued due to this event.

LVHG Subject 1384809 is an 80-year-old with hypertension, a history of bilateral lung nodules, dementia and exertional dyspnea who received placebo in the double-blind phase, was hospitalized with congestive heart failure and mild bilateral pleural effusion 6 days into the open-label extension. His admission ECG showed left ventricular hypertrophy and right bundle branch block. The patient was also febrile with a high neutrophil count and was started on intravenous antibiotic therapy. Blood cultures were negative and the neutrophil count normalized. He was successfully treated and discharged 3 days later. His ECG assessment at Visit 1, Visit 6, and Visit 12 presented sinus bradycardia, right bundle branch block, and 1st degree AV-block. The subject's blood pressure was normal at all study visits. The subject completed the study.

Reviewer's Comment: I would assume the dementia was acute and situational.

LVHG Subject 1233324 is a 63-year-old with CAD, sinus bradycardia, hypertension and ED, who received tadalafil 2.5 mg in the double-blind phase, reported cardiac arrest at Visit 11. The subject called the study site (between Visits 10 and 11) and stated, "feels like I'm having a heart attack". He was admitted to the hospital on (b) (6) where he subsequently stated he was diagnosed as having had a cardiac arrest. He was released from the hospital on (b) (6). Per the investigator then, corrective treatment was not given and the event was listed as improved. Overall ECG assessment at Visits 2 and 6 were abnormal with early R wave progression. No ECG was available at endpoint. The subject decided to discontinue the study at Visit 11. Six months after the subject discontinued, the subject continued to have occasional chest pain.

Reviewer's Comment: Being discharged from the hospital two days after a "cardiac arrest" with no documentation of an intervention such as angioplasty or pacemaker insertion is on its face suspect for accuracy. The report lacks adequate detail to know what exactly transpired.

Reviewer's Comment: By my reckoning, there appears to be one case of coronary artery disease (1233315). The case of congestive failure was confounded by hyperpyrexia. The case of atrial fibrillation had a previous history of atrial fibrillation. The case of "cardiac arrest" is incomplete in detail and offers no evidence as to the nature of the event requiring hospitalization.

Two subjects had non-cardiac chest pain.

LVHG Subject 1132315 is a 71-year-old who received tadalafil 5 mg in the placebo controlled, double-blind period. Eleven days (Visit 8) into the open-label extension, the subject went to the hospital because of chest pain lasting for a couple of days. On Day 11 of the OLE period, the patient the patient had morning chest pain. He was unable to sleep, had mild diaphoresis, but no remarkable nausea or vomiting. The pain was across his chest and a "little fixated to his right shoulder." He thought the pain was related to his rotator cuff (previous laser shoulder surgery). The patient had some shortness of breath. Prior to going to the hospital, the subject took acetylsalicylic acid. The subject was treated with nitroglycerin in the hospital, but the clinical workup was negative for MI and the subject was discharged 3 days later with a diagnosis of non-cardiac chest pain. Per the investigator, the subject had the preexisting condition of hypertension and on the day of submission the following relevant AEs: non-cardiac chest pain, musculoskeletal pain, nervousness, asthenia, painful respiration, dyspnea, coronary artery disease, MI (small amount of infarcted myocardium shown on an old stress test), and atrial fibrillation. The subject decided to discontinue the study at Visit 8.

Reviewer's Comment: The use of nitroglycerin in hospital is a possible protocol violation.

LVHG Subject 1415101 is a 60-year-old with hypertension who received tadalafil 10 mg in the double-blind phase, experienced chest pain three months after receiving the first dose of open-label study drug and was admitted to the hospital. The clinical workup excluded coronary artery syndrome. Antihypertensive medication was initiated, chest pain subsided, and the patient was discharged after 2 days; the event was reported as non-cardiac chest pain at Visit 10. The subject's ECG showed left atrial enlargement at Visits 1, 6, and 12 and poor precordial R wave progression at Visits 6 and 12. The patient also complained of left arm numbness. A head CT scan and carotid ultrasound examination were negative. A prostate irregularity (suspicion of prostate neoplasm) identified while in the hospital was reexamined by the subject's urologist at Visit 10 and found to be without an abnormality. A follow up prostate exam and PSA was suggested. While in hospital the chest pain and arm numbness resolved. The subject completed the study.

One subject reported worsening of GERD:

LVHG Subject 1243417 with pre-existing coronary artery disease and GERD reported to the hospital with chest pain. He had had a previous percutaneous cardiac stent insertion in June

2003. His cardiovascular workup was normal and he was discharged with treatment for GERD (recorded as an SAE).

> *Reviewer's Comment: It is possible that tadalafil aggravated the patient's GERD leading to the acute event.*

One subject reported the SAE of global amnesia.

LVHG Subject 2041431 is a 53 year male who reported global amnesia for 1 hour after working out in a gym 4 days after completing the study. The event occurred after the patient used a weight machine and lasted for approximately 1 hour. The subject did not have any previous episodes of amnesia, memory problems, migraine, cerebrovascular disease or seizure disorder. His concomitant medications include multivitamins and ascorbic acid.

> *Reviewer's Comment: The event occurred 4 days after completing the study and was reported after vigorous exercise, making a causal relationship to tadalafil unlikely.*

Two subjects reported the SAE of arthritis:

LVHG Subject 1253516 has a past history of arthritis. He decided to have elective surgery for arthritis of the left knee while on study drug for worsening arthritis in the opinion of the investigator. Patient completed the study.

LVHG Subject 1415106 is a 65 year-old male with a history of arthritis for years not requiring medication. On May 16, 2007 the patient began the OLE phase of the clinical trial. He had been previously randomized to tadalafil 5 mg. On 10 November 2011, he reported to site staff that because of worsened arthritis he had undergone a right knee replacement which he had been considering for several months. He also underwent a repair of a torn left meniscus. The patient's last visit date was 29 November 2007. He was discontinued secondary to protocol violation.

Two Subjects underwent knee arthroplasty:

LVHG Subject 1415106 (See narrative above)
LVHG Subject 1253516 (See narrative above)

The following subjects reported more than one SAE:

LVHG Subject 118 2834: osteoarthritis, hip arthroplasty: This 75 year-old male (previously randomized to 2.5 mg tadalafil) has a history of left hip osteoarthritis. He began OLE study drug 12 June 2007. The patient's existing left hip osteoarthritis worsened on 20 December 2008. On 7 January 2008, approximately 7 months after beginning open-label tadalafil, underwent an elective and planned left hip replacement. The patient completed the study.

LVHG Subject 125 3516: arthritis, knee arthroplasty (see narrative above)

LVHG Subject 141 5106: arthritis, meniscus lesion (see narrative above)

LVHG Subject 100 1004 sustained a fibular fracture. This 75 year old patient slipped and fell. On (b) (6), one year after starting study drug he was hospitalized for a right displaced fibular fracture and on (b) (6) he was discharged to a nursing home where he remained until (b) (6). Prior to the fall the patient had not experienced syncope, near syncope or dizziness.

> *Reviewer's Comment: Arthritis and need for its interventional treatment is common in this age group of men. I do not see any indication that tadalafil was causal for these events.*

LVHG Subject 117 2710 sinus polyps pre-existed the subject's inclusion in the study according to the narrative and Sponsor has designated this as a non-valid clinical trial case. There is no other information. The subject completed the study.

LVHG Subject 102 1201 was noted to have Basedow's disease. There is little correlation with autoimmune hyperparathyroidism (Basedow's disease) and other autoimmune diseases. The etiology of Basedow's disease is uncertain.

LVHG Subject 140 5005 is 50 years-old US male and developed atypical bilateral pneumonia 10 months after receiving the first dose of study drug. He had previously received tadalafil 20 mg once-daily. His past medical history includes hypertension, acid reflux, and degenerative disc disease with surgery for L5-S1 in 1992. According to the CRF, the patient is a current user of tobacco products. No further details of tobacco use are provided. During hospitalization, he required mechanical ventilation and enteral nutrition. Upon discharge he "was sent to rehabilitation and was placed on albuterol and bronchodilators. The study drug was discontinued.

Discontinuations

There were 22 subjects who discontinued due to AEs. They appear to be roughly equally distributed relative to previous treatment groups.

Table 21: Events Leading to Discontinuation Study LVHG Open-Label Extension Period

	Previous Double-Blind Therapy					
	Placebo N=92	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with ≥ 1 AE	6 (6.5)	4 (4.2)	4 (4.8)	5 (5.9)	3 (4.2)	22 (5.2)
Dyspepsia	1(1.1)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	2(0.5)
Stomach discomfort	1(1.1)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	2(0.5)
Acute coronary syndrome	0(0.0)	0(0.0)	1(1.2)	0(0.0)	0(0.0)	1 (0.2)
Arrhythmia	0(0.0)	0(0.0)	0(0.0)	1(1.2)	0(0.0)	1 (0.2)
Bladder neoplasm	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)
Carpal tunnel syndrome	0(0.0)	0(0.0)	1(1.2)	1(1.2)	0(0.0)	1 (0.2)
Coronary artery disease	0(0.0)	0(0.0)	1(1.2)	1(1.2)	0(0.0)	1 (0.2)
Deafness unilateral	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)
GE Reflux	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1 (0.2)
Hepatic enzyme increased	0(0.0)	0(0.0)	1(1.2)	0(0.0)	0(0.0)	1 (0.2)
Hepatic function abnormal	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)
Hot flush	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)
Muscle tightness	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)
Esophagitis	0(0.0)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)
Pollakiuria	0(0.0)	0(0.0)	0(0.0)	1(1.2)	0(0.0)	1 (0.2)
Prostate cancer	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1 (0.2)
Prostatic intraepithelial neoplasia	0(0.0)	0(0.0)	0(0.0)	1(1.2)	0(0.0)	1 (0.2)
Residual urine	0(0.0)	0(0.0)	1(1.2)	0(0.0)	0(0.0)	1 (0.2)
Seasonal allergy	0(0.0)	0(0.0)	1(1.2)	0(0.0)	0(0.0)	1 (0.2)
Visual disturbance	1(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (0.2)

Source: Table LVHG 8.3, H6D-MC-LVHG Abbreviated Study Report, page 62.

There were 22 subjects who discontinued the open-label extension due to AEs. Dyspepsia (n=2, Subjects 202-1227 and 135-4503) and stomach discomfort (n=2, Subjects 205-8012 and 120-3009) were the only AEs leading to discontinuation which occurred in more than 1 subject. There were 3 subjects who discontinued due to AEs related to cardiovascular disorders (coronary artery disease, Subject 123-3315; acute coronary syndrome, Subject 205-8001; arrhythmia, Subject 138-4811). Additionally, 2 subjects discontinued due to abnormal prostate findings (prostate cancer, Subject 109-1919; prostatic intraepithelial neoplasia, Subject 123-3309) and 2 subjects discontinued due to abnormal liver function tests (hepatic function abnormal, Subject 140-5001; hepatic enzyme increased, Subject 118-2837 [known Hepatitis C disease]). There was 1 subject who discontinued due to deafness unilateral (Subject 106-1604); 1 subject who discontinued due to residual urine (Subject 126-3633); and 1 subject who discontinued due to visual disturbance (Subject 106-1608).

While data is provided for the 4 subjects with dyspepsia and stomach discomfort, no textual narrative is provided.

LVHG Subject 202-1227 Patient discontinued 24 days after enrollment complaining of abdominal discomfort and dyspepsia.

LVHG Subject 135-4503 Patient discontinued approximately 6 weeks after enrollment complaining of moderate dyspepsia.

LVHG Subject 205-8012 Patient discontinued 6 months after enrollment complaining of continuous GI upset.

LVHG Subject 120-3009 Patient discontinued 6 weeks after enrollment complaining of flatulence, gas, and nausea.

Three patients discontinued due to AEs related to cardiac disorders:

LVHG Subject 123-3315 is a 71-year-old who received tadalafil 5 mg in the placebo controlled, double-blind period. Eleven days (Visit 8) into the open-label extension, the subject went to the hospital because of chest pain lasting for a couple of days. On Day 11 of the OLE period, the patient the patient had morning chest pain. He was unable to sleep, had mild diaphoresis, but no remarkable nausea or vomiting. The pain was across his chest and a “little fixated to his right shoulder. He thought the pain was related to his rotator cuff (previous laser shoulder surgery). The patient had some shortness of breath. Prior to going to the hospital, the subject took acetylsalicylic acid. The subject was treated with nitroglycerin in the hospital, but the clinical workup was negative for MI and the subject was discharged 3 days later with a diagnosis of non-cardiac chest pain. Per the investigator, the subject had the preexisting condition of hypertension and on the day of submission the following relevant AEs: non-cardiac chest pain, musculoskeletal pain, nervousness, asthenia, painful respiration, dyspnea, coronary artery disease, MI (small amount of infarcted myocardium shown on an old stress test), and atrial fibrillation. The subject decided to discontinue the study at Visit 8.

Reviewer's Comment: The use of nitroglycerin in hospital is a possible protocol violation.

LVHG Subject 205-8001 is a 72-year-old with a history of atrial fibrillation who received tadalafil 5 mg in the double-blind phase, had atrial flutter and ventricular arrhythmia reported at Visit 12. The subject was successfully treated with electrophysiology ablation and reverted into sinus rhythm. ECG assessment at Visit 1, Visit 6, and Visit 12 presented 1st degree AV-block. One of the ECGs in hospital also revealed an inferior infarct age undetermined per the physician who interpreted the ECG. It is noted that the ECG obtained on Visit 1 in the OLE data set under EGASMLBL states "myocardial infarction." After expert cardiologist review the interpretation for the ECG at Visit 1 is under EGRDESC "no infarct present." The same sequence of interpretive events is repeated through Visit 12. The patient had a past history of fluctuating blood pressure and hypercholesterolemia. Additionally, his ALT laboratory values were marginally elevated at Visits 1, 3, and 8; at Visit 12, the subject had elevated alanine transaminase (ALT) levels reported as "ALT increased." The last dose of study drug was 3 February 2008. OLE enrollment date was 31 January 2007.The subject completed the study.

Reviewer's Comment: The ECG changes interpreted as "an inferior infarct age undetermined" were present at Visit 1. The patient had a past history of atrial fibrillation.

LVHG Subject 138-4811 is a 56-year-old with hypertension and mild cardiac arrhythmia who received tadalafil 10 mg in the double-blind phase, had worsening of his cardiac arrhythmia at Visit 10. His ECG at Visit 1 showed 1st degree AV block and left atrial enlargement; Visit 6 and Visit 12 ECG showed atrial fibrillation; his heart rate at Visit 10 was 115 bpm. This event led to his discontinuation from the study.

Reviewer's Comment: With a decreased dose of tadalafil in the OLE period, this AE occurred, casting doubt on the relation to the study drug.

Two patients discontinued due to abnormal prostate findings:

LVHG Subject 109-1919 is a 70-year-old who received tadalafil 20 mg in the double-blind phase, reported prostate cancer at Visit 11 which was verified with biopsy. His PSA levels were 3.85 ng/mL (Visit 1), 3.91 ng/mL (Visit 3), 3.69 ng/mL (Visit 6), and 4.38 ng/mL (Visit 10). The investigator did not believe the event was related to study drug. The subject discontinued the study due to this event. Six months after his final visit the subject had completed prostate radiation.

LVHG Subject 123-3309 is a 68-year-old who received tadalafil 10 mg in the double-blind phase, had "PSA increased" recorded as an AE at Visit 10. His PSA values were at Visit 1, 3.69 ng/mL; Visit 3, 3.47 ng/mL; Visit 6, 2.77 ng/mL; Visit 10, 4.08 ng/mL; and endpoint, 3.29 ng/mL). A prostate biopsy was completed within 1 month of Visit 10 and showed high-grade prostatic intraepithelial neoplasia in less than 5% of tissue examined. The subject was scheduled

for a follow-up 2 months later, but did not show up. The subject discontinued due to prostatic intraepithelial neoplasia at Visit 11.

Two subjects discontinued due to abnormal liver tests.

LVHG Subject 140-5001 is a 72-year-old with hypertension, hypercholesterolemia, and diabetes who received placebo in the double-blind phase, had the AE "hepatic enzyme increased" recorded at Visit 6 (while on placebo) and "hepatic steatosis" at Visit 9. Hepatic enzymes increased in the double-blind period from Visit 1 to Visit 3 and from Visit 3 to Visit 6 (Visit 1: AST 47 U/L, ALT 69 U/L; Visit 3: AST 47 U/L, ALT 72 U/L; Visit 6: AST 82 U/L, ALT 111 U/L) and decreased from Visit 6 to Visit 8 (Visit 8: AST 59 U/L, ALT 88 U/L). Bilirubin values were normal. The subject was taking multiple concomitant medications (which include gemfibrozil, glyburide/metformin, hydrochlorthiazide, omeprazole, Lotrel, metoprolol, and warfarin. The subject discontinued at Visit 9 due to subject decision.

LVHG Subject 123-2837 is a 52-year-old with hepatitis C who received tadalafil 5 mg in the double-blind phase, had the AE "hepatic enzyme increase" recorded at study entry of the open label extension, which led to study discontinuation. The subject had elevated ALT levels (> 5 ULN) and elevated AST levels (>5 ULN) at Visit 6 of the double-blind phase (Visit 1: AST 31 U/L, ALT 29 U/L, GGT 28 U/L; Visit 3: AST 26 U/L, ALT 24 U/L, GGT 35 U/L; Visit 6: AST 181 U/L, ALT 254 U/L, GGT 105 U/L). Bilirubin values were normal. At the subject's discontinuation visit 3 days later, his hepatic enzymes were: AST 110 U/L, ALT 200 U/L, and GGT 106 U/L.

> *Reviewer's Comment: The patient's background hepatitis C condition may have played a role in the apparent increase in hepatic enzymes observed at Visit 6.*

1 patient discontinued for hearing loss.

LVHG Subject 106-1604 a 48-year-old who received tadalafil 2.5 mg in the double-blind phase, reported deafness unilateral at Visit 11 which lasted 17 days. According to the subject's otolaryngologist the subject had previously experienced neurosensory hearing loss (October 2006). The event occurred 2 months after a previous check-up and the otolaryngologist replied that there was minimal progression. The subject discontinued the study due to this event. Prior to the event of deafness unilateral the subject reported vertigo positional which occurred prior to Visit 10 and lasted for 63 days. One month after the deafness unilateral the subject reported tinnitus which lasted approximately 2 weeks. To treat the tinnitus, the patient used hydrogen peroxide ear drops. Concomitant medications were ascorbic acid and fluticasone for allergy.

> *Reviewer's Comment: This might be an exacerbation of a pre-existing condition.*

1 subject discontinued due to residual urine.

LVHG Subject 126-3633 is a 55-year-old who received tadalafil 5 mg in the double-blind phase, had the AE of residual urine at Visit 9. His PVR at Visit 1 was 164 mL, at Visit 6 was 194 mL, Visit 8 was 220 mL, and at Visit 9 was 319 mL. At Visit 9, the patient was taking Desentol, a medication for cough which he started on 1 December 2007 and continued until 7 December 2007. The active ingredient in Desentol is diphenhydramine which can increase PVR. Eleven days after Visit 9, his PVR was 183 mL. The subject discontinued the study due to this event. The site did not respond to a follow-up questionnaire.

> *Reviewer's Comment: This patient's increased PVR may have been affected in part by diphenhydramine.*

1 patient discontinued secondary to a visual disturbance.

LVHG Subject 106-1608 a 62-year-old who received placebo in the double-blind phase, reported visual disturbance, tinnitus (duration 40 days), and vertigo (duration 40 days) at Visit 10. Blood pressure and heart rate at all visits were normal. The event of visual disturbance led to study discontinuation. Subsequent follow-up with the site: the subject had experienced a "change in focus" which lasted a few months. The subject did not need treatment, was doing well, and the issue had resolved.

Treatment Emergent Adverse Events

Table 22: Treatment-Emergent Adverse Events Occurring in Greater Than 2% of Subjects in Any Previous Treatment Group Study LVHG Open-Label Extension Period Study LVHG

	Previous Double-Blind Therapy					
	Placebo N=92	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients ≥1 TEAE	25 (27.2)	28 (29.2)	27 (32.5)	22 (25.9)	25 (35.2)	127 (29.7)
Dyspepsia	4(4.3)	2(2.1)	3(3.6)	3(3.5)	2(2.8)	14(3.3)
GE Reflux	0(0.0)	2(2.1)	1(1.2)	5(5.9)	3(4.2)	11(2.6)
Back Pain	2 (2.2)	2 (2.4	2 (2.4)	1 (1.2)	1 (1.4)	10 (2.3)
Headache	2 (2.2)	0 (0.0)	0 (0.0)	3 (3.5)	3 (4.2)	8 (1.9)
Myalgia	3 (3.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.4)	5 (1.2)
Cough	0 (0.0)	3 (3.1)	0 (0.0)	0 (0.0)	1 (1.4)	4 (0.9)
Hypertension	0 (0.0)	1 (1.0)	2 (2.4)	1 (1.2)	0 (0.0)	4 (0.9)
Sinusitis	0 (0.0)	0 (0.0)	2 (2.4)	1 (1.2)	1 (1.4)	4 (0.9)
Depression	1 (1.1)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	3 (0.7)
Upper Respiratory Tract Infection	2 (2.2)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Rash Generalized	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Renal Cyst	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Throat Irritation	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)

Source: Table LVHG 8.6, H6D-MC-LVHG Abbreviated Study Report, page 68.

Overall, the percentage of subjects reporting ≥1 TEAE was similar (54.2% to 57.6%) between the previous treatment groups (placebo and tadalafil 2.5, 5, 10 mg) whereas subjects previously treated with tadalafil 20 mg reporting ≥1 TEAE was 67.6%. Dyspepsia, gastroesophageal reflux disease, back pain, headache, sinusitis, hypertension, and cough were the most commonly reported TEAEs.

The Sponsor also performed an analysis of AEs after one month of treatment in the OLE period to understand if either dose escalation or dose de-escalation is related to the occurrence of some AEs.

Table 23: TEAEs in >2% of Tadalafil Treated Subjects in Any Previous Treatment Group Following 1 Month of Treatment in the OLE Period

	Previous Double-Blind Therapy					
	Placebo N=92	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients ≥1 TEAE	17 (18.5)	12 (12.5)	7 (8.4 0	4 (4.7)	7 (9.9)	47 (11.0)
Dyspepsia	4(4.3)	1(1.0)	0(0.0)	0(0.0)	0(0.0)	5(1.2)
Myalgia	4(4.3)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	5(1.2)
Back Pain	2(2.2)	1(1.0)	1(1.2)	0(0.0)	0(0.0)	4(0.9)
Sinusitis	0(0.0)	0(0.0)	2(2.2)	1(1.2)	0(0.0)	3(0.7)
Headache	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(2.8)	2(0.5)
Rash Generalized	0(0.0)	2(2.1)	0(0.0)	0(0.0)	0(0.0)	2(0.5)
Renal Cyst	2(2.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.5)

Source: Table LVHG 8.8, H6D-MC-LVHG Abbreviated Study Report, page71.

> *Reviewer's Comment: The appearance of renal cysts without significant clinical detail would be difficult for me to attribute to dose escalation or new exposure to tadalafil as would the generalized rash noted in patients previously on tadalafil 2.5 mg once daily. Dyspepsia, myalgia, and back pain are compatible with the known AE profile of tadalafil. I do not discern any new information.*

Below are adverse event topics of special interest.

Subjects who had AEs that could possibly be due to Hypotensive Symptoms are discussed below:

LVHG Subject 101-1141 is a 76-year-old who received tadalafil 20 mg in the double-blind phase, reported dizziness at Visit 10 which had lasted 1 day. The event was moderate in severity. The subject's ECG findings showed 1st degree AV block, poor precordial R wave progression, and left axis deviation at Visit 1, 6, and 12. His blood pressure and heart rate were normal at all visits. Concomitant medications included atenolol and hydrochlorothiazide. The subject completed the study.

LVHG Subject 104-1413 is a 49-year-old who received tadalafil 10 mg in the double-blind phase, reported dizziness at Visit 11 which had lasted 13 days. The event was mild in severity. His blood pressure and heart rate were normal at Visits 10, 11, and 12. Per the subject's ECG, heart rate at Visit 1 and 12 were 55 and 59, respectively. The subject completed the study.

LVHG Subject 107-1752 is a 61 year-old who received placebo in the double-blind phase, reported dizziness at Visit 10 which had lasted 55 days. The event was mild in severity. The subject's blood pressure was 109/52 at entry and 106/53 at endpoint; his heart rate was normal. The subject also had elevated ALT (<2 ULN) at Visit 8, and elevated CPK at Visits 1 (204 U/L), 3 (213 U/L), 8 (3744 U/L), and endpoint (253 U/L). The subject decided to discontinue the study and is further discussed under adverse events related to the hepatic system.

LVHG Subject 125-3521 is a 58-year-old with hypertension, a prior MI and coronary artery bypass who received placebo in the double-blind phase, reported moderate dizziness 121 days into the open-label extension (prior to Visit 10) which lasted 170 days; at Visit 11 the event was reduced in severity to mild. The subject also reported onset of fatigue at the same time which lasted 154 days. Between Visit 10 and 11, 186 days into the open-label extension, the subject had transient complete AV block; two weeks later the subject had a cardiac pacemaker insertion. The day prior to the pacemaker insertion, treatment was initiated with zolpidem tartrate and cefazolin sodium for 1 day, levofloxacin for 1 week, and Propacet and metoprolol tartrate for 2 weeks. The subject's ECGs showed 1st degree AV block and MI at Visits 1 and 6, and increased PR interval at Visit 6. The subject's blood pressure and heart rate were normal. The subject completed the study.

Subject 106-1604, a 48-year-old who received tadalafil 2.5 mg in the double-blind phase, reported vertigo positional (benign paroxysmal vertigo with ageotropic findings) 170 days into the open label extension (prior to Visit 10) which lasted 63 days. The subject also reported deafness unilateral (left ear hearing loss) 185 days into the open-label extension which led to discontinuation at Visit 11 (Section 8.3.4.6), and tinnitus (bilateral ear crackling) 216 days into the open label extension which lasted 2 weeks. To treat the tinnitus, the subject used urea hydrogen peroxide ear drops. His blood pressure and heart rate were normal at all study visits. This case is also discussed in discontinuation narratives.

> *Reviewer's Comment: The vertigo is more likely related to the inner ear AE and not to hypotension. Two of the above patients also had AV block and one (of the two with AV block) was on antihypertensive medications*

An additional event related to the Cardiovascular System is below:

LVHG Subject 110-2001 is a 73-year-old who received tadalafil 20 mg in the double-blind phase, reported renal artery occlusion and increased blood pressure at Visit 9 and again at Visit 11; both events were moderate in severity. The event of hypertension was reported at Visit 9 and had lasted 35 days. The subject had a history of renal artery stenosis and stent placement in 2003. The subject completed the study.

> *Reviewer's Comment: The hypertension could be related to the renal artery occlusion.*

Cardiovascular Adverse Events are discussed below:

Some of these cases were discussed in previous sections but are included here again to include all cases under one heading.

LVHG Subject 113-2315 was a 71year-old who received tadalafil 5 mg in the placebo controlled, double-blind period. Eleven days (Visit 8) into the open-label extension, the subject went to the hospital because of chest pain lasting for a couple of days. Prior to going to the hospital, the subject took acetylsalicylic acid. The subject was treated with nitroglycerin in the hospital, but the clinical workup was negative for MI and the subject was discharged 3 days later with a diagnosis of non-cardiac chest pain. Per the investigator, the subject had the preexisting condition of hypertension and on the day of submission the following relevant AEs: non-cardiac chest pain, musculoskeletal pain, nervousness, asthenia, painful respiration, dyspnea, coronary artery disease, MI (small amount of infarcted myocardium shown on an old stress test), and atrial fibrillation. The subject decided to discontinue the study at Visit 8.

> *Reviewer's Comment: This case discussed in discontinuations and is a possible protocol violation in light of nitroglycerin use.*

LVHG Subject 117-2713 is a 58-year-old with hypertension who received tadalafil 5 mg in the double-blind phase, reported atrial fibrillation at Visit 12 which had occurred for 81 days. His blood pressure and heart rate at study visits were normal during, before, and after the period of this event. He was treated with digoxin and heparin. Overall ECG assessment at visit 6 was abnormal, but no ECG was available at endpoint. Concomitant medications included Tylenol® Sinus (acetaminophen 325 mg/guaifenesin 20 mg/phenylephrine HCL 5 mg). This subject also had an increase in aspartate transaminase (AST) >3 times the upper limit normal at Visit 12. The subject completed the study and the site follow-up indicated that his condition was stable and he was feeling fine.

LVHG Subject 118-2804 is a 60-year-old with right bundle branch block, dyspnea, and hypertension who received placebo in the double-blind phase, had unstable angina and a cardiac clinical workup performed between Visit 11 and Visit 12. This revealed an ECG stress test with poor performance, ventricular hypokinesia, coronary artery disease, and coronary artery stenosis. Five weeks after the clinical workup, the coronary stenosis was corrected with stent insertion. The subject completed the study.

LVHG Subject 123-3315 is a 62-year-old with coronary artery disease (CAD), sinus bradycardia, and hypertension who received tadalafil 10 mg in the double-blind phase, experienced a worsening of CAD and was hospitalized before Visit 10. The subject was successfully treated with a stent insertion. The investigator believed this event was possibly related to study drug. The subject discontinued due to this event.

LVHG Subject 123-3324 is a 63-year-old with CAD, sinus bradycardia, hypertension and ED, who received tadalafil 2.5 mg in the double-blind phase, reported cardiac arrest at Visit 11. The subject called the study site (between Visits 10 and 11) and stated, "feels like I'm having a heart attack". He went to the hospital where he subsequently stated he was diagnosed as having had a cardiac arrest. Per the investigator then, details of corrective treatment were not given and

the event was listed as improved. He was discharged from the hospital within 2 days. Overall ECG assessment at Visits 2 and 6 were abnormal with early R wave progression. No ECG was available at endpoint. The subject decided to discontinue the study at Visit 11. Six months after the subject discontinued, the subject continued to have occasional chest pain.

Reviewer's Comment: This case was discussed in the discontinuations. The history and detail do not allow a conclusion as to what events actually took place, although it is unlikely that the patient experienced cardiac arrest and was discharged two days later..

LVHG Subject 138-4801 is a 72-year-old with a history of atrial fibrillation who received tadalafil 5 mg in the double-blind phase, had atrial flutter and ventricular arrhythmia reported at Visit 12. The subject was successfully treated with electrophysiology ablation and reverted into sinus rhythm. ECG assessment at Visit 1, Visit 6, and Visit 12 presented 1st degree AV-block. Additionally, his ALT values were marginally elevated at Visits 1, 3, and 8; at Visit 12, the subject had elevated alanine transaminase (ALT) levels reported as "ALT increased. The subject completed the study.

Reviewer's Comment: This case was discussed previously.

LVHG Subject 138-4809 is an 80-year-old with hypertension, a history of bilateral lung nodules, and exertional dyspnea who received placebo in the double-blind phase, was hospitalized with congestive heart failure and mild bilateral pleural effusion 6 days into the open-label extension. His admission ECG showed left ventricular outflow tract obstruction, left ventricular hypertrophy and right bundle branch block. He was successfully treated and discharged 3 days later. His ECG assessment at Visit 1, Visit 6, and Visit 12 presented sinus bradycardia, right bundle branch block, and 1st degree AV-block. The subject's blood pressure was normal at all study visits. The investigator did not believe the congestive heart failure was related to study drug. The subject completed the study.

Reviewer's Comment: This patient is discussed under SAEs. It is of note that on admission the patient was febrile (See discussion under SAEs) which may have been contributory to the congestive heart failure.

LVHG Subject 138-4811 is a 56-year-old with hypertension and mild cardiac arrhythmia who received tadalafil 10 mg in the double-blind phase, had worsening of his cardiac arrhythmia at Visit 10. His ECG at Visit 1 showed 1st degree AV block and left atrial enlargement; Visit 6 and Visit 12 ECG showed atrial fibrillation; his heart rate at Visit 10 was 115. The investigator did not believe the worsening of the arrhythmia was related to study drug. This event led to his discontinuation from the study.

LVHG Subject 141-5101 is a 60-year-old with hypertension who received tadalafil 10 mg in the double-blind phase, experienced chest pain three months after receiving the first dose of open-label study drug and was admitted to the hospital. The clinical workup excluded coronary artery syndrome. Antihypertensive medication was initiated, chest pain subsided, and the patient was discharged after 2 days; the event was reported as non-cardiac chest pain at Visit 10. The

subject's ECG showed left atrial enlargement at Visits 1, 6, and 12 and poor precordial R wave progression at Visits 6 and 12. A prostate irregularity (suspicion of prostate neoplasm) identified while in the hospital was reexamined by the subject's urologist at Visit 10 and found to be without an abnormality. The subject completed the study.

LVHG Subject 143-5316 is a 62-year-old with mild hypertension who received tadalafil 2.5 mg in the double-blind phase, reported palpitations at Visit 9 which had occurred for 48 days. At Visit 8, the subject's hypertension increased in severity from mild to moderate. Just prior to Visit 8, he initiated temazepam (reportedly for hypertension) and pantoprazole (for gastroesophageal reflux disease); the subject stopped temazepam 10 days prior to Visit 9 on the same date the palpitations ended. The subject completed the study.

> *Reviewer's Comment: There is no ECG evidence provided or vital sign evidence of an abnormal cardiac rate and the patient has gastroesophageal reflux which can mimic cardiac symptoms.*

Subject 205-8001 is a 57-year-old who received tadalafil 5 mg in the double-blind phase, reported acute coronary syndrome at Visit 11. The subject was treated with a nitrate for this event while in the emergency room. The subject discontinued the study due to this event.

> *Reviewers Comment: There does not appear to be a significant difference in coronary related AEs in patients previously on tadalafil in the double-blind period relative to those previously on placebo in the double-blind period.*

One patient sustained a cerebrovascular accident:

LVHG Subject 107-1706 is a 79-year-old who received tadalafil 2.5 mg in the double-blind phase, reported a cerebrovascular accident at Visit 11 which had lasted for 1 day. He was treated with Asasantine and followed by a cardiologist. His ECG assessment showed abnormal rhythm assessment at both entry and final visits. His blood pressure and heart rate were normal at all visits. The subject had previously had an angioplasty with stent replacement in June 1999 and a mild MI in 2002 and a history of hypercholesterolemia and hypertension. The subject decided to discontinue the study.

Below are Adverse Events Related to Vision/Eyes:

LVHG Subject 104-1411 is a 46-year-old who received tadalafil 2.5 mg in the double-blind phase, reported vision blurred in his right eye at Visit 11 which lasted 154 days.
The event was mild in severity and the subject reported his right eye had always been weaker than the left. He had been to an ophthalmologist, who felt that the event was related to eye strain and eye fatigue because it occurred late in the day. Eight months following the event, the subject was re-evaluated by his ophthalmologist with no changes in his eye evaluation from the previous

year. Of note, this subject's concomitant medications included Flonase® (fluticasone propionate) since August 2007. The subject completed the study.

LVHG Subject 107-1723 is a 77-year-old who received tadalafil 10 mg in the double-blind phase, reported vision blurred at Visit 9 in both eyes. The event was mild in severity. The subject completed the study.

LVHG Subject 141-5104 is a 71-year-old who received tadalafil 10 mg in the double-blind phase, reported vision blurred at Visit 9. The event was mild in severity.
According to the site, the event was caused by contacts and cataracts for which the subject was seeing an ophthalmologist. The subject decided to discontinue the study at Visit 9.

LVHG Subject 102-1212 is a 53-year-old subject who received tadalafil 5 mg in the double-blind phase, reported blurred vision at Visit 4 of the double-blind phase which persisted to Visit 10 of the open-label extension. His blood pressure at Visit 3 was 114/66 mm Hg and at Visit 4 was 106/80 mm Hg (first visit after the onset of event). There were no ECG changes between Visits 1 and 6. The subject completed the study

> *Reviewer's Comment: Tthis subject was discussed previously in the review of the double-blind portion of LVHG.*

LVHG Subject 106-1608 is a 62-year-old who received placebo in the double-blind phase, reported visual disturbance, tinnitus (duration 40 days), and vertigo (duration 40 days) at Visit 10. Blood pressure and heart rate at all visits were normal. The event of visual disturbance led to study discontinuation. Subsequent follow-up with the site: the subject had experienced a "change in focus" which lasted a few months. The subject did not need treatment, was doing well, and the issue had resolved.

> *Reviewer's Comment: This case was discussed previously.*

LVHG Subject 140-5009 is a 55-year-old who received tadalafil 10 mg in the double-blind phase, reported an eye hemorrhage (broken blood vessel in right eye) at Visit 12.
Blood pressure and heart rate were normal; the subject's body mass index (BMI) was 32.3 kg/m2. The subject completed the study. Subsequent follow-up with the site: the subject had no testing done and no treatment was given; he voiced the issue had cleared up and he had no further issue with his eye.

> *Reviewer's Comment: The "change in focus" in Subject 106-1608 is the only AE I could possibly attribute to tadalafil.*

Below are Adverse Events related to the Hepatic System:

LVHG Subject 140-5001 is a 72-year-old with hypertension, hypercholesterolemia, and diabetes who received placebo in the double-blind phase, had the AE "hepatic enzyme increased" recorded at Visit 6 (while on placebo) and "hepatic steatosis" at Visit 9. Hepatic enzymes

increased in the double-blind period from Visit 1 to Visit 3 and from Visit 3 to Visit 6 (Visit 1: AST 47 U/L, ALT 69 U/L; Visit 3: AST 47 U/L, ALT 72 U/L; Visit 6: AST 82 U/L, ALT 111 U/L) and decreased from Visit 6 to Visit 8 (Visit 8: AST 59 U/L, ALT 88 U/L). Bilirubin values were normal. The subject was taking multiple concomitant medications. The subject discontinued at Visit 9 due to subject decision.

> *Reviewer's Comment: This case was discussed previously. The patient was noted to have an increase of hepatic enzymes while receiving placebo and was on multiple concomitant medications.*

LVHG Subject 118-2837 is a 52-year-old with hepatitis C who received tadalafil 5 mg in the double-blind phase, had the AE "hepatic enzyme increase" recorded at study entry of the open label extension, which led to study discontinuation. The subject had elevated ALT levels (> 5 ULN) and elevated AST levels (>5 ULN) at Visit 6 of the double-blind phase (Visit 1: AST 31 U/L, ALT 29 U/L, GGT 28 U/L; Visit 3: AST 26 U/L, ALT 24 U/L, GGT 35 U/L; Visit 6: AST 181 U/L, ALT 254 U/L, GGT 105 U/L). Bilirubin values were normal. At the subject's discontinuation visit 3 days later, his hepatic enzymes were: AST 110 U/L, ALT 200 U/L, and GGT 106 U/L.

> *Reviewer's Comment: This case was discussed previously. The patient had known hepatitis C and had an apparent increase in hepatic enzymes at Visit 6. It is not possible to directly attribute this event to tadalafil.*

LVHG Subject 101-1181 is a 66-year-old with prior diagnosis of jaundice who received placebo in the double-blind phase, had the AEs of "blood bilirubin increased" and "hepatic function abnormal" reported at Visit 10, which reportedly lasted 191 days until study completion. The subject had marginally elevated bilirubin, AST, and ALT while on placebo at Visit 6. At Visit 10, AST and AST were marginally elevated, while bilirubin was within normal range. At Visit 12, bilirubin, AST, and ALT, were within normal range; GGT was slightly elevated. The subject completed the study and the site reported that the subject was doing well and is following up with his primary care physician.

LVHG Subject 138-4801 is a 72-year-old who received tadalafil 5 mg in the double-blind phase, had the AE of "ALT increased" reported at Visit 12 (AST, GGT and bilirubin normal). His ALT laboratory values were marginally elevated at Visits 1, 3, and 8. At Visit 12, the subject also had increased blood potassium, and reported atrial flutter and ventricular arrhythmia which required hospitalization. The subject completed the study.

LVHG Subject 138-4803 is a 55 year-old who received placebo in the double-blind phase, had the AE of "AST increased" (66 U/L; normal range: 11 to 36 U/L) and "blood CPK increased" (4768 U/L; normal range: 18 to 198 U/L) at Visit 10 which lasted 22 days (Visit 10 follow-up CPK results were 308 U/L). Three days prior to these events, the subject reported muscle injury (right thigh muscle tear) which lasted 100 days. None of these events were listed as related to study drug. The subject completed the study.

Reviewer's Comment: Two subjects had minimal and sporadic liver function test abnormalities. The third subject had CPK and AST increases explained by a muscle injury.

There were two subjects who developed prostatic malignancies: 109-1919 and 112-2219. Additionally there were four subjects who were noted to have abnormal digital rectal exams. In three cases a biopsy was not done. In one case the nodule was not a constant finding (141-5101) and in 2 cases no additional action was taken (101-1144 and 127-3718). In the fourth subject (123-3309), the PSA was normal and a biopsy revealed high grade prostatic intraepithelial neoplasia.

There were two adverse events related to the urinary tract:

Subject 119-2905 is a 69-year-old who received tadalafil 2.5 mg in the double-blind phase, reported urinary retention 99 days into the open-label extension (between Visits 8 and 9). His PVR at Visit 8 was 22 mL. The day after he reported urinary retention he initiated treatment with alfuzosin; 2 months later, laser surgery was performed. The subject reported feeling much better. The investigator did not believe the event was related to study drug. The subject was discontinued due to protocol violation (alfuzosin treatment).

Subject 126-3633 is a 55-year-old who received tadalafil 5 mg in the double-blind phase, had the AE of residual urine at Visit 9. His PVR at Visit 1 was 164 mL, at Visit 6 was 194 mL, Visit 8 was 220 mL, and at Visit 9 was 319 mL. Eleven days after Visit 9, his PVR was 183 mL. The subject discontinued the study due to this event. The site did not respond to a follow-up questionnaire.

Reviewer's Comment: Subject 126-3633 was using a cold medication containing diphenhydramine which could have contributed to the increase of PVR between Visit 8 and 9. This case was previously discussed under discontinuations.

Below are other notable adverse events:

LVHG Subject 106-1604 is a 48-year-old who received tadalafil 2.5 mg in the double-blind phase, reported deafness unilateral at Visit 11 which lasted 17 days. According to the subject's otolaryngologist the subject had previously experienced neurosensory hearing loss (October 2006). The event occurred 2 months after a previous check-up and the otolaryngologist replied that there was minimal progression. The subject discontinued the study due to this event. Prior to the event of deafness unilateral the subject reported vertigo positional. One month after the deafness unilateral the subject reported tinnitus which lasted approximately 2 weeks.

Reviewer's Comment: This patient had a pre-existing neurosensory hearing loss with minimal progression.

LVHG Subject 109-1915 is a 61-year-old who received tadalafil 10 mg in the double-blind phase, reported penile vein thrombosis at Visit 11. The site reported that the event was a rare occurrence that did not require follow-up or treatment. The subject completed the study.

> *Reviewer's Comment: There is no information relating to whether the patient's frequency of intercourse or intercourse duration had increased secondary to tadalafil. Both of these factors are thought to be possibly related to penile vein thrombosis.*

LVHG Subject 109-1921 is a 70-year-old who received tadalafil 2.5 mg in the double-blind phase, reported thrombocytopenia at Visit 10. Platelet count for this subject at Visit 1 (151 bill/L) was within normal limits (130 to 483 bill/L); platelet count was low at Visit 6 (109 bill/L), Visit 8 (108 bill/L), and Visit 10 (90 bill/L). At Visit 6, the subject also reported herpes zoster which was treated with Valtrex® (valacyclovir hydrochloride) starting 5 days prior to Visit 6. The subject decided to discontinue the study.

LVHG Subject 118-2834 is a 74-year-old who received tadalafil 2.5 mg in the double-blind phase, reported anemia postoperative at Visit 11. The event was secondary to hip arthroplasty conducted because of moderate-severity osteoarthritis. The investigator did not believe the event was related to study drug. The subject completed the study.

LVHG Subject 128-3801 is a 69-year-old who received tadalafil 2.5 mg in the double-blind phase, reported prolonged erection which was coded to spontaneous penile erection at Visit 11 which lasted 2 days. The site did not respond to follow-up questionnaires. The subject completed the study.

Clinical Laboratory Evaluation

Five subjects with elevations of serum liver chemistry test results have been previously discussed. No subject had an elevation of bilirubin levels >1.5 ULN. No clinically adverse changes were observed in laboratory values, or PSA.

There were 56 subjects who had normal to abnormal shifts in UA-Protein Random Urine between baseline and end of therapy. O f these 56 subjects, 15 had abnormal proteinuria values at Visit 1 that shifted to normal at baseline. Of the remaining 41, 36 subjects had documented confounding factors (including hypertension, diabetes, nephrolithiasis, hyperglycemia, Lyme disease, and renal impairment) that could contribute to proteinuria or were taking medications that could contribute to proteinuria. There were a few subjects in the open label extension that had positive hematuria and leucocyte esterase.

Post Void Residual Urine

Of the subjects who entered the open-label extension, there were 31 who had PVR volumes > 200 mL at Visit 1 or Visit 3; 53 subjects with PVR volumes ≥ 200 mL at any visit throughout the study, and 13 subjects had PVR volumes ≥200 mL at endpoint. The average PVR volumes for

placebo and all tadalafil subjects at baseline were 58.9 and 61.1 mL respectively. At Week 12 they were 67.7 and 63.0 mL respectively. It is of note that in the 20 mg per day tadalafil dose group, the average PVR at Week 12 was 47 mL. At Week 64, the OLE period endpoint, the average PVR was 51.2 mL.

Vital Signs

There were no clinically adverse changes observed in vital signs.

In DATASET-VISIT.XPT 14 patients had an AE designated as hypertension as a study adverse event by preferred term as shown in the table below:

Table 24: Patients with AE of Hypertension in LVHG Open-Label Extension

(b) (4)

Reviewer's Comment: Of the 14 patients, 12 subjects had blood pressures in the hypertensive range at Visits 1, 2, or 3. the remaining 2 subjects (1071763 and 1233315) had no blood pressures recorded which I consider hypertensive. The last recorded blood pressure was in the hypertensive range in only 4 subjects at study completion. In three of these 4 subjects, the final blood pressures were below those recorded at Visit 1. Upon review of patient line listings, I would consider none of the patients above to have treatment emergent hypertension.

Electrocardiograms

An external cardiologist evaluated 164 ECGs for 82 subjects at endpoint in the open-label extension comparing with the Visit 6 ECG. According to the external cardiologist, 60 subjects had an abnormality on ECG according to the Lilly Interpretive Standards. There were 15 subjects with paired observations that had a significant change from the baseline ECG (Visit 6 ECG) during treatment; of these, 3 subjects (112-2216, 119-2919, and 129-3905) had clinically significant changes. There were 3 subjects with suspicion of myocardial infarctions (MI) detected on electrocardiography at any time during the study. The subjects with significant changes from baseline were further described by the external cardiologist. Summaries for patients in whom the external cardiologist did not consider the changes to be significant will only be listed and not discussed. The following summaries represent the opinion of the external cardiologist:

Subject 101-1102 had premature ventricular depolarization at Visit 6 that was no longer present at the subsequent visit and was judged not clinically significant.

Subject 105-1507 at Visit 6 had nonspecific ST- and T-wave changes. At the subsequent visit, the subject also developed second-degree AV block (Mobitz Type I) and judged not clinically significant.

Subject 107-1704 displayed nonspecific T-wave changes at Visit 6. The subsequent ECG showed normalization of these T waves and the emergence of PVCs and judged not clinically significant.

Subject 108-1817 at baseline displayed first-degree AV block. The subsequent ECG also showed atrial premature depolarizations and ventricular premature depolarizations and judged not clinically significant.

Subject 108-1821 at Visit 6 displayed left atrial enlargement and nonspecific T-wave changes. The subsequent ECG showed new T-wave inversions that were possibly clinically significant, as per the adjudicator, and needs to be correlated with clinical findings. This 54 year-old subject received tadalafil 20 mg in the double-blind phase. His pre-existing conditions include hypertension and hypercholesterolemia. At Visit 1, the subject's hypertension was being treated with co-divan, amlodipine and metoprolol succinate. He was also taking acetylsalicylic acid. The subject's blood pressure was normal from Visit 1 to Visit 5 in the double blind period and at

Visit 11 in the open-label extension (126/70). The subject's blood pressure was elevated from Visit 6 (220/146) to Visit 10 (190/80) and at Visit 12 (177/88). No AEs were recorded for this subject. The subject completed the study. The site did not respond to follow-up questions.

> *Reviewer's Comment: The patient had baseline hypertension and was taking 3 anti-hypertensives for BP control. The left atrial enlargement noted on ECG at Visit 6 may have been secondary to his baseline hypertension. Further, the patient's blood pressure returned to normal while still enrolled in the open-label extension. Therefore, the ECG change and fluctuation in blood pressure cannot be definitely attributed to tadalafil.*

Subject 109-1921 developed sinus bradycardia at a rate of 49 bpm and judged not clinically significant.

Subject 112-2213 at baseline [Visit 6], displayed left axis deviation, voltage for left ventricular hypertrophy, and met criteria for an inferior MI. At the subsequent visit, the tracing no longer met the criteria for inferior MI. The subject was a 53-year-old subject who received tadalafil 10 mg in the double-blind phase. During the double blind phase the subject had an MI identified by the external cardiologist in his ECG; the event was not clinically verified and was not registered as a TEAE, SAE, or AE leading to discontinuation. This event was discussed in the double blind phase. No cardiovascular or other relevant historical or pre-existing diagnoses were reported. The subject completed the open-label extension study.

> *Reviewer's Comment: This subject met ECG criteria for an MI on the Visit 6, which subsequently reversed on ECG, and there was no clinical correlation*.

Subject 112-2216 between Visit 6 and the subsequent tracing, developed findings of a new lateral MI and junctional rhythm and was judged clinically significant.

Subject 112-2220 displayed abnormal T waves at Visit 6. At the subsequent visit, these T waves normalized and were judged not clinically significant.

Subject 119-2919 developed new nonspecific ST segment changes and criteria for left ventricular hypertrophy and was judged clinically significant. This 45 year-old subject received tadalafil 10 in the double-blind period. He has known mitral valve prolapse. At Visit 3 of the double-blind phase the subject's overall ECG assessment was abnormal. The subject's CPK was elevated at Visit 1 (212 U/L), Visit 8 (208 U/L), Visit 10 (522 U/L and 207 U/L one-month later at follow-up), and Visit 12 (200 U/L). The subject's systolic blood pressure ranged from 105-126 mm/Hg and heart rate ranged from 51-64 bpm from Visit 1 to Visit 12. There were no cardiovascular AE's recorded. No concomitant medications were recorded for this subject during the open-label extension. The subject completed the study. There was no further information available from the site.

> *Reviewer's Comment: CPK was elevated at Visit 1. Without CPK subunit analysis, I cannot attribute the elevated CPK to the heart muscle. The patient was not hypertensive.*

The left ventricular hypertrophy could be possibly due to the mitral valve prolapse. The external cardiologist provided no qualification regarding the ST segment changes.

Subject 124-3432 displayed premature ventricular depolarization at baseline that resolved on the subsequent trace and judged not clinically significant.

Subject 128-3801 displayed sinus bradycardia at baseline that resolved on the subsequent tracing and was judged not clinically significant.

Subject 129-3905 developed a new left axis deviation at follow-up judged clinically significant and needs clinical correlation. This 66-year-old subject received tadalafil 10 mg in the double-blind phase. His pre-existing conditions included arthritis, multiple allergies, insomnia, and chronic sinusitis. At Visit 1, the subject was concomitantly taking naproxen sodium and clonazepam. Between Visits 4 and 5 in the double-blind phase, the subject was treated with: two 1-week treatments of prednisone for allergies; a 2-week treatment of omeprazole for gastroesophageal reflux disease (GERD); and a 3-week treatment of amoxicillin, all corresponding to the same time period. At Visit 11, omeprazole was initiated for GERD. The subject had elevated CPK at Visit 3 (213 U/L) and Visit 8 (214 U/L). The subject's blood pressure and heart rate were normal at all visits. No cardiovascular AEs were reported for this subject. The subject completed the study. The site did not respond to follow-up questions.

Reviewer's Comment: In the absence of CPK subunit analysis, interpretation of the CPK elevations is not possible. There is no clinical correlation with the new LAD noted on ECG or any significant cardiac symptomatology.

Subject 145-5500 developed a new first degree AV block judged not clinically significant.

Subject 145-5502 had nonspecific T-wave abnormalities at baseline that normalized on the subsequent trace judged not clinically significant.

There were three ECGs with a diagnosis of MI:

Subject 112-2213 see summary above.

Subject 112-2200 at baseline had inferior MI of indeterminate age and no change on the subsequent tracing.

Subject 112-2216 between Visit 6 and the subsequent ECG developed findings of a new lateral MI and junctional rhythm. This appears to be an infarct that was treatment emergent and needs clinical correlation. This event was asymptomatic and not reported as an AE. According to the cardiologist, the MI appeared to be treatment emergent on ECG. The subject discontinued the study at Visit 9. The subject stated that since discontinuation from the study, he had an ECG the result of which he believed was normal. He denied having any cardiac complications or medical problems during or since completing the study. The subject's pre-existing conditions included hypertension, hypercholesterolemia, gout, arthritis, and gastroesophageal reflux disease.

Reviewer's Comment: Two of the three MI's had baseline ECG findings of MI. In the third MI subject, subsequent ECGs are reported as normal as reported by the patient and there were no clinical correlative findings.

707 ECGs were evaluated by the CRO. Over the 64 week course Study LVHG open-label extension there appeared to be minimal changes in heart rate, PR interval, QRS interval, QTC interval, and RR interval at Visits 1, 6, and endpoint, and change from Visit 1 to Visit 6 to endpoint for the overall population and when evaluated by previous treatment.

Most subjects (94.2%) had no axis treatment-emergent abnormalities by ECG assessment. Left axis deviation was the most frequently reported axis abnormality reported on ECGs (2.7%). Most subjects (92.1%) had no conduction treatment emergent abnormalities by ECG assessment. First-degree AV block was the most frequently reported conduction abnormality reported on ECGs (4.1%).

Most subjects (97.8%) had no ischemia treatment emergent abnormalities by ECG assessment. Most subjects (78.5%) had no treatment-emergent morphology abnormalities; early R-wave progression (7.1%), poor precordial R-wave progression (7.1%), and left atrial enlargement (5.8%) were the most frequently reported morphology abnormalities, and the incidence of other morphology abnormalities was low.

Study LVHJ: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia

Study LVHJ was a "pivotal", Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of tadalafil 5 mg once daily for 12 weeks versus placebo in men with BPH-LUTS.

The enrollment criteria for Study LVHJ were generally similar to those for Study LVHG with minor modifications that aligned with FDA feedback (End-of-Phase 2 Meeting, Minutes 23 October 2008; revised exclusion criteria for subjects with PSA ≥4.0 to ≤10.0 ng/ml at screening to rule out prostate cancer to the satisfaction of an urologist instead of documentation of a histologic biopsy of the prostate negative for cancer within 12 months and added exclusion criteria for subjects with clinically significant microscopic hematuria. In addition, subjects who had received dutasteride treatment within 6 months, rather than the 12 months as required in Study LVHG, before the start of the placebo lead-in period were excluded). Subjects were excluded from enrollment if within 6 months of Visit 1 the systolic blood pressure was >160 mmHg or less <90 mmHg and/or the diastolic blood pressure was >100 mmHg or <50 mmHg.

The study consisted of 3 periods:

- Screening/Washout Period: Subjects signed an ICD at Visit 1 prior to participating in any study procedure. The first period was for screening and to accommodate a 4-week washout of BPH, OAB, or ED treatments, if needed, in order to assess symptoms and uroflowmetry data in the absence of therapy.

- Placebo Lead-In Period: After the screening/washout period, subjects returned for Visit 2 to assess whether eligibility criteria (IPSS ≥13 and Qmax ≥4 to ≤15 mL/second) were met in order to proceed to the placebo lead-in period. Subjects meeting these 2 criteria began a 4-week single-blind, placebo lead-in period to assess treatment compliance and establish baseline levels at its conclusion.

- Treatment Period: At Visit 3 (randomization), subjects who were at least 70% compliant with therapy during the placebo run-in period were eligible to be randomly assigned to treatment (tadalafil 5 mg or placebo) in a 1:1 ratio and begin the 12-week treatment period.

After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period. Randomization was stratified by baseline LUTS severity (IPSS <20 or ≥20), geographic region (US, Latin America [Argentina and Mexico], or Europe [Germany and Italy]), and history of ED. The subjects were randomized in a 1:1 ratio. 325 subjects were randomized. 300 subjects completed the study (148 tadalafil and 152 placebo).

Subjects had a mean age of 64.9 years with a range of 44.8 to 87.0 years. Overall, 20.0% of randomized subjects (placebo, 21.3%; tadalafil, 18.6%) were at least 75 years of age or older. Most subjects (91.1%) were white. The tadalafil and placebo treatment groups were well-balanced with respect to age, ethnicity, and region. 31.4% (102) of the subjects in Study LVHJ were from the United States.

At randomization, approximately one-third of subjects (35.4%) were categorized as having severe LUTS (IPSS >20) with the remainder (64.6%) having a total IPSS <20. At randomization, approximately one-half of subjects (47.5%) had a peak urine flow rate (Q_{max}) of 10 to 15 mL/second; 38.0% had a Q_{max} <10 mL/second. Overall, mean PVR volume at randomization was 54.2 mL (placebo, 63.3 mL; tadalafil, 44.9 mL). At screening, mean PSA was 2.1 ng/mL, overall. Overall, 30.5% of subjects reported taking previous alpha blocker therapy, 8.6% reported taking previous LUTS therapy other than an alpha blocker, and 1.2% reported previous use of OAB therapy. Overall, the majority of subjects (68.9%) reported a history of ED at screening. Of those with a history of ED, 86.2% reported ED duration of ≥1 year, 53.6% reported ED of moderate severity, 33.0% reported ED of mild severity, and 49.1% reported ED of mixed etiology (psychogenic and organic). Of all randomized subjects, 79.1% reported being sexually active with a female partner with >99% of these subjects expecting to remain sexually active. Both treatment groups were well-balanced with respect to baseline characteristics associated with BPH-LUTS, previous alpha-blocker or other BPH-LUTS therapy, and ED and sexual activity related characteristics.

The 325 subjects randomized for treatment had similar demographics between the treatment groups. Subjects had a mean age of 64.9 years with a range of 44.8 to 87.0 years. Overall, 20.0% of randomized subjects (placebo, 21.3%; tadalafil, 18.6%) were at least 75 years of age or older. Most subjects (91.1%) were white. The tadalafil and placebo treatment groups were well-balanced with respect to age, ethnicity, and region. The mean BMI for the tadalafil 5 mg daily group was 27.1 kg/m^2 versus 28.4 $kg/m^{2\ for}$ the placebo group. The mean systolic/diastolic blood pressure for the placebo group was 135.5/81.3 mm Hg versus 132.9/80.5 mm Hg for the tadalafil group.

At randomization, approximately one-third of subjects (35.4%) were categorized as having severe LUTS (IPSS ≥20) with the remainder (64.6%) having a total IPSS <20. At randomization, approximately one-half of subjects (47.5%) had a peak urine flow rate (Qmax) of 10 to 15 mL/second; 38.0% had a Qmax <10 mL/second. Overall, mean PVR volume at randomization was 54.2 mL (placebo, 63.3 mL; tadalafil, 44.9 mL). At screening, mean PSA was 2.1 ng/mL, overall. The median post void residual urine was 63.3 mL for the placebo group and 44.9 mL for the tadalafil group; otherwise, both treatment groups were well-balanced with respect to these baseline characteristics associated with BPH-LUTS.

Overall, 30.5% of subjects reported taking previous alpha blocker therapy, 8.6% reported taking previous LUTS therapy other than an alpha blocker, and 1.2% reported previous use of OAB therapy. Both treatment groups were well-balanced with respect to previous alpha-blocker or other BPH-LUTS therapy.

The majority of subjects (68.9%, n=224) reported a history of ED at screening. Of those with a history of ED, 86.2% reported ED duration of ≥1 year, 53.6% reported ED of moderate severity, 33.0% reported ED of mild severity, and 49.1% reported ED of mixed etiology (psychogenic and organic). Of all randomized subjects, 79.1% reported being sexually active with a female partner with >99% of these subjects expecting to remain sexually active approximately one-half of these subjects (53.1%) reported ED of mixed etiology, 55.4% reported ED of moderate severity, 34.9% reported ED of mild severity, and 84.0% reported an ED duration ≥1 year. 22.8% of subjects (tadalafil, 24.8%; placebo, 20.7%) reported having had previous ED therapy. The tadalafil and placebo treatment groups were well-balanced with regards to ED- and sexual activity-related characteristics.

The majority of randomized subjects in both treatment groups (tadalafil, n=148 [91.9%]; placebo, n=152 [92.7%]) met the definition of the per protocol population, that is, they completed (as indicated by the investigator) the 12-week double-blind treatment period and were ≥70% compliant. The most common reason for study discontinuation among tadalafil treated subjects was entry criteria not met (n=4, 2.5%). 1.9% of the tadalafil treated patients discontinued for an adverse event. There was 1 death and this will be discussed under safety evaluations. The most common reason for study discontinuation among placebo-treated subjects was subject decision (n=4, 2.4%).

Table 25: Reasons for Study Discontinuation Double-Blind Treatment Period Study LVHJ

	Placebo	Tadalafil 5 mg
	N=164	N=161
	n (%)	n (%)
Randomized Population	164 (100.0)	161 (100.0)
Completed 12 weeks Double- Blind Treatment	152 (92.7)	148 (91.9)
Discontinued	12 (7.3)	13 (8.1)
Primary Analysis Population (randomized and started study Drug)	164 (100.0)	161 (100.0)
Reason for Discontinuation		
Adverse Event	1 (0.6)	3 (1.9)
Death	0 (0.0)	1 (0.6)
Entry Criteria Not Met	1 (0.6)	4 (2.5)
Lack of Efficacy	0 (0.0)	1 (0.6)
Lost to Follow Up	3 (1.8)	0 (0.0)
Physician Decision	0 (0.0)	2 (1.2)
Protocol Violation	3 (1.8)	1 (0.6)
Subject Decision	4 (2.4)	2 (1.2)

Source: Table LVHJ 10.1, H6D-MC-LVHJ Amended Study Report, page 78

The primary objective for Study LVHJ was to evaluate the efficacy of tadalafil 5 mg once daily for 12 weeks compared to placebo in improving total IPSS in men with BPH-LUTS.

The key secondary analyses comparing the changes from baseline between tadalafil 5 mg and placebo in other clinical outcomes, and were performed in the following pre-specified order:

- IIEF EF Domain score after 12 weeks (in sexually active subjects with ED);
- Total IPSS after 4 weeks of treatment;
- BII after 12 weeks of treatment;
- Total modified IPSS (mIPSS) after 1 week of treatment; and
- BII after 4 week of treatment.

The key secondary endpoints, shown below, were assessed for statistical significance only if the result of the total IPSS hypothesis (primary efficacy analysis) after 12 weeks of treatment was significant at a 2-sided 0.05 significance level. The key secondary analyses comparing the changes from baseline between treatment groups were performed in the following pre-specified order at 2-sided significance level of 0.05.

The analysis of efficacy data is conducted using the following general considerations:

- Primary and secondary efficacy outcomes are analyzed on intent –to- treat basis.
- Subjects included in the efficacy analysis are referred to as the Primary Analysis Population.

- Analysis of covariance (ANCOVA) is the primary analysis methods used to evaluate continuous efficacy data. Treatment differences are examined based on Type III sums of squares and associated two-sided p-values.
- Both last-observation-carried-forward (LOCF) and mixed model repeated measures (MMRM) methods are used to handle missing data in the statistical models. For analyses of change from baseline to Weeks 4 and 8 post base-line, no imputation for missing data is applied.
- Missing responses to any individual IPSS or BII question are not imputed for analysis. If a subject had a missing response to any IPSS question(s) at a specific visit, the total IPSS and any subscore containing said question(s) are missing at that visit. If a subject had missing responses to any individual BII question at a specific visit, the BII score is missing at that visit.
- If the score of a component question of the IIEF EF Domain score is missing at a specific visit, the missing score is imputed with the mean of non missing scores at that visit, rounded to the nearest integer. If 2 or more component questions for the IIEF EF Domain score are missing at a visit, the IEFF EF Domain score is treated as missing for that visit.
- A repeated measures model is applied separately to total IPSS, BII and IIEF-EF domain with the change from baseline to 4, 8, and 12 weeks as the response in the primary analysis population. The model included terms for treatment group, region, and visit, centered-baseline of the efficacy endpoints, visit-by-treatment interaction, centered baseline-by-treatment interaction and treatment-by-region interaction.

In Study LVHJ, 99.7% of subjects were ≥70% compliant with study drug treatment. Treatment compliance was assessed by reconciling the number of doses dispensed at Visits 2, 3, 5 and 6 with the number of doses returned at Visit 3, 5,6, and 7, respectively. The visit-wise compliance rate was calculated as follows:

([Number of doses dispensed – number of doses returned]/number of days of exposure) × 100.

Efficacy Evaluation

The primary objective for Study LVHJ was to evaluate the efficacy of tadalafil 5 mg once daily for 12 weeks compared to placebo in improving total IPSS in men with BPH-LUTS. The LS mean changes from baseline to endpoint were -5.6 for the tadalafil 5 mg group and -3.6 for the placebo group. The LS mean difference of these changes (-1.9) was statistically significant for the tadalafil treatment group compared to the placebo group (p=.004) [95% CI (-3.2, 0.6)].

Table 26: Total IPSS Change from Baseline to Endpoint Study LVHJ

Treatment		Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)		Baseline	164	16.6	5.99	
		Endpoint	164	13.0	7.22	
		Change	164	-3.6	3.0	-3.6
Tadalafil 5 mg (N=161)		Baseline	160	17.0	6.06	
		Endpoint	160	11.4	6.71	
		Change	160	-5.7	7.18	-5.6

Source: Table LVHJ 11.13, H6D-MC-LVHJ Amended Study Report, page 102.

Key secondary efficacy analyses are those analyses that were pre-specified for inclusion in the fixed-sequence testing procedure. As the primary efficacy analysis showed a statistically significant difference between the tadalafil and placebo groups, the following key secondary efficacy measures were analyzed sequentially in the prespecified order below for the primary analysis population:

- IIEF-EF domain after 12 weeks of treatment in sexually active patients with ED;
- Total IPSS after 4 weeks of treatment;
- BII after 12 weeks of treatment;
- Modified IPSS after 1 week of treatment (Visit 4); and
- BII after 4 weeks of treatment,

For the IIEF-EF domain, the LS mean changes from baseline to endpoint were 6.7 for the tadalafil 5 mg group and 2.0 for the placebo group. The LS mean difference of these changes (4.7) was statistically significant for the tadalafil treatment group compared to placebo ($p<.001$) (95% CI [2.5, 6.9]).

Table 27: IIEF EF Domain Change From Baseline to Endpoint Sexually Active Subjects with ED in Study LVHJ

Treatment		Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)		Baseline	84	16.8	8.68	
		Endpoint	84	18.1	9.08	
		Change	84	1.3	8.44	2.0
Tadalafil 5 mg (N=161)		Baseline	88	14.3	8.35	
		Endpoint	88	21.8	7.90	
		Endpoint	88	7.5	5.5	6.7

Source: Table LVHJ 11.14, H6D-MC-LVHJ Amended Study Report, page 105.

The LS mean changes from baseline to Week 4 in total IPSS in the primary analysis population for the total IPSS score after 4 weeks were -5.3 for the tadalafil 5 mg group and -3.5 for the placebo group. The LS mean difference of these changes (-1.8) was statistically significant for the tadalafil treatment group compared to placebo (p=.003) (95% CI [-3.0, -0.6]).

Table 28: Total IPSS Change from Baseline to Week 4 Study LVHJ

Treatment		Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)		Baseline	162	16.6	6.01	
		Endpoint	162	13.2	6.90	
		Change	162	-3.4	5.52	-3.5
Tadalafil 5 mg (N=161)		Baseline	158	17.2	5.94	
		Endpoint	158	11.7	6.31	
		Endpoint	158	-5.5	6.34	-5.3

Source: Table LVHJ 11.15, H6D-MC-LVHJ Amended Study Report, page 106.

For the BPH Impact Index, the LS mean changes from baseline to endpoint were -1.8 for the tadalafil 5 mg group and -1.3 for the placebo group. The LS mean difference of these changes (-0.6) was not statistically significant for the tadalafil group compared to placebo (p=.057) (95% CI [-1.2, 0.0]). As analysis results for this key secondary efficacy measure did not reach statistical significance, results of analyses for the 2 remaining key secondary efficacy measures cannot be claimed as being statistically significant even if the p-value is <05.

Table 29: BPH Impact Index (BII) Change from Baseline to Endpoint Study LVHJ

Treatment		Time Point	n	Mean	SD	LS Mean Δ
Placebo (N=164)		Baseline	163	4.8	3.17	
		Endpoint	163	3.7	3.07	
		Change	163	-1.1	3.09	-1.3
Tadalafil 5 mg (N=161)		Baseline	160	5.1	3.08	
		Endpoint	160	3.2	3.01	
		Endpoint	160	-1.9	3.22	-1.8

Source: Table LVHJ 11.16, H6D-MC-LVHJ Amended Study Report, page 107.

The modified IPSS mean change from Baseline to Week 1 was -2.6 for placebo and -3.5 for tadalafil 5 mg once daily. This was not statistically significant (p-value .146). The BII mean change from baseline at Week 4 was -1.1 for placebo and -1.8 for tadalafil 5 mg once daily (p-value .029).

The treatment-by-baseline LUTS severity interaction was statistically significant (p=.033), indicating a difference in treatment effect between the 2 groups based on total IPSS at baseline. In subjects with a baseline total IPSS <20, the mean changes from baseline to endpoint were -3.7 for the tadalafil 5 mg group and -2.8 for the placebo group. The LS mean difference of these changes between the tadalafil and placebo treatment groups was -0.87. In subjects with a baseline total IPSS ≥20, the mean changes from baseline to endpoint were -9.0 for the tadalafil 5 mg group and -5.1 for the placebo group. The LS mean difference of changes between the tadalafil and placebo treatment groups was -3.98.

Treatment by region interaction was not significant indicating that there was no difference in treatment effect between the 2 treatment groups based on geographic region.

The treatment-by-age category (≤65, >65 years) interaction was not statistically significant (p=.627), indicating there was no difference in treatment effect between the 2 groups based on age ≤65 and >65 years. In subjects ≤65 years of age, the mean changes from baseline to endpoint were -6.2 for the tadalafil 5 mg group and -4.4 for the placebo group. The LS mean difference of changes between the 2 treatment groups was -1.62. In subjects >65 years of age, the mean changes from baseline to endpoint were -5.3 for the tadalafil 5 mg group and -2.7 for the placebo group.

The treatment-by-age category (<75, ≥75 years) interaction was not statistically significant (p=.940), indicating there was no difference in treatment effect between the 2 groups based on age <75 and ≥75 years. In subjects <75 years of age, the mean changes from baseline to endpoint were -5.8 for the tadalafil 5 mg group and -3.6 for the placebo group. The LS mean difference of changes between the 2 treatment groups was -1.90. In subjects ≥75 years of age, the mean changes from baseline to endpoint were -5.5 for the tadalafil 5 mg group and -3.5 for the placebo group. The LS mean difference of changes between the 2 treatment groups was -2.03.

The treatment-by-ED status interaction was not statistically significant (p=.145), indicating there was no difference in treatment effect between the 2 groups based on ED status.
In subjects with a history of ED, the mean changes from baseline to endpoint were -6.3 for the tadalafil 5 mg group and -3.4 for the placebo group. The LS mean difference of changes between the 2 treatment groups was -2.58.

Reviewer's Comment: The primary efficacy analysis was statistically significant. There does not appear to an age related efficacy difference. The key secondary efficacy measures of changes in the IIEF-EF domain after 12 weeks of treatment in sexually active patients with ED and changes in the Total IPSS after 4 weeks of treatment also were statistically significant. (b) (4)

Safety

At total of 161 subjects were randomized to tadalafil and 164 to placebo. The mean duration of exposure for tadalafil was 83.0 days and for placebo was 84.1 days. The mean number of doses/week taken for tadalafil and placebo was 7.2 and 7.0 respectively. The cumulative number of doses per patient was 111.3 for placebo and 111.7 for tadalafil.

There was 1 death reported that being in the tadalafil group; this subject is included in the total number of tadalafil subjects reporting an SAE and discontinuing due to an SAE. Two subjects, both in the tadalafil group, reported SAEs. Three subjects (1.9%) in the tadalafil group and 1 subject (0.6%) in the placebo group discontinued due to an AE during the double-blind treatment period. During the double-blind treatment period, 42 subjects (26.1%) in the tadalafil group and 36 subjects (22.0%) in the placebo group reported at least 1 TEAE.

Table 30: Overview Adverse Events Double-Blind Period Study LVHJ

Adverse Event	Placebo (N=164) n (%)	Tadalafil (N=161) n (%)
Deaths	0 (0.0)	1 (0.6)
Serious Adverse Events	0 (0.0)	2 (0.6)
Serious Adverse Events Leading to Discontinuation	1 (0.6)	3 (1.9)
Treatment Emergent Adverse Events	36 (22.0)	42 (26.1)

Source: Table LVHJ 12.2, H6D-MC-LVHJ Amended Study Report, page 125.

Table 31: TEAEs Occurring > 1% More Frequently in Tadalafil Group as Compared to the Placebo Group Study LVHJ

Preferred Term	Placebo (N=164) n (%)	Tadalafil (N=161) n (%)
Subjects with >= 1 TEAE	36 (22.0)	42 (26.1)
Headache	1 (0.6)	6 (6.7)
Arthralgia	0 (0.0)	3 (1.9)
Dizziness	0 (0.0)	3 (1.9)
Gastroesophageal reflux disease	0 (0.0)	2 (1.2)
Insomnia	0 (0.0)	2 (1.2)
Myalgia	0 (0.0)	2 (1.2)
Pain in Extremity	0 (0.0)	2 (1.2)
Sinusitis	0 (0.0)	2 (1.2)

Source: Table LVHJ 12.3, H6D-MC-LVHJ Amended Study Report, page 127.

The majority of reported TEAEs were of mild or moderate severity; 2 subjects in each treatment group reported a TEAE (tadalafil – 1 acute MI and 1 headache; placebo – 1 back pain and 1 urinary retention) having a maximum severity of severe.

Reviewer's Comment: The incidence of hypertension as TEAE was 3% in both the placebo and the tadalafil treatment groups.

Death Narrative

LVHJ-303-3316: This LVHJ subject was an 81-year old white male in the tadalafil 5-mg group who had preexisting conditions of hyperlipidemia and hypertension (BP 140/90 mm Hg while on lisinopril and study drug), co-arthrosis, cervical lumbar syndrome, polyneuropathy, tinnitus, tension headaches, recurrent gastritis. The patient was characterized as having a moderate sexual dysfunction and was sexually active with a female partner. Concomitant medications included lisinopril and simvastatin. Approximately 2.5 months after receiving the first dose of study drug (tadalafil 5 mg), the subject was hospitalized with chest pain and diagnosed with an acute posterior myocardial infarction (MI) and third degree atrioventricular block; study drug was discontinued. Cardiac catheterization was performed and demonstrated 75%, 90%, and 90% occlusion of the LAD, circumflex and right coronary arteries, respectively. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequent intra-aortic balloon pump. The subject's condition worsened and he died 3 days later.

Reviewer's Comment: This patient had significant coronary artery disease is likely to have been pre-existing and had hypertension and hyperlipemia. When adverse events are examined by the Cardiac Disorders SOC, there are no additional AEs attributable to the coronary vasculature including MI, acute coronary syndrome, angina, coronary artery disease or myocardial ischemia. In the Vascular Disorders SOC, the only preferred term is hypertension which is equally divided between placebo and tadalafil (3 to 3).

Serious Adverse Events

Table 32: Serious Adverse Events Study LVHJ

Preferred Term	Placebo (N=164)	Tadalafil 5 mg (N=161)
	n (%0)	
Subjects with>= 1 SAE	0(0.0)	2(1.2)
Acute Myocardial Infarction	0(0.0)	1(0.6)
Endocarditis	0(0.0)	1(0.6)

Source: Table LVHJ 12.5, H6D-MC-HVHJ Amended Study Report, page 140

LVHJ-303-3316: See death narrative above.

LVHJ-301-3101: The patient is a 65 year-old Caucasian male with a medical history of cardiac arrhythmias, paroxysmal atrial fibrillation, essential hypertension, reflux esophagitis, hyperuricemia, glaucoma, focal fatty sparing right liver lobules, lumbago left disc prolapse (L5/S1). Concomitant medications include phenprocoumon for cardiac arrhythmias, metoprolol for hypertension, hydrochlorthiazide/irbesartan for glaucoma, allopurinol for hyperuricemia, and omeprazole for reflux esophagitis. The patient was randomized to 5 mg tadalafil once-daily. Approximately three months after starting the study drug and 5 days after his last drug dose on (b) (6), the patient was hospitalized with recurrent fever at 39 degrees centigrade for one week. Because hepatic enzymes were increased (AST 74 [11-36 normal] and ALT 105 [6-43]) on (b) (6), initially, a hepatobiliary infection was suspected; however, a transesophageal echocardiography showed endocarditis of the aortic valve. Blood cultures were negative. He was treated with 7 days of gentamicin therapy in ceftriaxone for 28 days and ampicillin/sulbactam for 28 days. The patient was discharged on (b) (6) in stable cardiopulmonary condition. The study medication was maintained and the patient completed the study.

AE Discontinuations

Table 33: Adverse Events Leading to Discontinuation Study LVHJ

Preferred Term	Placebo (N=164)	Tadalafil 5 mg (N=161)
	n (%)	
Subjects Discontinued due to AE	1(0.6)	3(1.9)
Abdominal Pain Upper	0(0.0)	1(0.6)
Acute Myocardial Infarction	0(0.0)	1(0.6)
Headache	0(0.0)	1(0.6)
Back Pain	1(0.6)	0(0.0)

Source: Table LVHJ 12.6, H6D-MC-HVHJ Amended Study Report, page 142

LVHJ 107-1712: The patient is a 61 year-old male randomized to tadalafil 5 mg once-daily. He started treatment on 21 July 2009. On 22 July 2009, he developed a severe headache which resulted in discontinuation on 12 August 2009. Treatment stopped on 10 August 2009. His blood pressures in mm Hg were at Visit 1 137/66, at Visit 2 142/83 (pre-randomization), Visit 5 134/80 (supine) and 143/92 (standing).

> *Reviewer's Comment: This case does not appear to be associated with a clinically meaningful increase in blood pressure from Visit 2 to Visit 5.*

LVHJ 400-4010: The patient is a 64 year-old Caucasian male randomized to 5 mg tadalafil once-daily. He started treatment on 14 May 2009. On 1 July 2009, he developed upper abdominal pain which stopped 13 July 2009. Treatment was stopped 11 July 2009. The last study visit was 15 July 2009.

LVHJ 401-4101: Patient is 65 year-old Caucasian male randomized to placebo. He started therapy 26 February 2009 and discontinued treatment on 19 April 2009 secondary to back pain.

Other Notable Adverse Events (Special Safety Topics)

The Sponsor has identified 3 subjects with MedDRA preferred terms used for the focused and expanded analyses of TEAEs possibly related to hypotension.

LVHJ Subject 102-1200 was a 66-year-old white male who, approximately 6 weeks post-randomization, reported dizziness (actual term "lightheaded"). Further follow up with the site revealed that the subject had been outside on a hot day driving stakes into the ground; the subject reported the lightheadedness lasted about 10 seconds and that after sitting for approximately 2 minutes, he felt fine upon standing and did not experience any more episodes. The subject did not report hypertension or other risk factors related to cardiovascular disease, did not report concomitant medications that might have resulted in dizziness, nor did he meet any positive orthostatic test criteria during the study. The subject completed the study.

LVHJ Subject 107-1701 was a 53-year-old white male who reported dizziness 5 days post-randomization. The subject reported onset of nasopharyngitis ("head cold") 2 days prior to the dizziness. The subject did not report hypertension or other risk factors related to cardiovascular disease, did not report any concomitant medications, nor did he meet any positive orthostatic test criteria during the study. The subject completed the study.

LVHJ Subject 107-1711 was a 79-year-old white male who experienced dizziness approximately 7 weeks post-randomization. Further follow up with the site revealed the subject had indicated the dizziness had occurred upon awakening. Preexisting conditions included hypertension, coronary artery disease with prior coronary artery bypass graft, peripheral arterial disease and hypercholesterolemia; concomitant medications included metoprolol, aspirin, and simvastatin. He met the criterion for a positive orthostatic test at Visit 7 (DBP decreased from 92 to 82 mmHg), but did not report any symptoms during orthostatic testing. The subject completed the study.

The criteria for a positive orthostatic test were:
1) Decrease in SBP of ≥20 mm Hg from the supine to the standing position;
2) Decrease in DBP of ≥10 mm Hg from the supine to the standing position;
3) Increase in HR of ≥20 bpm from the supine to the standing position; or
4) Inability to remain standing during the orthostatic assessment (as indicated on the CRF).

The Sponsor identified a total of 12 subjects (tadalafil 10 [6.2%]; placebo 2 [1/2%]) who experienced at least 1 TEAE possibly related to hypotension from the expanded list of terms which possibly represented hypotension. 7 subjects experienced headache (tadalafil 6; placebo 1), 3 subjects (all in the tadalafil group) experienced dizziness and 2 subjects, 1 from each group experienced asthenia.

Reviewers Comment: It appears that dizziness was experienced in a greater number of tadalafil subjects than placebo. This AE is already in tadalafil labeling.

In their discussion, the Sponsor also notes an additional subject:

LVHG Subject 601-1712 was a 57 year-old white male who experienced asthenia 11 days post randomization. Further follow-up with the site revealed the asthenia was described as physical weakness occurring when getting up from bed. The subject had preexisting hypertension and concomitant medications included telmisartan, hydrochlorothiazide, and verapamil. The subject did not meet any positive orthostatic test criteria postrandomization and completed the study.

Reviewer's Comment: Two patients have noted either dizziness or asthenia upon awakening or "getting up from bed." In these two cases, there is no documentation of temporally related orthostatic vital signs.

Table 34: Adverse Events Possibly Related to Hypotension Study LVHJ (Expanded List of Terms)

Preferred Term	Placebo (N=164)	Tadalafil 5 mg (N=161)
	n (%)	
Subjects with >= 1 TEAE	1(1.2)	10(6.2)
Headache	1(0.6)	6(3.7)
Dizziness	0(0.0)	3(1.9)
Asthenia	1 (0.6)	1(0.6)

Source: Table LVHJ 12.8, H6D-MC-HVHJ Amended Study Report, page 147.

Reviewers Comment: The AEs of headache and dizziness are already included in Sponsor's labeling.

Cardiac Disorders

LVHJ Subject 301-3101 had an SAE of endocarditis (actual reported term "endocarditis of the aortic valve"). A brief medical summary for this subject was previously presented.

LVHJ Subject 303-3316 had an SAE of acute MI from which he subsequently died. A brief medical summary for this subject was previously presented.

Hepatic Enzyme Increased

LVHJ Subject 301-3101 reported hepatic enzyme increased as a TEAE at his last visit. A brief medical summary was provided for this subject's SAE of endocarditis, which occurred 3 days after his last visit at which time the abnormal hepatic enzymes were noted. The AST increased from 20 International Units (IU)/L at baseline to 74 IU/L at endpoint (ULN=36 IU/L) and his ALT increased from 24 IU/L at baseline to 120 IU/L at endpoint (ULN=43 IU/L); total bilirubin was normal at baseline and endpoint. The subject had a history of fatty liver ("focal fatty sparing

right liver lobules"). No new medications were reported as being initiated during the double-blind treatment period. With the exception of a SAE of endocarditis reported 3 days after final visit, no other TEAEs were reported and the subject completed the study.

Hearing Disorders

LVHJ Subject 302-3210, an 82-year old white male, reported a TEAE of deafness (actual term "acute hearing loss") approximately 12 weeks post-randomization. Further follow-up with the site revealed that the subject had reported tinnitus in the left ear during the study and an audiogram showed impaired hearing capacity. The subject received infusion therapy of pentoxifylline and prednisolone. The event was reported as resolved at the final visit. No historical diagnoses, preexisting conditions, or concomitant medications were reported. Approximately 2 months prior to the onset of the deafness, the subject received a 10-day course of doxycycline for a wound infection. The subject completed the study.

> *Reviewer's Comment: Doxycycline is not known to be associated with hearing loss. There were no pre-existing conditions. Therefore, it is not possible to exclude a casual relationship to tadalafil in this case. This case is reflected appropriately in the current labeling under adverse events reported in clinical trials in <2% of subjects where a causal relationship uis uncertain.*

Urinary Disorders

A total of 3 subjects (1 tadalafil, 2 placebo) reported 4 treatment-emergent urinary disorders (dysuria [1 placebo], micturition urgency [1 tadalafil], nocturia [1 tadalafil, the same subject reporting micturition urgency], and urinary retention [1 placebo]).

LVHJ Subject 401-4205 was randomized to tadalafil 5 mg daily treatment. At Visit 1, he had a PSA of 5.63 ng/dL. There are no other PSA values in the patient's data base. The patient did complete the study. At Visit 2 (Week -4) in the micturition history, the patient attested to the following symptoms:

- Bothersome urinary urgency for 72 months.
- Nocturia for 12 months

At 33 days of treatment (Visit 60), the nocturia was characterized as "moderate" and the urgency was characterized as "moderate." The investigator did not feel that these observations were related to treatment. No action was taken.

> *Reviewer's Comment: In my opinion, I cannot attribute the above events to tadalafil treatment.*

Orthostatic Vital Signs

The criteria for a positive orthostatic test were:
1) Decrease in SBP of ≥20 mm Hg from the supine to the standing position;
2) Decrease in DBP of ≥10 mm Hg from the supine to the standing position;

3) Increase in HR of ≥20 bpm from the supine to the standing position; or
4) Inability to remain standing during the orthostatic assessment (as indicated on the CRF).

A treatment-emergent positive orthostatic test was defined as one in which one of the criteria specified above (criteria 1 – 4) was present at any post baseline visit but was not present at baseline (Visit 3).

Table 35: Treatment Emergent Positive Orthostatic Tests Study LVHJ (All randomized Subjects)

		Placebo (N=164)	Tadalafil 5 mg (N=161)
		n (%)	
Subjects with ≥1 Positive Orthostatic Test		38(23.2)	31(19.3)
Criterion 1		12(7.3)	12(7.5)
Criterion 2		29(17.7)	21(13.0)
Criterion 3		5(3.0)	3(1.9)
Criterion 4		0(0.0)	0(0.0)

Source: Table LVHJ 12.9, H6D-MC-HVHJ Amended Study Report, page 150.

In addition, the Sponsor evaluated the orthostatic test results over time, and by age sub-grouping (≤65, >65, <75, ≥75 year of age). The Sponsor concluded that there were no statistically significant differences in orthostatic test results either over time or by age group. There were no adverse events during the orthostatic testing.

> *Reviewer's Comment: There does not appear to increased orthostatic phenomena in the LVHJ tadalafil patient population compared to placebo.*

Hypertension

Three patients (one placebo, two tadalafil) in Study LVHG were identified with hypertension as a study adverse event based on the preferred term (and "arterial hypertension" using the lower level term by reviewer's JMP9 search).

Reviewer's Comment: Subject's 5006 and 5023 were hypertensive prior to exposure to study drug and in the case of 5006 the study drug was placebo. Subject 5002 was normotensive through Visit 3 and after study drug administration did meet hypertensive criteria. The occurrence of this one case does not constitute a new safety signal or concern in my opinion.

Uroflowmetry and Post Void Residual

For all randomized subjects, changes from baseline to endpoint for Qmean (mean flow rate) were small for both treatment groups (0.6 mL/second for tadalafil; 0.5 mL/second for placebo). For Vcomp (voided volume), change from baseline to endpoint was 16.9 mL for the tadalafil group and 3.9 mL for the placebo group.

Baseline mean PVR volumes were 64.0 mL and 44.4 mL, respectively, for placebo subjects and tadalafil subjects. From baseline to endpoint, there were small increases in PVR in both treatment groups (tadalafil, 8.8 mL; placebo, 4.5 mL). 3 subjects (1 tadalafil, 2 placebo) at endpoint had a PVR ≥ 300 mL.

LVHJ Subject 105-1508 was a 59-year-old white male randomized to tadalafil; at baseline he had a PVR of 145 mL; at final visit (Visit 5) it was 329 mL. He decided to discontinue (transportation/old car issues/round trip of 100 miles to office) from the study at Visit 5. He did not report any TEAEs during the study.

Reviewer's Comment: There appear to be no significant differences noted in PVR and flow rate with tadalafil compared to placebo in the LVHJ study population.

Clinical Laboratory

With respect to hematology, four subjects in the tadalafil group shifted from normal at baseline to low at endpoint. No placebo subject shifted from normal at baseline to low at endpoint. Subjects 105-1504 and 107-1711 had platelet counts within the normal range at screening and baseline; endpoint counts for both subjects (118 billion/L and 122 billion/L, respectively) were below the lower limit of normal (LLN). Subject 210-2108 had a platelet count (124 billion/L) below LLN at screening; at baseline the count (130 billion/L) was at the LLN, and at endpoint the count was (122 billion/L) was below the LLN. Subject 601-6162 had a platelet count (125 billion/L) at screening which was below the LLN; the count (137 billion/L) was within normal range at baseline but was below the LLN at endpoint (128 billion/L). There were no bleeding-related TEAEs for any of these subjects and all completed the study. There was a slightly reduced lymphocyte count in the tadalafil group at endpoint (-0.0297 billion/L versus 0.0802 billion/L for placebo). There were no tadalafil patients who shifted from a normal or high baseline result to a low endpoint result.

Reviewer's comment: I do not regard these changes as clinically significant.

Five (5) subjects in the tadalafil group and no subjects in the placebo group shifted from normal at baseline to high at endpoint for chemistry laboratory analytes. Liver function enzymes are discussed separately in the next section.

LVHJ Subject 105-1504, serum creatinine (normal range: 40-119 μmole/L) was elevated at screening (133 μmole/L), within normal range at baseline (97 μmole/L), and elevated at endpoint (124 μmole /L), but still lower than at screening. His creatinine clearance (normal range 1.42-2.08 mL/second) was elevated at baseline (2.37 mL/second) and within normal range at endpoint (1.72 mL/second). Preexisting conditions included diabetes mellitus and hypertension. The subject did not report any TEAEs and completed the study.

LVHJ Subject 301-3101, serum creatinine (normal range: 40-119 μmole/L) was normal at baseline (112 μmole/L) but elevated at endpoint (122 μmole/L). His creatinine clearance (normal range 1.42-2.08 mL/second) was within normal range at baseline (1.53 mL/second) but was low at endpoint (1.41 mL/second). Preexisting conditions included hypertension and hyperuricemia. The subject had an SAE (endocarditis, previously discussed as an SAE) and a notable TEAE of hepatic enzyme increased; he completed the study.

LVHJ Subject 400-4002, serum creatinine (normal range: 40-119 μmole/L) was normal at baseline (108 μmole/L) but elevated at endpoint (143 μmole/L). His creatinine clearance (normal range 1.42-2.08 mL/second) was low at screening (1.08 mL/second), baseline (1.02 mL/second), and endpoint (0.75 mL/second). No preexisting conditions or TEAEs were reported and he completed the study.

LVH Subject 500-5032, serum creatinine (normal range: 40-137 μmole/L) was missing at screening, normal at baseline (133 μmole/L), and elevated at endpoint (177 μmole/L). His creatinine clearance (normal range 1.42-2.08 mL/second) was missing at screening, low at

baseline (0.88 mL/second), and low at endpoint (0.70 mL/second). No preexisting conditions or TEAEs were reported and he completed the study.

LVHJ Subject 600-6008, serum creatinine (normal range: 40-119 µmole/L) was normal at baseline (97 µmole/L) but elevated at endpoint (133 µmole/L). His creatinine clearance (normal range 1.42-2.08 mL/sec) was low at screening (0.90 mL/sec), baseline (1.05 mL/sec), and endpoint (0.80 mL/sec). A preexisting condition of chronic renal failure was reported; no TEAEs were reported and the subject completed the study.

> *Reviewer's Comment: Of these five patients, only 2 did not have a confounding condition. The average rise of creatinine for the tadalafil treatment group was 2.1447 (SD 11.598) µmole/L versus 1.6556(SD 11.079) µmole/L for placebo. I question the clinical significance of this finding*.

The only statistically significant clinical change was a decrease in alkaline phosphatase versus placebo.

For subjects reporting hepatic dysfunction or enzyme elevations through the evaluation of TEAEs, changes in hepatic enzyme (ALT, AST, and total bilirubin) analytes from baseline to endpoint were evaluated, and subjects meeting pre-specified treatment-emergent categorical changes (see Section 9.7.1.12.8) were summarized by treatment group (Table LVHJ.12.12). One subject in the placebo group met the criteria of having an elevated ALT ≥ 3-times the upper limit of normal, and 4 subjects (3 placebo; 1 tadalafil) met the criteria of having elevated total bilirubin ≥1.5-times the ULN.

Table 37: Elevated Hepatic-Related Chemistry Results LVHJ

	Placebo (N=164)	Tadalafil 5 mg (N=161)
	n (%)	
ALT ≥ 3 ULN	1(0.6)	0(0.0)
AST ≥ 3 ULN	0(0.0)	0(0.0)
Total Bilirubin ≥ 1.5 ULN	3(1.8)	1(0.6)
ALT ≥3 ULN & Total Bilirubin ≥1.5 ULN	0(0.0)	0(0.0)
AST ≥3 ULN & Total Bilirubin ≥1.5 ULN	0(0.0)	0(0.0)

Source: Table LVHJ 12.12, H6D-MC-HVHJ Amended Study Report, page 159.

LVHJ Subject 109-1900 was a 48-year-old white male randomized to tadalafil. At baseline, AST and ALT were within normal limits (normal ranges 11-36 IU/L and 6.0-43.0 IU/L, respectively) and at the final visit; total bilirubin (normal range 0.2-1.2 mg/dL) was elevated at the screening visit (1.6 mg/dL), at baseline (1.5 mg/dL), and at the final visit (1.8 mg/dL). The subject had a history of hepatitis A and preexisting conditions of gastroesophageal reflux disease, sleep apnea, herniated disc, and seasonal allergic rhinitis. Concomitant medications were fexofenadine, azelastine, fluticasone, ibuprofen, and lansoprazole. He did not report any TEAEs and completed the study.

Eleven subjects (7 tadalafil; 4 placebo) shifted from normal urinary glucose at baseline to abnormal urinary glucose at the endpoint of the trial. The majority of tadalafil subjects with shifts had preexisting diabetes and elevated Hb1Ac at screening. Further, none reported notable TEAEs except Subject 301-3101, who had an SAE of endocarditis (and a TEAE of hepatic enzyme increased). The investigators did not report any of these laboratory abnormalities as being clinically significant. All subjects completed the trial except Subject 500-5016 who was discontinued due to physician decision, as HbA1c could not be evaluated because according to (b) (4) the subject had a genetic variation that made it impossible to read the chromatogram.

ECGs were not assessed during Study LVHJ.

The incidence of discontinuations due to adverse events was 1.9% for tadalafil and 0.6% for placebo subjects. The incidence of TEAEs in the tadalafil group (42 subjects, 26.1%) was numerically higher than placebo (36 subjects, 22.0%). The most commonly reported TEAEs (incidence ≥2% in the tadalafil treatment group and reported more frequently than in the placebo group) were headache and back pain. These are consistent with the known safety profile of tadalafil.

More subjects (n=10, 6.2%) in the tadalafil group than placebo group (n=2, 1.2%) reported TEAEs possibly related to hypotension using an expanded list of preferred terms which included headache, asthenia, and fatigue (p=.019). Headache was the most commonly reported TEAE possibly related to hypotension both overall (n=7) and in the tadalafil group (n=6); however, none of the subjects reported other events suggestive of clinical hypotension. As headache is a common TEAE reported with tadalafil therapy, a post-hoc analysis excluding the preferred term of headache showed 4 tadalafil subjects and 1 placebo subject reporting at least 1 TEAE possibly related to hypotension (p=.212).

Reviewer's Comment: No new safety concerns were identified. The safety profile appears similar to other patient populations using tadalafil and is acceptable.

Study LVHR: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluated the Efficacy and Safety of Tadalafil 2.5- and 5-mg Once-Daily Dosing for 12 Weeks for the Treatment of Erectile Dysfunction and Sign and Symptoms of Benign Prostatic Hyperplasia in Men with Both Erectile Dysfunction and Benign Prostatic Hyperplasia

Study LVHR was a "pivotal", Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of tadalafil 2.5 mg and 5 mg once daily for 12 weeks versus placebo for the treatment of ED and the treatment of signs and symptoms of BPH in men with ED and BPH symptoms.

Study LVHR enrolled subjects ≥ 45 years of age who presented with BPH-LUTS (as diagnosed by an urologist and evidenced by IPSS ≥ 13 points, and Qmax of ≥ 4 to ≤ 15 mL/sec) for >6 months and a history of ED for ≥ 3 months. Subjects in Study LVHR were also required to be sexually active with an adult female partner, expected to remain sexually active with the same adult female partner for the duration of the study, and expected to make at least 4 sexual intercourse attempts during the 4-week placebo lead-in period. In general, inclusion and exclusion criteria used in Study LVHR were similar to the inclusion and exclusion criteria used for the BPH Studies LVHG and LVHJ and in once-daily ED studies. Subjects were excluded from enrollment if within 6 months of Visit 1 the systolic blood pressure was >160 mmHg or less <90 mmHg and/or the diastolic blood pressure was >100 mmHg or <50 mmHg.

After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

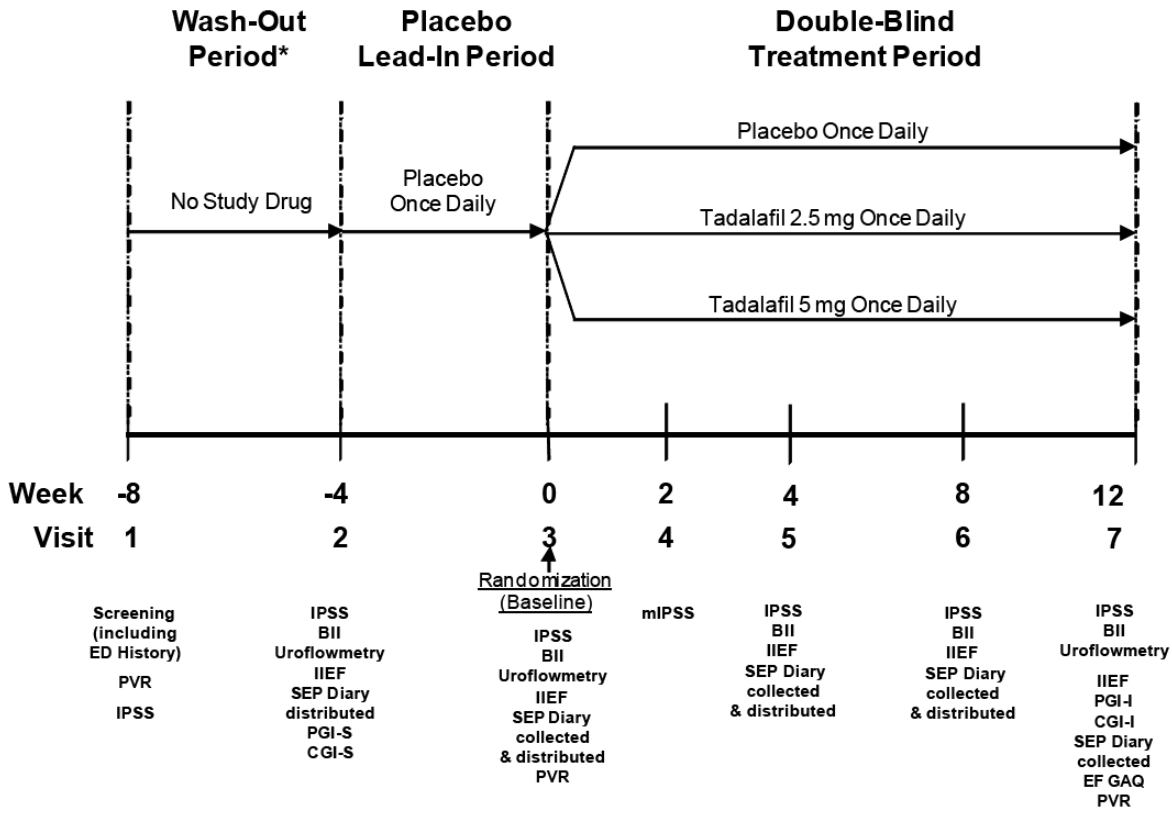
The study consisted of 3 periods:

- Screening/Washout Period: The first period was for screening (and to accommodate a 4-week washout of BPH, overactive bladder [OAB], or ED treatments, if needed) in order to assess symptoms and uroflowmetry data in the absence of therapy.

- Placebo Lead-In Period: After the screening/washout period, subjects returned for Visit 2 to assess whether eligibility criteria (IPSS ≥13 and Qmax of ≥4 to ≤15 mL/second) were met in order to proceed to the placebo lead-in period. Subjects meeting these 2 criteria began a 4-week single-blind, placebo lead-in period to assess treatment and study procedure compliance and to establish baseline levels at its conclusion.

- Treatment Period: At Visit 3 (randomization visit), subjects who were at least 70% compliant during the placebo lead-in period were eligible to be randomly assigned to treatment (placebo, tadalafil 5 mg, or tadalafil 2.5 mg) in a 1:1:1 ratio and begin the 12–week treatment period.

Table 38: Overall Study Design LVHR



Source: Scanned Copy Figure LVHR 9.1, Study Report H6D-MC-LVHR, and page 31.

Randomization was stratified by baseline LUTS severity (IPSS <20 or ≥ 20), baseline ED severity (mild, moderate, or severe as defined by the IIEF EF Domain score), and geographic region (North America [Canada and US], Mexico, and Europe [France, Germany, Greece, Italy, Portugal, and Russian Federation]). 46.4% (281) patients were from North America. Subjects were randomized in a 1:1:1 ratio. 606 subjects were randomized and 526 subjects completed the study (184 tadalafil 5 mg, 172 tadalafil 2.5 mg and 170 placebo).

9.2% of subjects were 75 years of age or older (placebo, 11.5%; tadalafil 5 mg, 10.1%; tadalafil 2.5 mg, 6.1%). Most subjects were white (93.2%) and non-Hispanic (84.5%). The majority of subjects were either from North America (46.4%) or Europe (41.1%). Demographics and baseline characteristics were well balanced across all treatment groups. At randomization, 39.0% of subjects were categorized as having severe LUTS (IPSS ≥ 20), while 61.0% were categorized as having mild to moderate LUTS (IPSS <20). At randomization, approximately one-half (50.6%) of subjects had a Qmax of <10 mL/sec, 39.9% had a Qmax of 10 to 15 mL/sec, and 9.5% had a Qmax of >15 mL/sec. Mean PVR volume at randomization was 53.2 mL. Mean PSA at screening was 1.9ng/mL. All treatment groups were well-balanced with respect to these BPH-associated characteristics.

23.4% of subjects reported previous alpha blocker therapy, 8.6% reported previous BPH-LUTS therapy other than alpha blockers, and 2.0% reported previous OAB therapy. All treatment groups were well-balanced for previous use of these therapies.

The majority of subjects (91.6%) reported ED of ≥ 1 year duration. At randomization, 48.8% had mild ED (IIEF EF Domain score 17 through 30), 24.6% had moderate ED (IIEF EF Domain score 11 through 16), and 26.6% had severe ED (IIEF EF Domain score 1 through 10). The most commonly reported ED etiologies were organic (36.3%) and mixed (36.6%). Overall, 28.5% of subjects reported previous ED therapy; the most commonly reported previous ED therapies were tadalafil (13.4%) and sildenafil (12.0%). All treatment groups were well balanced for ED profile parameters and previous use of ED therapies.

The most common reasons for discontinuation among subjects in the placebo group were lack of efficacy (8; 4.0%) and subject decision (8; 4.0%). The most common reasons for discontinuation among subjects in the tadalafil 5-mg group were adverse event (6; 2.9%) and entry criteria not met (6; 2.9%). The most common reason for discontinuation among subjects in the tadalafil 2.5-mg group was entry criteria not met (8; 4.0%). The majority of randomized subjects (526; 86.8%) completed the 12-week double-blind treatment period, with a similar number of completed subjects in each treatment group (placebo, 170 [85.0%]; tadalafil 5 mg, 184 [88.5%]; tadalafil 2.5 mg, 172 [86.9%]).

Table 39: Reason for Study Discontinuation Study LVHR

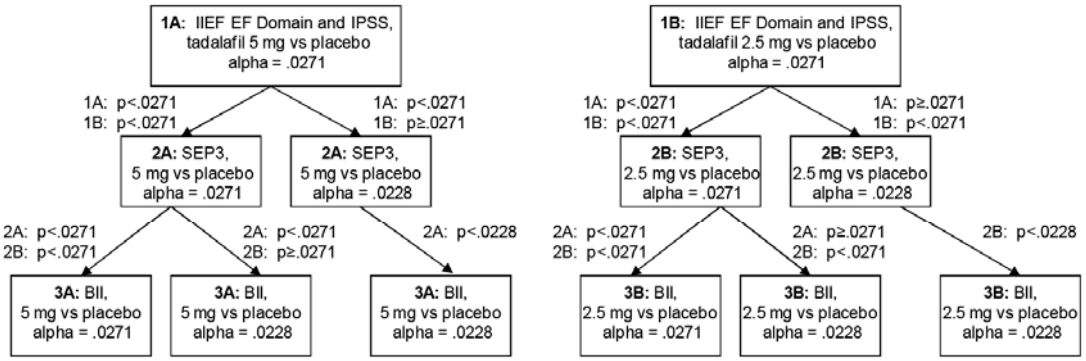
	Placebo (N=200)	Tadalafil 2.5 mg (N=198)	Tadalafil 5 mg (N=208)
	n (%)		
Randomized Population	200(100.0)	198(100.0)	208(100.0)
Completed 12 weeks of treatment	170 (85.0)	172 (86.9)	184 (86.8)
Discontinued	30 (15.0)	26 (13.1)	24 (11.5)
Primary Analysis Population	200(100.0)	198(100.0)	208(100.0)
Reason for Discontinuation			
Adverse event	3 (1.5)	3 (1.5)	6 (2.9)
Death	0 (0.0)	1 (0.5)	0 (0.0)
Entry criteria not met	3 (1.5)	8 (4.0)	6 (2.9)
Lack of efficacy	8 (4.0)	(1 (0.5)	3 (1.4)
Lost to follow-up	1 (0.5)	1 (0.5)	3 (1.4)
Physician decision	1 (0.5)	0 (0.0)	0 (0.0)
Protocol violation	6 (3.0)	6 (3.0)	2 (1.0)
Subject decision	8 (4.0)	7 (3.5)	4 (1.9)

Source: Table LVHR 10.1, Study Report H6D-MC-LVHR, page 75.

Reviewer's Comment: There appeared to be no change in discontinuations related to the drug versus placebo and to increasing drug dose.

The co-primary objectives of Study LVHR were to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared with placebo in improving both total IPSS and IIEF EF Domain score in men with both ED and BPH-LUTS. Key secondary efficacy objectives were to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared with placebo in improving the Patient SEP Q3 and BII. To control the Type I error rate associated with these primary and key secondary endpoints for comparison of 2 doses of tadalafil with placebo, a 3-step gatekeeping procedure was applied based on a Dunnett-Bonferroni gatekeeping procedure. In brief, if the co-primary endpoint's change from baseline in total IPSS and change from baseline to endpoint in IIEF EF Domain score for either dose did not reject the null hypothesis for that dose, than secondary claims for that dose would not be allowed. If the co-primary endpoint's change from baseline in total IPSS and change from baseline to endpoint in IIEF EF Domain score for either dose did reject the null hypothesis for that dose, than secondary claims for that dose would be allowed according to a secondary claim hierarchy. Once a secondary claim did not reject the null hypothesis, that claim and claims below it in the hierarchy would not be allowed. In this manner a 2-sided alpha = 0.0271 could be applied to each endpoint. See figure below:

Figure 1: LVHR Testing Strategy for Primary and Key Secondary Efficacy Hypotheses



Abbreviations: BII = Benign Prostatic Hyperplasia (BPH) Impact Index, EF = erectile function, IIEF = International Index ofErectile Function, IPSS = International Prostate Symptom Scale, SEP3 = Sexual Encounter Profile Question 3.

Source: Scanned Copy, Figure LVHR.9.2, H6D-MC-LVHR Clinical Study Report, page 54.

In Study LVHR, 98.5% of subjects were ≥70% compliant with study drug treatment.

Efficacy

The table below summarizes the efficacy outcomes for the co-primary efficacy endpoints and the key secondary efficacy endpoints in Study LVHR:

Table 40: Co-Primary and Key Secondary Efficacy Outcomes - All Randomized Subjects in the Primary Analysis Population Study LVHR

Outcome	Placebo	Tadalafil 2.5 mg (N=198)			Tadalafil 5 mg (N=208)		
	N=200	n	Treatment Difference		n	Treatment Difference	
	n LS Mean	LS Mean	LS Mean (±SE)	p-value	LS Mean	LS Mean (±SE)	p-value
Co-primary							
Total IPSS	194 -3.8	191 -4.6	-0.8 (0.59)	.181	206 -6.1	-2.3 (0.58)	<.001
IIEF EF Domain	190 1.8	190 5.2	3.4 (0.67)	<.001	203 6.5	4.7 (0.66)	<.001
Key Secondary							
SEP Q3 (% "yes")	187 12.0	148 -2.8	12.5 (2.85)	<.001	199 31.7	19.7 (2.80)	<.001
BII	190 -1.2	190 -1.6	-0.4 (0.26)	.156	203 -2.1	-0.9 (0.26)	<.001

Source: Table 2.7.3.5, Summary of Clinical Efficacy, current submission, page 44.

Treatment with tadalafil 5 mg favorably affected the total IPSS change from baseline to endpoint compared with placebo as well as the IEFF EF Domain Score change from baseline to endpoint compared to placebo. The co-primary objectives were met after 12 weeks of tadalafil 5 mg once-daily dosing. However, treatment with tadalafil 2.5 mg daily was not as favorable. The co-primary objectives were not met after 12-weeks of tadalafil 2.5 mg once-daily dosing due to a failure to achieve a statistically significant improvement in the total IPSS.

As the co-primary objectives were not met after 12 weeks of treatment with tadalafil 2.5 mg once-daily dosing, further tests for the 2.5 mg dose would not results in claims for that dose.

> *Reviewer's Comment: Treatment with tadalafil 5 mg dosed once daily demonstrated statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo in subjects with BPH-LUTS in Studies LVHG and LVHJ. The 5 mg once-daily dose of tadalafil demonstrated statistically significant improvement in total IPSS as well as in the EF Domain of the IIEF in patients with both ED and BPH-LUTS. The 2.5 mg dose of tadalafil failed to show statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo in subjects with BPH-LUTS and ED. It, therefore, appears that for both indications (BPH-LUTS and BPH-LUTS/ED) there is one effective tadalafil dose, 5 mg.*

Safety

Drug exposure was evaluated for 604 randomized subjects. The mean duration of therapy was similar for all treatment groups (placebo, 78.5 days; tadalafil 5 mg, 79.6 days; tadalafil 2.5 mg, 80.2 days). The mean number of doses for all treatment groups, and the mean cumulative number of doses taken was similar for all 3 treatment groups (placebo, 77.3; tadalafil 5 mg, 79.8; tadalafil 2.5, 78.8).

Table 41: Overview of Adverse Events Study LVHR

Adverse Events	Placebo (N=200)	IC 2.5 mg (N=198)	IC 5 mg (N=208)
	n (%)		
Deaths	0 (0.0)	1 (0.5)	0 (0.0)
SAEs	1 (0.5)	2 (1.0)	1 (0.5)
Discontinuation AE	3 (1.5)	3 (1.5)	6 (2.9)
TEAE	39 (19.5)	50 (25.3)	57 (27.4)

Source: Table LVHR 12.2, H6D-MC-LVHR Clinical Study Report, page 128. SAES are those for randomized patients

Table 42: Treatment-Emergent Adverse Events 1% or Greater in Incidence as Compared to Placebo Study LVHR.

	Placebo (N=220)	Tadalafil 2.5 mg (N=198)	*Tadalafil 5 mg (208)*
Preferred Term	n (%)		
Subjects with >= 1 TEAE	39 (19.5)	50 (25.3)	57 (27.4)
Headache	6 (3.0)	5 (2.5)	12 (5.8)
Back Pain	5 (1.5)	1 (0.5)	6 (2.9)
Nasopharyngitis	4 (2.0)	6 (3.0)	5 (2.4)
Dyspepsia	0 (0.0)	1 (1.0)	3 (1.4)
Upper Respiratory Tract Infection	0 (0.0)	0 (0.0)	3 (1.4)
Muscle Spasms	0 (0.0)	0 (0.0)	2 (1.0)
Oropharyngeal Pain	0 (0.0)	0 (0.0)	2 (1.0)
Pharyngitis	0 (0.0)	0 (0.0)	2 (1.0)
Vision Blurred	0 (0.0)	0 (0.0)	2 (1.0)
Blood creatine phosphokinase	0 (0.0)	2 (1.0)	0 (0.0)
Tooth infection	0 (0.0)	2 (1.0)	0 (0.0)

Source: Table LVHR 12.3, LVHR Clinical Study Report, page 131

LVHR Subject 208-2806: Death Narrative: The patient was a 67-year old Caucasian male. The patient's medical history included back pain, sinusitis, and orthopedic surgery on his ankle (all in 1984). Concomitant medications included tiaprofenic acid, a multivitamin, ascorbic acid, vitamin B, and ergo calciferol. On 14-APR-2009, the patient began the placebo lead-in period of the study and stopped on 14-MAY-2009. On 15-MAY-2009, the patient began the treatment period with study drug for erectile dysfunction with signs and symptoms of benign prostatic hypertrophy. The patient was last seen at visit 6 on 10-JUL-2009 and was on study drug at that time. The patient's last dose of study drug prior to the event was 13-JUL-2009. On (b) (6) the investigator received a telephone call from the patient's wife who informed him that the patient had died. She said she had found him dead in his house on (b) (6) and he had probably been dead for two to three days. There is no witness report to provide medical details at and around the time of death. Immediate cause of death per medical certification of death document was myocardial infarction, and date of death was documented as (b) (6). I t is also noted by the patient's primary care physician that the patient had a cardiac arrhythmia. What role this may have played in the patient's death is uncertain. Other significant conditions contributing to the death included impaired glucose tolerance, sleep apnea, mild mitral valve prolapse, and episodic atrial fibrillation. An autopsy was not performed. The investigator stated that he did not believe that the myocardial infarction was related to drug or protocol.

> *Reviewer's Comment: In the absence of observation of the acute episode, the lack of autopsy findings, as well as the absence of a history cardiac disease, I am unable to conclude that this death is related to tadalafil.*

LVHR Subject 103-1303: SAE: The patient is a 46 year-old Caucasian US male patient. Medical history included: depression, insomnia, diabetes mellitus type II, hyperlipidemia, hypercholesterolemia, hypertension and lower back pain. Concomitant medications included duloxetine hydrochloride, quetiapine fumarate, gemfibrozil, metformin, glibenclamide, simvastatin, acetylsalicylic acid, methocarbamol, tramadol, and metoprolol. The patient was smoking five to six bowls of "medical marijuana" daily, therefore leading to severe financial difficulties, spending $200 weekly and was on social security disability insurance (SSDI).The patient began treatment during the placebo lead-in period of the study on 15Jul2009 for erectile dysfunction and signs and symptoms of benign prostatic hypertrophy (BPH). He was not randomized to treatment. On 04Aug2009, approximately three weeks after starting the study, the patient was discontinued from the protocol (reason for discontinuation not provided). The patient's wife called the site to report her husband had been admitted to the psychiatric ward for observation on (b) (6) A clinical diagnosis of depression and psychotic disorder was made. Upon admission, the patient was prescribed trazodone 100mg at bedtime, oxycodone 5mg every four hours as needed (prn) and lithium extended release (ER) 300mg twice daily.

LVHR Subject 400-4003: SAE: Patient is a 56 year old Caucasian Italian male. The patient was randomized to placebo. The patient had no relevant medical history. The patient did not take any concomitant medications. On 17-Jun-2009 the patient first received placebo 2 tablets daily in the lead-in period of the study (last dose taken 14-Jul-2009) and on 15-Jul-2009 first received blinded study drug (placebo) in the double-blind treatment period, for the treatment of erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. The date of the last dose of blinded study drug, prior to event onset, was 27-Jul-2009. On 27-Jul-2009, 14 days after the last dose of placebo, and the same day as the last dose of blinded study drug, the patient was diagnosed with lymphoma, reported as medically significant. It was reported that the patient was not hospitalized. Biopsy of the lymph node on an unknown date showed a non-Hodgkin's lymphoma. No other test results were reported. Planned corrective treatment included a chemotherapy cycle. At the time of the initial report the patient had not recovered from the event and was performing chemotherapy in a day hospital. Blinded study drug was discontinued on 28-Jul-2009.

LVHR Subject 401-4104: SAE: The patient is a 69-year-old Caucasian male. The patient had no relevant medical history. Concomitant medications included ramipril for hypertension, fluticasone propionate/salmeterol xinafoate for chronic obstructive bronchopneumopathy and pantoprazole sodium. On 27-Oct-2009, the patient started the placebo lead-in period of the study and completed this phase on 30-Nov-2009 for the treatment of erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. On 01-Dec-2009, the patient commenced the treatment period with blinded therapy (tadalafil 5 mg). The last dose of blinded study medication prior to the event onset was on 25-Dec-2009 and therapy was then stopped. On (b) (6), the patient was admitted initially to hospital for acute pancreatitis. This was (b) (6) post the first dose of blinded study therapy, the patient required prolonged hospitalization due hemorrhagic pancreatitis. There were no laboratory data, examination findings or corrective treatments specified. On (b) (6) a cholecystectomy was performed and on (b) (6) an endoscopic retrograde cholangio-pancreatography was performed. At the time of the report, the patient had

recovered from the event, but was not discharged from hospital. Study drug was permanently discontinued in response to the event and the patient was withdrawn from the study.

> *Reviewer's Comment: The fact that the patient underwent a cholecystectomy and at a later date an endoscopic procedure to possibly assess the patency of the hepatobiliary duct system raises the question of an obstructive etiology of the patient's pancreatitis. There is no discussion of the findings or indications for the cholecystectomy as well as the endoscopy findings. I am therefore not able attribute the pancreatitis to the study drug.*

LVHR Subject 600-6012: SAE: The patient is a 71 year old male patient of Indian origin living in Denmark. The patient was participating in a randomized, double blind, placebo controlled parallel design, multinational study to evaluate the efficacy and safety of tadalafil 2.5mg and 5 mg once daily for 12 weeks for the treatment of erectile dysfunction and signs and symptoms of benign prostate hyperplasia in men with both erectile dysfunction and benign prostatic hyperplasia. No medical history was reported other than a cholecystectomy in 1986. In further information, it was reported that the patient had a pre-existing condition of aortic valve insufficiency which the investigator was not aware about until this adverse event. Concomitant medication information was not provided. On 28 October 2009, the patient first received unspecified oral placebo, two tablets daily, for the treatment of erectile dysfunction and benign prostatic hyperplasia. Last dose of study drug received prior to the event was on 03 November 2009 and the patient did not receive any further doses after that. The patient was not randomized. On (b) (6), exactly nine days after last dose of study drug was received, the patient was hospitalized due to unspecified breast pain (no heart attack and no stomach pain). It was reported that electrocardiogram and heart echo examinations showed aortic valve insufficiency. In further information it was confirmed that these examinations did not reveal anything new and that the aortic valve insufficiency was not related to the event of breast pain. A gastroscopy done of the (b) (6) showed UCS (definition not clarified in report). As corrective treatment, the patient received acetylsalicylic acid and metoprolol. Patient recovered from the event on the (b) (6) and was discharged on the same day. It was reported that patient presented himself on the (b) (6) for a gastroscopy as the patient had relapse of burning stomach pain. No nausea, no vomiting, no heart burn, no tarry stools and no blood in urine were reported. However the patient had lost of 2kg in weight within the last weeks due to lack of appetite was reported. Observations of gastroscopy were as follows: red stripes as if the patient had gastritis, axial hiatal hernia and no pathological findings in upper intestine. It was recommended that the patient should be treated with proton pump inhibitors.

LVHR Subject 702-7212: SAE: The patient is a 70 year old Caucasian French male. The patient was randomized to tadalafil 2.5 mg. The patient had no relevant medical history. Concomitant medications included ginkgo biloba for memory trouble. On 08 July 2009, the patient entered the open-label placebo lead in period, then on 05 August 2009 first received blinded study drug, for the treatment of erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. The date of the last dose of placebo, prior to event onset, was 04 August 2009 and blinded study drug was 31 August 2009. The patient had experienced back pain since 31 August 2009 and on (b) (6) since the last dose of placebo and (b) (6) days after the last dose of

blinded study drug, the patient was admitted to hospital to undergo surgery. The patient was diagnosed with discal hernia and an electromyogram on (b) (6) revealed severe nerve denervation of muscles deriving from L4 and L5 nerve roots and a lesion of left L4 and L5 nerve roots was seen. Surgery (type not specified) was performed on (b) (6) Subsequently blinded study medication was withheld. The patient was discharged from hospital on (b) (6) and recovered from the event on 12 September 2009. Study medication was restarted on 17 September 2009 until 20 September 2009, and then permanently stopped. The patient was then removed from the study on 22 September 2009 (reason not provided).

LVHR Subject 705-7503: SAE: The patient is a 57-year old French male. The patient's medical history was not provided. Concomitant medication included: paracetamol for fever. On 29-Oct-2009, the patient received the first dose of blinded study drug for benign prostatic hyperplasia (tadalafil 2.5 mg). The last dose of study drug administered prior to the event was on 25-Nov-2009, and the investigator stated that the study drug was discontinued prematurely on this date at the request of Lilly and due to patient not meeting protocol entry criteria at V2 (stated as criteria number 4: Make at least 4 sexual intercourse attempts during the 4-week placebo lead-in period and be sexually active with the same female partner for the duration of the study). The investigator did not prescribe another treatment for benign prostatic hyperplasia as patient was due to receive tadalafil (Cialis) 5 mg prescribed by investigator but supplied by Lilly on a special basis, a few days after withdrawal. However tadalafil was not received. On 02-Dec-2009, the patient developed fever, and on 03-Dec-2009 was given paracetamol, as general practitioner thought it was flu. On 03-Dec-2009, the patient developed pollakiuria and was “disturbed with micturition”, and urinated all the time during the night of 03-Dec-2009. The patient developed acute prostatitis on 03-Dec-2009. On 04-Dec-2009, the patient was treated with tamsulosin. On 04-Dec-2009, urine analysis was stated as positive (IE 10000000, ref. range not provided). The patient was treated with ofloxacin antibiotic, but symptoms increased and he developed acute urinary retention. The patient went to emergency department in the night between (b) (6) (b) (6), and was transferred to another clinic to be treated by urologist. Over one month after the first dose of study drug, on (b) (6), the patient was hospitalized for acute prostatitis. Fever was noted. A cysto catheter was implanted, and the patient received unspecified bladder perfusion treatment. The patient was discharged from hospital on (b) (6) The patient was discharged with a prescription of ofloxacin and gentamicin sulfate. It appears that at discharge the patient could urinate but had pollakiuria.

Reviewer’s Comment: This AE developed after patient stopped taking tadalafil.

Table 43: Adverse Events Leading to Discontinuation All Randomized Patients Study LVHR

	Placebo (N=220)	Tadalafil 2.5 mg (N=198)	*Tadalafil 5 mg (208)*
	n (%)		
Preferred Term			
Subjects Discontinued due to AE	3(1.5)	3(1.5)	6(2.9)
Back Pain	0(0.0)	0(0.0)	1(0.5)
Headache	0(0.0)	0(0.0)	1(0.5)
Muscle Spasms	0(0.0)	0(0.0)	1(0.5)
Myalgia	0(0.0)	0(0.0)	1(0.5)
Pancreatitis Hemorrhagic	0(0.0)	0(0.0)	1(0.5)
Syncope	0(0.0)	0(0.0)	1(0.5)
Abdominal Discomfort	1(0.5)	0(0.0)	0(0.0)
Creatine Phosphokinase Increased	1(0.5)	0(0.0)	0(0.0)
Dizziness	0(0.0)	1(0.5)	0(0.0)
Myocardial Infarction	0(0.0)	1(0.5)	0(0.0)
Nocturia	0(0.0)	1(0.5)	0(0.0)
Non-Hodgkin's Lymphoma	1(0.5)	0(0.0)	0(0.0)

Source: Table LVHR, LVHR Clinical Study Report, page 146

Reviewer's Comment: None of these AEs leading to discontinuation occurred in more than 1 patient and most are compatible with the known safety profile of tadalafil.

Notable Discontinuation Narratives of Randomized Non-Placebo Patients

LVHR Subject 208-2806: Previously discussed as a Death.

LVHR Subject 705-7503: SAE of prostatitis after study discontinuation. Previously discussed as SAE.
LVHR Subject 401-4104: Pancreatitis, previously discussed as SAE.

LVHR Subject 207-2710 Patient is a 57-year-old Hispanic male randomized to tadalafil 5 mg, reported mild syncope with an event start date of 19 September 2009, which was 33 days post-randomization, and an end date of 6 October 2009; last dose of study drug was taken on 25 September 2009. Concurrent with the syncope, the subject also reported headache of the same duration. Follow-up with the site indicated that the subject had episodic events of lightheadedness over the period of time between the event start and end dates. The subject did not have one episode of syncope (i.e., loss of consciousness) lasting 18 days nor did he have an isolated syncopal episode, but rather intermittent episodes of headache and lightheadedness. The subject's medical history included emphysema and asthma. His SBP was elevated at the

randomization visit, but otherwise all BP measurements were within normal limits. He met the criterion for a treatment emergent positive orthostatic test (supine heart rate was 82 bpm and standing was 106 bpm) at Visit 6 (approximately 2 months after randomization). The subject discontinued at Visit 6 due to "syncope".

LVHR Subject 104-1404 is a 64-year-old white male randomized to tadalafil 2.5 mg, reported dizziness on the day of randomization which persisted for 2 days. The subject's medical history included hypercholesterolemia, diabetes mellitus, tinnitus, and hypoesthesia. His concomitant medications included pramipexole and pregabalin. The subject reported that the dizziness began after taking 1 dose of double-blind study drug; he discontinued the study 1 day later due to this AE. His sitting blood pressure at Visit 1 was 153/86 mmHg. At Visit 2, his supine blood pressure was 150/86 mmHg and his standing blood pressure was 148/97. At Visit 3, his supine blood pressure was 158/93 mmHg and his standing blood pressure was 160/97. The PI assessed the subject's dizziness as possibly related to study drug.

> *Reviewer's Comment: This patient was hypertensive prior to tadalafil exposure. There is no documented blood pressure which shows that the dizziness was due to hypotension or hypertension.*

LVHR Subject 112-2216 There is no narrative provided for this subject randomized to tadalafil 5 mg who 12 days after randomization was discontinued due the adverse event of headache. At Visit 1, the patient's sitting blood pressure was 131/87 mmHg. At Visit 2, the supine blood pressure was 123/72 mmHg and the standing blood pressure was 121/74 mmHg. At Visit 3 the blood pressure was 126/68 mmHg supine and 120/72 standing. At Visit 4 (the last Visit), the supine blood pressure was 134/68 mmHg and the standing blood pressure was 130/62 mmHg.

> *Reviewer's Comment: There is no data to implicate either hypotension or hypertension with the AE of headache*.

LVHR Subject 702-7215 There is no narrative provided for this subject randomized to tadalafil 5 mg who 12 days after randomization was discontinued due the adverse event of back pain.

LVHR Subject 704-7405 This 64 year-old subject was randomized to tadalafil 2.5 mg and discontinued secondary to increase of nocturia. Tamsulosin had been stopped 4 months prior to randomization. His post-void residual urine volumes at Visit 1 and Visit 3 were 82 and 43 mL, respectively. His reported nocturia frequency at Visits 1, 2, 3, and 4, were 2, 2, 2, and 3 respectively. His Qmax' at Visit 2 and his final Visit (4) were 8.4 mL and 5.2 mL respectively. He reported worsening of nocturia at Visit 2.

> *Reviewer's Comment: I cannot attribute this event to tadalafil therapy. In addition, analysis of reasons for discontinuation has not identified any new safety concerns or signals.*

Notable Adverse Events

Adverse Events Possibly Related to Hypotension

The Sponsor performed focused and expanded analyses of TEAEs possibly related to hypotension. The focused analysis included the following 7 MedDRA terms: dizziness, dizziness postural, procedural dizziness, hypotension, orthostatic hypotension, syncope and presyncope. For the focuses analysis, similar proportions of subjects in each treatment group experienced at least 1 TEAE possibly related to hypotension (placebo, 1.5%; tadalafil 5 mg, 1.4%; and tadalafil 2.5 mg, 1.5%).

For the expanded analysis of TEAEs possibly related to hypotension included the MedDRA preferred terms headache, asthenia, and fatigue. Similar proportions of subjects in each treatment group experienced at least 1 TEAE (placebo, 4.5%; tadalafil 5 mg, 6.7%; and tadalafil 2.5 mg, 1.5%).

Table 44: Treatment Emergent Adverse Events Possibly Related to Hypotension Including Headache, Asthenia, and Fatigue Study LVHR

	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
	N=200	N=198	N=208
Preferred Term	n (%)		
Subjects with >= 1 TEAE	9(4.5)	7(3.5)	14(6.7)
Headache	6(3.0)	5(2.5)	12(5.8)
Dizziness	2(1.0)	2(1.0)	2(1.0)
Syncope	0(0.0)	1 (0.5)	1(0.5)
Orthostatic Hypotension	1(0.5)	1(0.5)	0(0.0)

Source: Table LVHR 12.8, LVHR Clinical Study Report, page 152 and EVENTS.XPT dataset.

It is also noted that syncope occurred in tadalafil 2.5 mg subject 902-9217 on October 13, 2009. The Visit 2 date for this patient was September 10, 2009. Asthenia was also noted in the same subject on the same day. This event is listed in EVENTS. XPT dataset. Table 43 has been altered to reflect this event. There were no other syncopal events in the AETERM data category. No narrative is provided. Asthenia was also noted in tadalafil 5 mg subject 701-7100 on 15 May 2009. On 18 May 2009, he experienced postural dizziness during orthostatic vital signs (Table 14.78 Study LVHR report, page 370).

> *Reviewer's Comment: Asthenia occurred in 1 tadalafil 2.5 mg patient and 1 tadalafil 5 mg patient and syncope occurred in one tadalafil 5 mg patient. These small numbers do not generate a safety concern. The AE of Headache was increased in the tadalafil 5 mg group but this was not associated with increased incidence of orthostasis or signs of hypotension and may be related to the known incidence of headache in patients using tadalafil.*

During the orthostatic vital sign assessments, 3 tadalafil 5 mg subjects experienced mild dizziness. Their orthostatic tests were not positive, but they were not able to remain standing during the episode.

Dizziness

LVHR Subject 101-1148 Patient is a 64-year-old white male randomized to tadalafil 2.5 mg, who reported mild dizziness 15 days post-randomization, which persisted for 3 days, and intermittent dizziness (lightheadedness) 47 days post-randomization which persisted for 3 days. The subject had no pertinent preexisting conditions or concomitant medications. He did not meet any of the criteria for a treatment-emergent positive orthostatic test. The subject completed the study.

LVHR Subject 102-1208 Patient is a 78-year-old Asian male randomized to tadalafil 5 mg, reported dizziness 17 days post-randomization, which persisted for 37 days. The subject's medical history included obesity, type 2 diabetes mellitus, hypercholesterolemia, edema peripheral, and hypertension, for which he was receiving atenolol (start date 1998). The subject did not meet any of the criteria for a treatment-emergent positive orthostatic test. According to follow-up information received from the PI, the subject's dizziness resolved upon discontinuation of atenolol, and he completed the study.

LVHR Subject 104-1404 Patient is a 64-year-old white male randomized to tadalafil 2.5 mg, reported dizziness on the day of randomization which persisted for 2 days. The subject's medical history included hypercholesterolemia, diabetes mellitus, tinnitus, and hypoesthesia. His concomitant medications included pramipexole and pregabalin. The subject reported that the dizziness began after taking 1 dose of double-blind study drug; he discontinued the study 1 day later due to this AE.

LVHR Subject 107-1708 Patient is a 77-year-old white male randomized to tadalafil 5 mg, reported dizziness (lightheadedness) 15 days post-randomization. The subject's medical history included blood cholesterol increased and vertigo. In addition to the report of ongoing dizziness, this TEAE was also reported as a clinical symptom upon standing during orthostatic vital signs assessment at Visits 4, 5, and 6. The subject did not meet any of the criteria for a treatment-emergent positive orthostatic test. The TEAE was unresolved upon subject's completion of the study.

LVHR 208-2804 Patient is 64-year-old white male randomized to tadalafil 2.5 mg, reported dizziness 41 days post-randomization. The subject was diagnosed with hypertension approximately 1 month prior to randomization and initiated treatment with hydrochlorothiazide at that time. In addition, the subject had been taking gabapentin for back pain since 2007. He did not meet any of the criteria for a treatment-emergent positive orthostatic test. The TEAE was unresolved upon subject's completion of the study.

> *Reviewer's Comment: Of these 5 subjects who reported dizziness and were taking tadalafil, one had "dizziness" on the day of randomization (LVHR Subject 104-1404),*

leaving 4 out of 406 tadalafil-treated subjects reporting dizziness (1%). In the placebo group, 2 out of 200 subjects (1%) reported dizziness. Based on the lack of difference between groups, there does not appear to be evidence of tadalafil causing dizziness as an AE in this study.

Syncope

LVHR Subject 207-2710 Patient is a 57-year-old Hispanic male randomized to tadalafil 5 mg, reported mild syncope with an event start date of 19 September 2009, which was 33 days post-randomization, and an end date of 6 October 2009; last dose of study drug was taken on 25 September 2009. Concurrent with the syncope, the subject also reported headache of the same duration. Follow-up with the site indicated that the subject did not have a discrete syncopal episode, but rather had episodic events of lightheadedness over the period of time between the event start and end dates. The subject did not have one isolated episode of syncope (i.e., loss of consciousness) lasting 18 days nor did he have any isolated syncopal episode, but rather intermittent episodes of headache and lightheadedness. The subject's medical history included emphysema and asthma. His SBP was elevated at the randomization visit, but otherwise all BP measurements were within normal limits. He met the criterion for a treatment emergent positive orthostatic test (supine heart rate was 82 bpm and standing was 106 bpm) at Visit 6 (approximately 2 months after randomization). The subject discontinued at Visit 6 due to syncope.

Reviewer's Comment: While initially classified as syncope, it does not appear that syncope occurred, but at a later date the subject did have a positive orthostatic test.

Orthostatic Hypotension

LVHR Subject 116-3801 Patient is a 72-year-old African-American male randomized to tadalafil 2.5 mg, who reported orthostatic hypotension 15 days post-randomization, which was ongoing at the time of study completion. The subject's medical history included pre-existing hypertension and hypercholesterolemia. His concomitant medications included nebivolol. Despite the subject's anti-hypertensive therapy, his blood pressure was elevated throughout the study (sitting blood pressure of 156/74 at screening [Visit 1]; supine blood pressure ≥171/84 mm Hg and standing blood pressure ≥145/76 at Visits 2-7). The subject met the criterion for a treatment-emergent positive orthostatic test (SBP) at all post-randomization visits (Visit 4 through Visit 7); however, he also met the criterion for a positive orthostatic test (SBP) at Visit 2 (beginning of the placebo lead-in period). Per follow-up with the site, the subject did not report any symptoms related to dizziness, fainting, or lightheadedness during orthostatic testing; the event was reported on the basis of the study coordinator's observations of blood pressure changes during orthostatic testing. The subject completed the study with no additional AEs reported.

Reviewer's Comment: In light of the positive orthostatic test (SBP) at Visit 2 and the fact that subsequent positive orthostatic test also involved the SBP, I cannot attribute the positive finding to tadalafil.

Headache

LVHR Subject 207-2710 reported headache and syncope concurrently. The syncope did not occur. See narrative above for this subject above.

Fall

Fall is not included in the prespecified list of events possibly related to hypotension but the Sponsor has included this report for completeness. Subject 107-1700, an 81-year-old white male, reported a fall 49 days post-randomization (2.5 mg tadalafil). The fall occurred when the subject was moving firewood and tripped over a piece of it. The fall was not preceded by dizziness, light-headedness, asthenia syncope or presyncope. The subject had right shoulder pain as a result of the fall, which was treated with naproxen. His vital signs were within normal limits for all visits, and he did not meet any of the criteria for a treatment-emergent positive orthostatic test. The subject completed the study.

Cardiac Disorders

A total of 5 subjects reported cardiac disorders, including 2 placebo-treated subjects (each reporting chest pain) and 3 subjects in the tadalafil 2.5-mg group (1 subject with chest pain, 1 subject with myocardial infarction (Subject 208-2806 described in death narrative) and 1 subject with palpitations.

LVHR Subject 101-1142 Patient is a 54-year-old white male randomized to tadalafil 2.5 mg, who reported (intermittent) chest pain 27 days post-randomization, which was unresolved at the time of study completion. The subject reported no pertinent medical history or use of concomitant medications. Although the subject's medical history did not include hypertension, his blood pressure was elevated throughout the study. He met both the SBP (Visit 6 and Visit 7) and HR (Visit 5 and Visit 6) criteria for a treatment-emergent positive orthostatic test, although both criteria were also met at Visit 2 (beginning of placebo lead-in period). Per follow-up with the site, the subject's symptoms included mild pressure in the chest and back, with no notable activity at the time of the event. No follow-up diagnostic tests were performed, and the event resolved without intervention approximately 1 month after study completion.

LVHR Subject 208-2809 Patient is a 64-year-old white male randomized to tadalafil 2.5 mg, who reported palpitations 4 days post-randomization which persisted for 1 day. The subject's medical history included hypercholesterolemia and gastrointestinal reflux disease (GERD), but he had no history of cardiovascular disorders. The subject also reported moderate arthralgia (deep hip pain) commencing on the same day as the palpitations. All vital signs were within normal limits throughout the study, with no treatment-emergent positive orthostatic tests. Per follow-up with the site, the subject experienced a pounding heartbeat while walking, which was

relieved with rest; no follow-up diagnostic tests were performed. The subject completed the study.

> *Reviewer's Comment: There does not appear be a preponderance of cardiac events in the tadalafil treated groups.*

Vision Disorders

50 year-old LVHR Subject 206-2612 who 38 days post-randomization to 5 mg tadalafil reported blurred vision which persisted through study completion. 1 month after completion the patient still reported blurred vision and he occasionally still takes tadalafil. 68 year-old LVHR Subject 206-2616 51 days post randomization to 2.5 mg tadalafil reported photopsia which was unresolved at study completion. The subject also reported vitreous floaters, left vitreous detachment, bilateral nuclear cataracts within the same period. 66 year-old LVHR Subject 209-2908 57 days post randomization to 5 mg tadalafil reported blurred vision which was unresolved at study completion. The patient has a history of medication treated glaucoma.

> *Reviewer's Comment: It is not possible to exclude tadalafil as a cause of blurred vision in the listed AEs. However, in one case, the patient experienced a vitreous detachment and had bilateral cataracts, and in another, the patient had medication-treated glaucoma. Blurred vision has been reported in previous clinical trials, at an incidence rate < 2%, where a causal relationship was uncertain. These cases are reflected appropriately in the current labeling under adverse events reported in clinical trials in <2% of subjects where a causal relationship is uncertain.*

Renal and Urinary Disorders

Eight subjects, 3 in the placebo group (worsening BPH symptoms, dysuria and nocturia), 2 in the tadalafil 5 mg group (1 subject with micturition disorder and pollakiuria, and 1 subject with renal impairment), and 3 in the tadalafil 2.5 mg group (1 subject with pollakiuria, 1 subject with terminal dribbling, and 1 subject with urinary tract infection) reported AEs in this category.

LVHR Subject 303-3313 Patient is a 58-year-old Hispanic male randomized to tadalafil 2.5 mg, who reported a mild urinary tract infection at his final study visit. The subject reported preexisting diabetes mellitus, which was being treated with glibenclamide and metformin. The subject's final urinalysis showed the presence of blood and protein, but leukocyte esterase results were normal. He completed the study with no report of urinary retention or required intervention.

LVHR Subject 500-5005 Patient is a 73-year-old white male randomized to tadalafil 5 mg, reported renal impairment (worsening renal function) 36 days post-randomization, which was ongoing at the time of study discontinuation. The subject reported pre-existing hypertension (since 2005) being treated with losartan. His creatinine clearance was low at baseline, and further reduced at his early discontinuation visit approximately 1 month later (baseline, 1.42 mL/sec;

endpoint, 0.37 mL/sec; reference range 1.42 – 2.08 mL/sec). In addition, the subject had a >2-fold increase in blood urea nitrogen (baseline, 8.3 millimole/L; endpoint, 20.4 millimole/L; reference range 2.9 –11.1 millimole/L), as well as elevated phosphorus and potassium. The subject was discontinued due to a protocol violation (less than 4 sexual attempts during placebo lead-in period) at Visit 5.

LVHR Subject 704-7405 This 64 year-old subject has been described previously. He was randomized to tadalafil 2.5 mg and discontinued secondary to increase of nocturia. Tamsulosin had been stopped 4 months prior to randomization. His post-void residual urine volumes at Visit 1 and Visit 3 were 82 and 43 mL, respectively. His reported nocturia frequency at Visits 1, 2, 3, and 4, were 2, 2, 2, and 3 respectively. His Qmax' at Visit 2 and his final Visit (4) were 8.4 mL and 5.2 mL respectively. He reported worsening of nocturia at Visit 2.

Reviewer's Comment: No new safety concerns appear in any AE Event Category.

Reproductive System Disorders

67 year-old LVHG Subject 300-3004 randomized to tadalafil 5 mg, reported priapism 2 days post-randomization which spontaneously resolved in 4 hours without intervention. The patient completed the study. LVHG Subject 705-7505 randomized to tadalafil 2.5 mg reported an SAE of prostatitis 8 days after study completion. This subject is extensively discussed as an SAE in this review.

Orthostatic Vital Signs

Overall, a similar proportion of subjects in each treatment group met at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test; neither the tadalafil 5 mg group nor the tadalafil 2.5 mg group was statistically different from placebo. No statistically significant differences were observed in either tadalafil treatment group versus placebo for any single criterion.

Table 45: Treatment Emergent Positive Orthostatic Tests Study LVHR

	Placebo (N=198)	Tadalafil 2.5 mg (N=198)	Tadalafil 5 mg (N=208)
Subjects with >= Positive Orthostatic Test	n (%)		
	42 (21.0)	41 (20.7)	38 (18.3)
Criterion 1 (SBP decrease >= 20 mmHg)	17 (8.5)	15 (7.6)	8 (3.8)
Criterion 2 (DBP Decrease >= 10mm Hg)	25 (12.5)	26 (13.1)	26 (12.5)
Criterion 3 (HR Increase >= 20 bpm	6 (3.0)	7 (3.5)	8 (3.8)
Criterion 4 (Unable to Remain Standing)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table LVHR 12.10, LVHR Clinical Study Report, page 158.

Reviewer's Comment: Analysis of shifts of positive orthostatic test shifts revealed no major differences between treatment groups. Review of Table LVHR 14.80 which provides listing of orthostatic vital signs for all subjects with at least 1 positive test at any visit did not show, in this reviewer's opinion, any significant group differences. In Visits after Visit 3, the largest decrease in blood pressure for placebo patients was -19 mm Hg diastolic and -29 mm Hg systolic. In Visits after Visit 3, the largest decrease in blood pressure for tadalafil patients was -22 mm Hg diastolic and -33 mm Hg systolic. The tadalafil 5 mg group had a lower proportion of subjects with shifts from negative to positive orthostatic tests for the SBP criterion than the tadalafil 2.5 mg or placebo groups.

Uroflowmetry

From baseline to endpoint, Qmax increased in both treatment groups (1.2 mL/sec, placebo; 1.7 mL/sec, tadalafil 2.5 mg; 1.6 mL/sec, tadalafil 5 mg); the change was statistically significant for the tadalafil 2.5-mg group (p=.016), but not for the tadalafil 5-mg group (p=.071), when compared to placebo. For Vcomp (voided volume), change from baseline to endpoint was 13.3 mL in the tadalafil 5-mg group, 18.5 mL in the tadalafil 2.5-mg group, and 11.4 mL in the placebo group.

Postvoid Residual Volume

There were 2 subjects (1 tadalafil 2.5 mg, 1 placebo) who had a PVR <300 mL at baseline, but a PVR ≥300 mL at endpoint. LVHR Subject 207-2716, a 75-year-old white male randomized to tadalafil 2.5 mg, had a baseline PVR of 232 mL and endpoint PVR of 407 mL. The subject reported pollakiuria 72 days after randomization. Ten days prior to the report of pollakiuria, the subject reported nasopharyngitis, for which he was taking pseudoephedrine. The

pseudoephedrine was stopped after 19 days of use on 29 December 2009. The post voiding residual of 407 mL occurred on 4 January 2010. The subject reported no further AEs and completed the study.

> *Reviewer's Comment: The use of pseudoephedrine may have played a role the increased PVR.*

Clinical Laboratory Evaluations

With respect to hematology, changes between treatment groups were statistically significant for lymphocytes (tadalafil 5 mg [-0.0369 BILL/L] versus placebo [0.0685 BILL/L, p=.014), eosinophils (tadalafil 2.5 mg [-0.0070 BILL/L] versus placebo [0.0095 BIL/L), p=.035) and basophils (tadalafil 5 [0.0016 BILL/L] versus placebo [0.0021 BILL/L], p=tadalafil 2.5 mg [-0.0008 BILL/L] versus placebo, p=.048).

> *Reviewers Comment: I do not feel that the changes in cellular component of the CBC differential rise to the level of clinical significance.*

Changes between treatment groups were statistically significant for potassium (tadalafil 2.5 mg [0.0506 mm/L versus placebo [-0.0763 mm/L], p=.017), alanine transaminase (ALT/SGPT) (tadalafil 5 mg [-2.5380 U/L] versus placebo [-0.4913 U/L], p=.016) and blood urea nitrogen (BUN) (tadalafil 5 mg [-0.1516 m/L] versus placebo [0.0854 mm/L], p=.045). Most subjects across all treatment groups were within normal range at both baseline and endpoint for all chemistry parameters except creatinine clearance. Approximately 30% of the subjects in all treatment groups had a creatinine clearance that was considered below normal limits (<1.43 mL/sec; <85mL/min) at baseline and endpoint (subjects with severe renal insufficiency were excluded from the study). A total of 49 subjects (10 placebo, 20 tadalafil 5 mg, and 19 tadalafil 2.5 mg) with a creatinine clearance within normal limits at baseline had a creatinine clearance below normal limits at endpoint. The Sponsor observes, "any interpretation of these data is confounded by the small absolute change seen in most of these subjects; a total study population median baseline creatinine clearance that was very close to the lower limit of normal; and the common occurrence of preexisting conditions that might influence renal function."

In reviewing shift tables for creatinine clearance for Studies LVHG, LVHJ, and LVHR, the rate of shift from normal at baseline to below normal limits at endpoint is highest in LVHR. The rate of shift in LVHJ is intermediate. This may indicate a difference in BPH versus BPH/ED patients. This could also be secondary to the increased age in patients in LVHR and LVHJ. See table below:

Treatment	Estimated Creatinine Clearance Shift From Normal to Low at Study Endpoint
Placebo	N (%)
LVHG N=210	0 (0.0)
LVHJ N=164 N1=151	11(7.3)
LVHR N=200 N1=174	10 (5.7)
Tadalafil 2.5 mg	
LVHG N=208	0(0.0)
LVHR N=198 N1=176	19(10.8)
Tadalafil 5 mg	
LVHG N=212	0(0.0)
LVHJ N=161 N1=152	12(7.9)
LVHR N=208 N1=186	20(10.8)
Tadalafil LVHG 10 mg N=216	0(0.0)
Tadalafil LVHG 20 mg N=208	0(0.0)

N1=subjects with non-missing data at baseline and endpoint
Source: Table LVHG 14.98(page 1077), Shift table LVHJ page 397, Shift table LVHR page 1350.

In addition, more subjects in the tadalafil treatment groups than in the placebo group had shifts from normal to high for creatine phosphokinase. This occurred in 7 tadalafil subjects (1 tadalafil 5 mg subject and 6 tadalafil 2.5 mg subjects) and 2 placebo subjects. It is also noted by Sponsor that most subjects had high CPK at the screening and or/baseline visit.

Reviewer's Comments:

1. *The creatinine clearance decreases with aging. The Sponsor included patents > 65 and > 75 years of age to ensure a representative patient population and this could in part account for observation that most patients did not enter the study with a normal creatinine clearance.*
2. *Creatine phosphokinase is a biomarker for muscle breakdown, rhabdomyolysis, myocardial infarction and muscular dystrophy. Without isoenzyme or M-band analysis, it is difficult to attribute the increase to one of these possibilities in isolation. Elevations of ALT often suggest other medical problems such as hepatitis, congestive heart failure, liver damage, bile duct problems, and myopathy. Alkaline phosphatase and bilirubin were not significantly changed versus placebo in Study LVHR. When considering the increase in creatinine kinase in these outlier patients, these changes could point to a muscular source of elevation in some patients. What is also to be noted is that the mean change in CPK in the study population showed an increase for placebo and a decrease for tadalafil: +3.9770 U/L in placebo subjects (N/n=200/174) vs. -4.1029 U/L in tadalafil 2.5mg subjects (N/n=198/175) and -21.5297U/L in 5 mg tadalafil subjects (N/n=208/185).*

One subject had preexisting hypertension and had endpoint BUN nearly 2-fold the upper limit of normal at his early termination visit.

LVHR Subject 500-5005, Patient is a 73-year-old white male randomized to tadalafil 5 mg, reported renal impairment (worsening renal function) 36 days post-randomization, which was ongoing at the time of study discontinuation. The subject reported pre-existing hypertension (since 2005) being treated with losartan. His creatinine clearance was low at baseline, and further reduced at his early discontinuation visit approximately 1 month later (baseline, 1.42 mL/sec; endpoint, 0.37 mL/sec; reference range 1.42 – 2.08 mL/sec). In addition, the subject had a >2-fold increase in blood urea nitrogen (baseline, 8.3 millimole/L; endpoint, 20.4 millimole/L; reference range 2.9 –11.1 millimole/L), as well as elevated phosphorus and potassium. The subject was discontinued due to a protocol violation (less than 4 sexual attempts during placebo lead-in period) at Visit 5.

> *Reviewer's Comment. While the subject did enter the trial with a low-normal creatinine clearance, he did not have a baseline history of renal insufficiency. It appears that he did sustain a clinically meaningful worsening in renal function while on treatment. Lacking an alternative etiology, it is not possible to exclude the role of tadalafil in the event. For this case, it would be appropriate to insert the adverse event term "renal impairment" in the list of adverse events reported infrequently in clinical trials and where a causal relationship is uncertain.*

One subject in the tadalafil 2.5-mg group met the criteria of having both ALT ≥3 times the upper limit of normal (ULN; age dependent) and of having AST ≥3 times the ULN (age-dependent); 3 subjects (1 in the placebo group, 2 in the tadalafil 2.5-mg group) met the criteria of having total bilirubin ≥1.5 times the ULN (ULN = 1.2 mg/dL).

Table 46: Treatment Emergent Elevated Hepatic-Related Serum Chemistry Results Study LVHR All Randomized Subjects.

	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
	N=200	N=198	N=208
	n (%)		
ALT >= 3X ULN	0 (0.0)	1 (0.5)	0(0.0)
AST >= 3X ULN	0 (0.0)	1 (0.5)	0 (0.0)
Total Bilirubin >= ULN	1 (0.5)	2 (1.0)	0 (0.0)
ALT >= ULN and Total Bilirubin >= 1.5X ULN	0 (0.0)	0 (0.0)	0 (0.0)
AST >= 3X ULN and Total Bilirubin >= 1.5X ULN	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table LVHR 12.13, LVHR Clinical Study Report, page 166

LVHR Subject 702-7220, Patient is a 71-year-old white male randomized to tadalafil 2.5 mg, had an endpoint total bilirubin ≥1.5 times the ULN (1.81 mg/dL); the subject's total bilirubin was also slightly elevated at screening (Visit 1; 1.46 mg/dL) and at randomization (Visit 3; 1.40

mg/dL). The subject reported no preexisting conditions or concomitant medications. The subject's AST, ALT, and GGT were all within normal limits at all visits, as was nonfasting glucose, and no TEAEs were reported. The subject completed the study.

LVHR Subject 802-8202, Patient is a 57-year-old white male randomized to placebo, had an endpoint total bilirubin ≥1.5 times the ULN (2.05 mg/dL); the subject's total bilirubin was also elevated at screening (Visit 1; 2.63 mg/dL) and at randomization (Visit 3; 1.58 mg/dL). The subject reported no preexisting conditions or concomitant medications. AST, ALT, and GGT were all within normal limits at all visits, as was nonfasting glucose, and no TEAEs were reported. The subject completed the study.

LVHR Subject 902-9210, Patient is a 68-year-old white male randomized to tadalafil 2.5 mg, had an endpoint total bilirubin ≥1.5 times the ULN (2.87 mg/dL); the subject's total bilirubin was also slightly elevated at randomization (Visit 3; 1.46 mg/dL), but was within normal limits at screening (Visit 1; 0.53 mg/dL). The subject reported no preexisting conditions or concomitant medications. The subject's AST, ALT, and GGT were all within normal limits at all visits, as was nonfasting glucose, and no TEAEs were reported. However, the subject's endpoint laboratory results revealed several abnormalities which represented changes from the screening and baseline values: albumin, calcium, chloride, creatinine, potassium, sodium, and total protein above normal limits. A retest was requested, but not performed; per the site, the subject confirmed a lack of symptomatology or illness. The subject completed the study.

LVHR Subject 905-9514, Patient is a 59-year-old white male randomized to tadalafil 2.5 mg, had an endpoint AST ≥3 times the ULN (244, ULN = 36 IU/L) and ALT ≥3 times the ULN (137, ULN = 43 IU/L); both were within normal limits at screening and randomization (Visits 1 and 3, respectively). The subject's medical history included only a prior stomach ulcer (recovered 1985), with no preexisting conditions or concomitant medications reported In addition to the endpoint elevations in ALT and AST, GGT was increased approximately 5-fold from baseline. Total bilirubin was within normal limits at all visits. The subject was a nonsmoker who reported alcohol use (3 spirits/week). Per follow-up with the site, the subject had recently consumed alcohol prior to endpoint (Visit 7). Both ALT and AST were within normal limits upon retest (29 IU/L and 28 IU/L, respectively). The subject completed the study.

> *Reviewer's Comment: There does not seem to be any significant indication of hepatotoxicity in this study population.*

Urinalysis

A total of 9 subjects (1 placebo, 3 tadalafil 5 mg, and 5 tadalafil 2.5 mg) had shifts from normal to abnormal in urine glucose. Additionally, 7 subjects (1 placebo, 1 tadalafil 5 mg, and 5 tadalafil 2.5 mg) had shifts from normal to abnormal in urine blood. Most tadalafil subjects with shifts from normal to abnormal for urinalysis parameters had abnormal urine screening results, preexisting lipid disorders, hypertension, and/or diabetes. Only 1 subject in the tadalafil

2.5-mg group with a shift in urine blood reported a urinary TEAE. This tadalafil 2.5 mg subject, 3003-3313, an adult onset diabetic since 2000 for which he was taking metformin and glibenclamide, had urine glucose and urine blood present as his screening and final visits. In addition, he developed a mild urinary tract infection at his final visit.

Safety Subgroup Analysis

Age

Overall the proportion of subjects reporting ≥ 1 TEAE was similar in those ≤ 65 years, regardless of treatment group (placebo, 22.0%; tadalafil 5 mg, 24.8%; tadalafil 5 mg, 25.0%). In subjects >65 years, a greater proportion of tadalafil-treated subjects (31.3%, 5 mg; 25.8%, 2.5 mg) reported ≥ 1 TEAE than placebo (15.6%). Across both age groups, headache was the most frequently reported AE and was more frequently reported in the tadalafil 5 mg group than in either of the other 2 treatment groups. In the ≤65 years group, it was reported by 5.6% of subjects (n=7) and in the >65 years group, it was reported by 6.0% of subjects (n-5) in the tadalafil 5 mg group.

The proportion of subjects reporting ≥1 TEAE was similar in those <75 years and those ≥ 75 years of age, regardless of treatment group (placebo, 20.9%; tadalafil 5 mg, 27.3%; tadalafil 2.5 mg, 24.7%). The most frequently reported event in the <75 years group was also headache, which was reported more frequently in the tadalafil 5-mg group (5.3% [n=10]) than in the other treatment groups (2.7% [n=5] for tadalafil 2.5 mg; 2.8% [n=5] for placebo).

Within all treatment groups, there was a total of 56 subjects who were ≥ 75 years (placebo, n=23; tadalafil 5 mg, n=21; tadalafil 2.5 mg, n=12). The proportion who reported ≥1 TEAE was 8.7% for placebo (n=2), 33.3% for tadalafil 2.5 mg (n=4), and 28.6% for tadalafil 5 mg (n=6). In the ≥75 years age group, the only events reported by more than 1 subject were dizziness (n=2) and headache (n=2) in the tadalafil 5-mg group, and nasopharyngitis (n=2) in the tadalafil 2.5-mg group.

> *Reviewer's Comment: The small number of adverse events in this study, and the relatively small number of subjects aged ≥ 75 years, preclude definitive conclusions regarding differences in incidence of adverse events in those ≥ 75 years of age compared to younger age groups. However, the safety profile does not appear markedly different in the older age groups compared to younger patients.*

Treatment-Emergent Positive Orthostatic Tests by Age

In general the proportion of subjects who met at least 1 of the four criteria for a treatment-emergent positive orthostatic test was similar across treatment and age groups. A somewhat *lower* proportion of subjects ≥75 years on tadalafil treatment met ≥1 criteria. No statistically significant differences were observed between tadalafil 5 mg and tadalafil 2.5 mg when compared to placebo in any age group. In no age group or treatment group was orthostatic Criterion 4 (Unable to remain standing) met.

Table 47: Treatment Emergent Positive Orthostatic Tests by Age Group Study LVHR

Subjects with >= 1 Positive Orthostatic Test	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
Age Category <=65 years	N=123	N=132	N=125
n (%)	24(19.5)	27(20.5)	23(12.8)
Age Category > 65 years	N=77	N=66	N=83
n (%)	18(23.4)	14(21.2)	15(18.1)
Age Category <75 years	N=177	N=166	N=35
n (%)	37(20.9)	39(21.0)	35(18.7)
Age Category >=75 years	N=23	N=12	N=21
n (%)	5(21.7)	2(16.7)	3(14.3)

Sources: Tables LVHR 14.91, 14.92, 14.93, 14.94, LVHR Clinical Study Report, pages 1568-1571.

Reviewer's Comment: There does not seem to be an increase in orthostatic hypotension either by age or dose group in the BPH/ED population in LVHR.

Hypertension as an Adverse Event

Four patients were identified by the reviewer's JMP search for the lower level term of hypertension as a study adverse event. Their blood pressures are presented in the table below.

Table 48: Hypertension as Study Event and Identified by Lower Level MedDRA Tern Study LVHR All Randomized Subjects

Reviewer's Comment: For Subject 100-1008, blood pressures were higher during Visits 2 and 3, than on Visits when he was using Tadalafil 5 mg. Therefore, I cannot classify this as related to drug. Subject 207-2708 was a placebo subject. For Subject 208-2804, Based on blood pressure ranges on Visits 1 thru 3, I cannot conclude there was any increase of the blood pressure during the study. For Subject 705-7507, on Visit 5, this subject while standing had an increase in the diastolic blood pressure and on Visit 7 while standing had an increase in the systolic blood pressure. These findings do not, in my opinion, indicate a signal for an increase in blood pressure for tadalafil especially for the 5 mg dose.

Reviewer's Overall Conclusions: With regard to efficacy, only the tadalafil 5-mg dose successfully met criteria for statistical significance. The tadalafil 2.5 mg dose group did not achieve success under criteria established by the gatekeeping procedure for the primary endpoints. Based upon the gatekeeping procedure, analysis of the key secondary efficacy measures of the percentage of "Yes" responses to SEP diary Question 3 and the BII were conducted sequentially only for the 5 mg tadalafil group. There was a statistically significant increase in the percentage of "Yes" responses to SEP diary Question 3 ($p<.001$) and a statistically significant decrease in the BII ($p<.001$) when compared to placebo. The BII is not a sufficiently validated assessment tool of the disease related, clinically meaningful impact of BPH symptoms and treatment outcomes in BPH studies (refer to Medical Officer's Memorandum, IND 73502 SDN105, 4 January 2001). (b) (4)

While the incidence of TEAEs in the tadalafil treatment groups was numerically higher than placebo, the most commonly reported TEAEs in the tadalafil 5 mg group were headache, back pain, and nasopharyngitis. Similar proportions of subjects in each treatment group reported at least 1 TEAE possibly related to hypotension. There was no evidence of an adverse impact of tadalafil on vital signs. No clinically adverse changes were observed in uroflowmetry assessments or in PVR in tadalafil-treated subjects compared to placebo. The overall safety results are acceptable and do not preclude approval.

LVHN: A Study to Evaluate the Pharmacokinetics of Tadalafil Administered Once Daily in Young and Elderly BPH (Benign Prostatic Hyperplasia) Subjects

Study LVHN: Study LVHN was an open-label, Phase 1, clinical pharmacology study conducted to evaluate the pharmacokinetics and hemodynamics of tadalafil 20 mg administered once daily in elderly men (70 to 76 years of age [n=12]; Median age 73) and young men (below and including 60 years (age range 42-60) of age [n=15]; median age 56) with BPH-LUTS. The BPH-LUTS inclusion criteria was an IPSS score of ≥ 12. Tadalafil was administered for 10 consecutive days. All subjects were Caucasian.

At baseline, three of the young male subjects had mild renal impairment and were without BPH-LUTS. They were included as a reference group. At baseline, as expected, elderly subjects had

reduced renal function compared to young subjects, with mean creatinine clearance values calculated by the standard Cock-Gault (CGCL) formula being approximately 37% lower (young CGCL=112 mL/min; elderly CGCL=71 ml/min). The three young subjects with mild renal impairment had individual CGCL values similar to those of the elderly subjects.

The estimates of tadalafil accumulation (approximately 1.8-fold for both AUC and Cmax) for elderly and young subjects with BPH were consistent with that expected for once-daily dosing (2-fold) based upon a $t_{1/2}$ of 25 hours and were similar to that demonstrated in healthy subjects (1.6-fold). In this study, there appears to have been no significant difference in the systemic exposure (based on AUC (0-24)) to tadalafil between elderly and young subjects with BPH following single- and multiple-dose administration of 20-mg tadalafil qd for 10 days. Mean tadalafil AUC and C_{max} values were actually reduced by approximately 13% following single- and multiple-dose administration of 20-mg tadalafil in elderly subjects compared to young BPH subjects; however, these slight differences were considered by the Sponsor not to be clinically meaningful nor statistically different. Despite the moderately reduced renal function in elderly subjects in this study (37% reduction in mean baseline Cockcroft-Gault creatinine clearance values in elderly compared to young subjects with BPH), tadalafil exposures did not exceed those estimated in young subjects. The Sponsor noted that the lack of an age effect was expected as tadalafil is cleared predominantly via hepatic metabolism by CYP3A, and the activity of CYP3A is proposed to be stable throughout normal aging, with intestinal and hepatic CYP3A induction being independent of age. However, there is a prominent renal role in elimination of tadalafil metabolites (such as IC710) and this resulted in a 47% difference between the highest total IC710 exposure in mild renal impairment and that in young BPH subject without renal impairment.

The hemodynamic profile in this study appeared broadly comparable for elderly and young subjects with BPH. Although there appeared to be a larger decrease from baseline (Day 1, predose) in supine and standing systolic and diastolic blood pressure for elderly subjects compared to young subjects with BPH over the first 4 hours postdose on Days 1 and 10, it is the Sponsor's opinion that this was attributable to a higher baseline blood pressure (Day 1, predose) in the elderly subjects and probable impaired baroreceptor function in this age group. None of the elderly subjects experienced adverse events associated with orthostatic changes in blood pressure, whereas 2 young subjects experienced orthostatic hypotension.

In the multiple dose period, there were no serious or severe adverse events reported, and no subjects were withdrawn due to adverse events. The incidence of adverse events was highest over the first 2 days of dosing. The most frequently-reported drug-related adverse events were myalgia, headache, dyspepsia, pain in extremity, back pain, diarrhea, and nausea. This adverse event profile was similar to that seen in previous studies with tadalafil. The incidence of myalgia, headache, and dyspepsia was similar for both age groups. Diarrhea was reported only by elderly subjects, whereas pain in extremity and nausea were reported by the young subjects only. Most incidences of back pain were reported by the elderly subjects.

Elderly subjects with BPH had higher mean baseline supine and standing systolic blood pressure compared to young subjects with BPH on Day 1 (predose) (supine blood pressure: 135/75 mmHg

[elderly] compared to 129/76 mmHg [young]; standing blood pressure: 140/81 mmHg [elderly] compared to 125/82 mmHg [young]). Following administration of 20-mg tadalafil on Day 1 (*a dose 5-fold greater than the dose proposed for the BPH indication*), for elderly subjects, maximum decreases of 17 mmHg (systolic) and 7 mmHg (diastolic) were observed in supine blood pressure, and maximum decreases of 16 mmHg (systolic) and 6 mmHg (diastolic) were observed in standing blood pressure over the 4-hour postdose period. In young subjects, maximum decreases of 9 mmHg (systolic) and 3 mmHg (diastolic) were observed in supine blood pressure, and maximum decreases of 8 mmHg (systolic) and 7 mmHg (diastolic) were observed in standing blood pressure, over the similar period. The changes in blood pressure were broadly temporally related to the pharmacokinetic profile of tadalafil to Cmax.

On Day 10, mean pre-dose standing and supine systolic and diastolic blood pressure was lower in both age groups compared to Day 1. Mean pre-dose supine blood pressure was similar in elderly and young subjects (127/74 mmHg [elderly] compared to 124/73 mmHg [young]), whereas mean standing blood pressure was higher for elderly subjects (133/79 mmHg [elderly] compared to 124/77 mmHg [young]). On Day 10, for elderly subjects, maximum decreases of 15 mmHg (systolic) and 6 mmHg (diastolic) were observed in supine blood pressure, and maximum decreases of 12 mmHg (systolic) and 7 mmHg (diastolic) were observed in standing blood pressure over the 4-hour postdose period. In comparison, for young subjects, maximum decreases of 9 mmHg (systolic) and 4 mmHg (diastolic) were observed in supine blood pressure, and maximum decreases of 4 mmHg (systolic) and 5 mmHg (diastolic) were observed in standing blood pressure, over the similar period. On Day 10, as observed on Day 1, the changes in blood pressure were broadly temporally related to the pharmacokinetic profile of tadalafil to Cmax.

Although 2 young subjects reported a total of 4 episodes of orthostatic hypotension, these episodes were mild in severity and of no clinical concern. None of the subjects experiencing potentially clinically significant blood pressure findings experienced associated adverse events at the time of the blood pressure changes.

Table 49: Frequency of Subjects with Clinically Significant Blood Pressure Findings Study LVHN

		Frequency of Subjects[episodes] Experiencing Clinically Significant Findings	
	Day	Elderly subjects	Young subjects
Standing			
Systolic BP <85 mmHg	1 10	0 [0] 0 [0]	0 [0] 0 [0]
Diastolic BP <45 mmHg	1 10	0 [0] 0 [0]	0 [0] 0 [0]
Decrease from baseline in systolic BP >30 mmHg	1 10	3 [3] 2 [3]	2 [1] 1 [1]
Decrease from baseline in diastolic BP >20 mmHg	1 10	1 [1] 1 [1]	2 [3] 1 [1]
Supine			
Systolic BP <85 mmHg	1 10	0 [0] 0 [0]	0 [0] 0 [0]
Diastolic BP <45 mmHg	1 10	0 [0] 0 [0]	0 [0] 0 [0]
Decrease from baseline in systolic BP >30 mmHg	1 10	3 [4] 3 [7]	0 [0] 2 [2]
Decrease from baseline in diastolic BP >20 mmHg	1 10	2 [3] 0 [0]	0 [0] 0 [0]

Source: Table LVHN 7.7: LVHN (a) Amended Study Report, page 41

There were no deaths, serious adverse events or discontinuations. There were no safety concerns in terms of clinical laboratory evaluations, ECGs, or physical examinations following administration of multiple doses of 20-mg tadalafil for 10 days.

There were 4 episodes of vomiting during the study. Three of these events were in young subjects. Symptoms of myalgia and headache occurred in approximately equal numbers of young and old subjects. Dyspepsia occurred with greater frequency in young versus elderly subjects. Two elderly subjects experienced chest pains with ECGs showing no changes.

Reviewer's Comment: Tadalafil was safe and reasonably tolerated when administered as single and multiple 20 mg daily doses for 10 days to elderly and young subjects with BPH in Study LVHN. There appeared to be no differences in tolerability profile between the age groups in Study LVHN. This study, in my opinion, indicates that it is reasonable to proceed in larger studies involving men with either BPH or BPH/ED(using 2.5 mg and 5 mg daily doses of tadalafil) who may be generally older than the overall ED population using tadalafil and who

may have mild impairment of renal function. Additionally, in Studies LVHR and LVHJ, orthostatic testing is to be done on each clinical visit.

Study LVHK: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multicenter Study to Evaluate the Urodynamic Effects of Tadalafil Once a Day for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia.

Study LVHK was a Phase 2, randomized, double-blind, placebo-controlled, parallel-design study to evaluate for potential adverse urodynamic effects of tadalafil once daily for 12 weeks in men with BPH-LUTS with or without bladder outlet obstruction. Patients were included in the study if they had BPH-LUTS diagnosed "by a qualified physician" and of >6 months duration at Visit 1. Patients were excluded from the protocol of the PVR by ultrasound was ≥350 mL at Visit 1.

The majority of subjects were categorized as having severe BPH-LUTS (IPSS Total Score ≥20) at baseline (64.0%) and more than half of subjects had BPH-LUTS for >3 years (54.5%). The majority of subjects had no previous alpha-blocker therapy within 12 months of Visit 1 (78.5%) and no previous BPH therapy (including alpha blockers) within 12 months of Visit 1 (68.5%). Postvoid residual volume was the only measure associated with BPH-LUTS that was not well balanced between treatment groups. The mean value for PVR was numerically lower in the tadalafil treatment group compared with placebo (tadalafil 20 mg: 45.65; placebo: 59.30). Subjects in both treatment groups were evenly distributed into the bladder outlet obstruction (BOOI) categories with approximately one-third of subjects in each severity category. Mean PSA was 1.55 (tadalafil 20 mg: 1.51; placebo: 1.60). The average age of the subjects, overall, was 59.6 years.

The primary objective was to compare the effect of tadalafil 20 mg once daily for 12 weeks on detrusor pressure at peak urinary flow rate (pdetQmax) versus placebo in men with signs and symptoms of BPH-LUTS. The general purpose of the study was to rule out any clinically meaningful effect of tadalafil on worsening urodynamic function. Secondary objectives included an examination of the urodynamic effects of tadalafil 20 mg once daily for 12 weeks (compared with placebo) in the treatment of men with BPH-LUTS on pressure flow and free flow urodynamic parameters including peak urinary flow rate (Qmax), mean urinary flow rate (Qmean), voided volume (Vcomp), maximum detrusor pressure (maxpdet) during voiding, post-void residual (PVR) volume measurement by catheterization (PVRcath), total bladder capacity, bladder contractility index (BCI), bladder outlet obstruction index (BOOI), bladder voiding efficiency (BVE), presence of involuntary detrusor contractions during bladder filling, and bladder volume at first involuntary detrusor contraction. The key issue was to discern any potential negative effect on bladder emptying. Secondary measures also included AEs, vital signs, and clinical laboratory tests. Subjects were randomly assigned to placebo or tadalafil 20 mg once daily for 12 weeks. Of the 200 randomized subjects, 101 were assigned to placebo and 99 to tadalafil 20 mg. 89 tadalafil and 92 placebo subjects in 2 countries completed the study. The date of the last subject visit was 5 May 2008.

A total of 92 tadalafil subjects (92.93%) and 96 placebo subjects (95.05%) were considered compliant (at least 70% of doses taken) with once-daily dosing.

The primary analysis showed neither statistically significant nor clinically adverse effects of tadalafil 20 mg on detrusor pressure at peak urinary flow rate (the mean difference of change from baseline between treatment groups was -4.95 cm H_2O; p=.068) in the primary analysis population. While this result represents a decrease in detrusor pressure in the actively treated tadalafil group versus the placebo group, it was not considered clinically adverse. Furthermore, the negative change was the result of a slight increase in pressure for the placebo treatment group with a slight decrease in pressure for the tadalafil treatment group. Upon review of the individual patient data by external consultants, 3 subjects (2 placebo, 1 tadalafil) were noted to have nonphysiologic changes from baseline to endpoint due to detrusor overactivity at the initiation of the voiding event. When data from these 3 subjects were removed from the analyses, the mean difference of the change from baseline in $P_{det}Q_{max}$ between active and placebo groups was smaller (-2.18 cm H_2O).

Table 50: Detrusor Pressure at Peak Urinary Flow Rate (pdetQmax) Tadalafil 20 mg versus Placebo Study LVHK

Treatment Group	Time Point	n	mean	SD
Placebo (N=91)			cm H_2O	
	Baseline	91	54.83	27.36
	Endpoint	91	56.75	26.64
	Change	91	1.92	19.71
Tadalafil 20 mg (N=94)				
	Baseline	94	56.87	29.67
	Endpoint	94	53.92	26.82
	Change	94	-2.95	15.92

Source: Table LJHK, Study LVHK Report, page 78

Reviewer's Comment: The results of data applied to the primary endpoint indicate that tadalafil does not have an unfavorable effect on $P_{det}Q_{max}$.

The external consultants also recommended that subjects who had free-flow parameters measured via mechanical fill after pressure-flow studies were inappropriate for inclusion and should be removed from all free-flow studies. This was done in post hoc analysis.

Secondary analyses on free-flow and pressure-flow urodynamic parameters (both prespecified including all subjects in the primary analysis population and post hoc excluding subjects with invalid tracings and/or mechanical fill) also showed neither statistically significant nor clinically adverse effects of tadalafil 20 mg. These parameters included peak urinary flow rate (Qmax), mean urinary flow rate (Qave), voided volume (Vcomp), maximum detrusor pressure during

voiding (max pdet), postvoid residual volume (PVR), total bladder capacity, bladder voiding efficiency (BVE), bladder contractility index (BCI), and bladder outlet obstruction index (BOOI).

Table 51: Urodynamic Parameters Study LVHK

Treatment Group	Qmax N(n) [mL/sec]		Qave N(n) [mL/sec]		PVR Cath N(n) [mL]	
	Placebo	IC 20 mg	Placebo	IC 20 mg	Placebo	IC 20 mg
	N=91(89)	N=94(82)	N=91(70)	N=94(59)	N=91(78)	N=94(79)
Time Point	Mean (SD)					
Baseline	13.03 (7.34)	14.75 (10.70)	7.10 (4.37)	7.23 (4.18)	59.62 (66.74)	48.99 (65.73)
Endpoint	13.55 (8.76)	14.75 (8.30)	7.09 (4.40)	8.23 (4.95)	57.77 (84.38)	39.86 (57.52)
Change	0.52 (7.83)	0.01 (8.83)	-0.01 (4.11)	1.00 (3.04)	-1.85 (80.92)	-9.13 (70.36)

IC=tadalafil
Source: Table LVHK, LVHK Study Report, page 82-83

In analyses of BOOI shift (obstructed, equivocal, and unobstructed) from baseline to end of therapy, there appeared to be a numerical trend toward less bladder outlet obstruction at endpoint in the tadalafil treatment group compared with placebo. A post hoc categorical shift analysis appears to show approximately two-fold greater proportion of subjects in the placebo treatment group with increased (worsened) BOOI category at endpoint than in the tadalafil treatment group (p=.025).

Mean change from baseline to endpoint in total International Prostate Symptom Score (IPSS) appeared clinically meaningful and significantly different (p<.001) for the tadalafil 20 mg treatment group (-9.13) compared with placebo (-5.04). Tadalafil 20 mg dosed once daily also appeared to result in statistically significant improvement in the IPSS Storage (Irritative) subscore, the IPSS Obstructive (Voiding) subscore, and the IPSS Quality of Life (QoL) index compared with placebo (p=.006). However, there appeared to be no statistically significant difference between tadalafil and placebo on IPSS Question 7 (Nocturia) subscore.

In this study, tadalafil 20 mg once daily for 12 weeks in men with BPH-LUTS appeared to be generally well tolerated. There was one death in a placebo subject. The incidence of discontinuations due to adverse events was low (tadalafil: n=2, 2.0%; placebo: n=1, 1.0%). There were 2 (2%) SAES in the placebo group and 1 (1%) SAE in the tadalafil group. Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity.

The incidence of TEAEs in the tadalafil treatment group (55 subjects, 55.6%) was numerically higher than placebo (28 subjects, 27.7%). The most commonly reported TEAEs (incidence >2%

in the tadalafil treatment group) were dyspepsia, headache, back pain, and gastroesophageal reflux disease (GERD). There was a higher percentage of subjects with adverse events assessed by the investigator to be possibly related to study drug in the tadalafil 20 mg treatment group than placebo (tadalafil: 26.3%, placebo: 3.0%). The majority of these adverse events included headache, back pain, flushing, dyspepsia, and GERD. These adverse events were consistent with the known safety profile of tadalafil and thus, were not unexpected considering the high tadalafil daily dose of 20 mg.

In this study, serious adverse events were reported in 3 subjects (placebo: 2 subjects; tadalafil 20 mg: 1 subject). One death was reported in this study (placebo). No clinically adverse changes were observed in laboratory values or vital signs with tadalafil treatment. There were no adverse event reports of urinary retention in tadalafil-treated subjects.

LVHK Subject 103-1311 is a 54 year old Caucasian US male. The patient's medical history included Attention deficit/hyperactivity disorder, and acid reflux. The patient was concomitantly receiving omeprazole and lansoprazole for acid reflux. On 28-Dec-2006, the patient first received blinded study drug for Benign Prostatic Hyperplasia (BPH) - Lower Urinary Tract Symptoms (LUTS). On an unspecified date, the patient was reportedly not feeling well and went to the emergency room with flu-like symptoms. On (b) (6) after receiving his first dose, he was hospitalized and diagnosed with pneumonia as well as pleurisy. An X-Ray showed nodular interstitial changes and a computerized tomography (CT) of his chest showed nodular infiltrate in the right upper lobe. The patient was treated with ceftriaxone, cefuroxime and azithromycin as well as ipratropium, salbutamol and methylprednisolone. He was discharged from the hospital on (b) (6). The events of pneumonia and pleurisy were considered to have ended on 30-Jan-2007. Study drug was continued.

A total of 2 subjects in the tadalafil treatment group reported adverse events that led to study discontinuation. These 2 adverse events leading to study discontinuation were headache and Peyronie's disease. Subject 113-2304 discontinued due to headache, which was considered study drug-related by the investigator. Subject 104-1405 reported an adverse event of Peyronie's disease 3 days after randomization. Peyronie's disease was a preexisting condition in the opinion of the investigator.

Notable Adverse Events

Bradycardia: LVHK Subject 100-1001 randomized to tadalafil was a 68-year-old male with hypertension whose heart rate at the time of the final study visit was 35 beats per minute (bpm). The subject's heart rate had been within normal limits (ranging from 74 to 88 bpm) during the other scheduled visits. Six days prior to the subject's final visit, he reported initiation of a second antihypertensive (olmesartan medoxomil). The subject was examined by his cardiologist later the same day and reported no further concerns with his vital signs.

Coronary Artery Disease: LVHK Subject 115-2523 reported coronary artery disease approximately 3 weeks after randomization to tadalafil. The investigator noted a fascicular block on the same date as the subject's screening visit based upon ECG results. This subject had

preexisting hyperlipidemia since May 2005. No additional adverse events were reported, and this subject completed the study without any additional reported adverse events.

Vasovagal Syncope: LVHK Subject 131-4131 is a 52-year-old male randomized to tadalafil who fainted during final study procedures. The investigator considered the adverse event related to study procedures, but not study drug-related.

Aminotransferase/Hepatic Enzyme Increased: LVHK Subject 115-2518 at endpoint alanine transaminase [ALT] for this subject was less than 2-fold the upper limit of normal [ULN] and aspartate transaminase [AST] was within normal limits. The bilirubin was within normal limits. This patient had been randomized to tadalafil.

Aminotransferase/Hepatic Enzyme Increased: LVHK Subject 132-4205 Although both the ALT and AST were less than 2-fold ULN, these values were considered clinically significant by the investigator. The bilirubin was within normal limits. The subject was randomized to tadalafil.

Aminotransferase/Hepatic Enzyme Increased: LVHK Subject 103-1338 randomized to placebo had an end of study AST >3-fold the ULN (at 116 U/L, reference range 11 – 36 U/L), which represented an approximately 2-fold increased from his elevated baseline value of 58 U/L. This subject reported preexisting conditions of abnormal liver function tests and hepatosplenomegaly, with both AST and bilirubin slightly elevated at baseline.

Aminotransferase/Hepatic Enzyme Increased: LVHK Subject 103-1357 randomized to tadalafil had ALT nearly 3-fold ULN (at 122 U/L, reference range 6 – 43 U/L) and elevated AST (at 88 U/L, reference range 11 – 36 U/L) at end of study, with bilirubin within normal limits. Repeat labs were performed and considered not clinically significant by the investigator. This subject had started acetaminophen/hydrocodone bitartrate approximately two weeks prior to his end of study visit.

Blurred Vision: LVHK Subject 103-1357 reported blurred vision 19 days after randomization to tadalafil. The subject informed the investigator that he had received a new eye glasses prescription which coincided with the occurrence of the adverse event. The event was ongoing at the time the subject completed the study.

Visual Disturbance: LVHK Subject 113-2323 reported visual disturbance (bilateral vision changes) 3 days after randomization to tadalafil. The subject informed the investigator that the changes were mainly upon waking, and he believed may be related to the C Pap for his sleep apnea. The subject did not report darkness, blindness, or color vision impairment. The event was ongoing at the time the subject completed the study.

Penis Disorder: LVHK Subject 117-2709 reported penis disorder (actual term “penis enlargement while flaccid”) 2 days after randomization to tadalafil. This adverse event was ongoing at the time the subject completed the study.

Dysuria: LVHK Subject 115-2509 randomized to tadalafil experienced dysuria which was considered study procedure-related and not drug related by the investigator.

Reviewer's Comment: These adverse events are not indicative of a new safety signal or concern, in my opinion.

Laboratory Values

Changes in clinical laboratory analytes were not clinically adverse or statistically significant, with the exception of change from baseline to endpoint in lymphocytes for which the change for tadalafil compared to placebo was statistically significant (p= 0.011).

Table 52: Lymphocytes Baseline, Endpoint, and Change from Baseline to Endpoint

Therapy	Baseline		Endpoint		Change	
	Lymphocytes (Bill/L)					
	Mean	SD	Mean	SD	Mean	SD
Placebo n=98	2.00	0.59	2.05	0.59	0.05	0.41
Tadalafil 20 mg n=94	1.93	0.54	1.84	0.53	-0.11	0.33

Source: Table LVHK 14.36, LVHK Study Report, page 326

Reviewer's Comment: I do not feel that the changes in lymphocyte counts are clinically significant.

Vital Signs

The mean change in heart rate from baseline to endpoint was 0.08 bpm for placebo and 0.97 bpm for tadalafil 20 mg. The mean change in systolic blood pressure from baseline to endpoint was -2.50 mmHg for placebo and -2.63 mmHg for tadalafil 20 mg subjects. The mean change in diastolic blood pressure from baseline to endpoint was -0.46 mmHg for placebo and -1.30 mmHg for tadalafil 20 mg subjects. The mean change in diastolic blood pressure from baseline to Visit 4 was -0.41 mmHg for placebo and -3.24 mmHg for tadalafil 20 mg subjects.

ECG

A 12-lead electrocardiogram was performed at Visit 1 for screening purposes only.

Reviewer's Safety Conclusions: The safety results were compatible with other tadalafil studies and the 20 mg dose of tadalafil was generally well tolerated. There does not appear to be an unfavorable effect on the urodynamic parameters used in Study LVHK in men with BPH-LUTS utilizing tadalafil 20 mg once daily for 3 months.

Study LVHS: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Evaluate the Safety and Efficacy of Daily Tadalafil for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia on Concomitant Alpha$_1$-Adrenergic Blocker Therapy

Study LVHS was a Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to assess the safety of tadalafil once daily for 12 weeks in men with BPH-LUTS on concomitant alpha-blocker therapy. The Division requested that Sponsor conduct this study, not to support concomitant use of tadalafil and alpha blockers for BPH, but rather to get a better understanding of the type of adverse events that could occur if the two drug classes were used in combination, contrary to the labeled precautions. To be enrolled, the subjects had to be using either: alfuzosin, doxazosin, silodosin, tamsulosin or terazosin for 4 weeks prior to Visit 1. Subjects were excluded if they had a history of symptoms associated with orthostasis, including recurrent episodes of dizziness, lightheadedness, loss of consciousness, or syncope. Patients were also excluded if they had a history of a pathological fall occurring under circumstances in which normal homeostatic mechanisms would ordinarily maintain stability, if within 6 months of Visit 1 the systolic blood pressure was >160 mmHg or less <90 mmHg, and/or the diastolic blood pressure was >100 mmHg or <50 mmHg. Evidence of congestive heart failure categorized as New York Heart Association (NYHA) ≥ Class III (NYHA 1994) within 6 months of Visit 1 also precluded enrollment.

The primary objective was to evaluate the proportion of men with BPH-LUTS experiencing treatment-emergent dizziness when adding tadalafil 5 mg once daily to concomitant alpha-blocker therapy compared to adding placebo to concomitant alpha-blocker therapy. Secondary measures (objectives) included AEs (including those possibly related to hypotension), orthostatic vital signs, PVR volume, uroflowmetry, and clinical laboratory tests. Subjects continued concomitant alpha-blocker therapy throughout the study and were randomly assigned to placebo or tadalafil 5 mg once daily for 12 weeks. A secondary efficacy objective was the change in baseline to endpoint for the International Prostate Symptom Score (IPSS) when adding tadalafil 5 mg once daily to concomitant alpha blocker therapy for 12 weeks in the treatment of men with BPH-LUTS. Of the 318 subjects randomized, 160 were assigned to placebo and 158 were assigned to tadalafil 5 mg. The study sites were in the United States and Puerto Rico.

Eligible subjects entered a 2-week single-blind, placebo lead-in period following the screening/washout period. At the start of the treatment period, eligible subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: placebo or tadalafil 5 mg once daily for 12 weeks. This multicenter study was designed to enroll approximately 300 subjects (approximately 150 subjects per treatment group). The study population was monitored upon enrollment to achieve inclusion of at least 20% of subjects taking a nonselective alpha blocker. Additionally, the study population was monitored to achieve inclusion of at least 20% of subjects 75 years of age or older.

The study consisted of 3 periods:

- Screening and Wash-Out Period: Candidates signed an ICD at Visit 1 prior to participating in any study procedures. The first period was for screening in order to assess subject eligibility and to accommodate a 4-week wash-out of BPH (excluding concomitant alpha blocker and 5- alpha reductase inhibitor (5-ARI) therapy [Section 9.3.1]), overactive bladder (OAB), or ED treatments, if needed.

- Placebo Lead-in Period: After the screening/wash-out period, subjects returned for Visit 2 to assess whether eligibility criteria were met to proceed to the placebo lead-in period. Eligible subjects began a 2-week single-blind, placebo lead-in period to assess treatment compliance and evaluate AEs prior to initiating the double-blind treatment period. During this period, if alpha blocker dose adjustments were necessary, only downward titration was allowed in order to avoid confounding safety data immediately prior to initiation of the double-blind treatment period.

- Treatment Period: At Visit 3 (randomization), eligible subjects were randomly assigned to treatment (placebo or tadalafil) in a 1:1 ratio. The treatment period was 12 weeks. During the first 4 weeks of this period, if alpha blocker dose adjustments were necessary, only downward titration was allowed in order to appropriately assess AEs which may be the result of the addition of tadalafil to alpha blocker therapy. For the final 8 weeks of this period, the subject's alpha blocker dose was permitted to be titrated up or down, as necessary. Visit 6 (Week 12) was the end-of-study visit (study termination).

Subjects must have had BPH-LUTS (as diagnosed by a qualified physician) >6 months at Visit 1. Lower urinary tract symptoms (LUTS) include those associated with voiding (obstructive symptoms, such as incomplete emptying, intermittency, weak stream, or straining) and/or storage (irritative symptoms, such as frequency, urgency, or nocturia). Subjects must agree to continuously use the same alpha blocker for the treatment of BPH for the entire duration of the study with no upward dose adjustments for at least 2 weeks prior to or 4 weeks following Visit 3.

Subjects were randomized by the following variables:

- Age (<75 or ≥75)
- Type of alpha blocker (selective or non selective)
- Baseline LUTS severity (IPSS mild to moderate [<13] to severe [≥13] assessed at Visit 3

The subjects had a mean age of 67 years. 24.5% of randomized subjects were 75 years of age or older. Most subjects were of non-Hispanic or non-Latino ethnicity (88.1%) and the majority of men reported race as white (88.4%). 58.2% of subjects were categorized as having moderate BPH-LUTS (total IPSS 8 to 19) at baseline. Baseline Qmax was ≤15 mL/sec for 78.2% of subjects. A numerically greater proportion of tadalafil subjects than placebo subjects had a baseline Qmax <10 mL/sec (42.0% and 34.7%, respectively). The mean baseline PVR was 75.35 mL and the mean PSA was 2.16 ng/mL. A total of 31(9.7%) subjects reported use of a BPH-LUTS therapy within 12 months of study Visit (excluding concomitant alpha blocker and 5-ARIs which were continued throughout the study). The duration of alpha blocker use and its duration were generally well balanced between groups. Selective alpha blockers were used in

108 of 160 (67.5%) of placebo subjects and 106 of 158 (67.1%) of tadalafil 5 mg subjects. Nonselective alpha blockers were used in 53 of 160 (33.1%) of placebo subjects and 52 of 158 (32.9%) of tadalafil 5 mg subjects.

A total of 156 tadalafil subjects (98.7%) and 159 placebo subjects (99.4%) were considered compliant (at least 70% of tadalafil doses were taken) with once-daily dosing during the double-blind treatment period.

The distribution of elderly and nonselective alpha blocker subjects in each treatment group was balanced.

Table 53: Treatment Emergent Dizziness Study LVHS

	Placebo N=159	Tadalafil 5 mg N=158
Preferred Term	n (%)	n (%)
Subjects with >= 1 TEAE	9(5.7)	11 (7.0)
Dizziness	8(5.0)	10(6.3)
Dizziness Postural	1(0.6)	1(0.6)
Procedural Dizziness	0(0.0)	0(0.0)

Source: Table LVHS 11.9, LVHS Study Report, page 92 (primary analysis population)

> *Reviewer's Comment: The primary analysis showed no difference between treatment groups in the proportion of subjects experiencing treatment emergent dizziness.*

In terms of secondary efficacy analysis, the LS mean change from baseline to endpoint in total IPSS was not significantly different (p= 0.13) for the tadalafil 5 mg treatment group (-2.20) compared with placebo (-1.33). Tadalafil 5 mg once daily did not result in statistically significant improvement in storage (irritative) symptoms, voiding (obstructive) symptoms, nocturia symptoms, or QoL when compared with placebo (all p>.169).

Table 54: Total International Prostate Symptom Score (IPSS) Study LVHS

Treatment	Time Point	n	Mean	SD
Placebo (N=159)	Baseline	156	13.30	6.57
	Endpoint	156	11.81	6.26
	Change	156	-1.49	5.29
Tadalafil 5 mg (N=158)	Baseline	156	13.87	7.15
	Endpoint	156	11.60	6.69
	Change	156	-2.28	5.65

Source: Table LVHS 11.10, LVHS Study Report, page 94.

Reviewer's Comment: These results do not indicate additional efficacy benefit of adding tadalafil 5 mg once daily to a BPH treatment regimen using either alpha blockers or 5 alpha reductase inhibitors, in my opinion.

Safety Evaluation

At total of 158 subjects were randomized to tadalafil and 160 randomized to placebo. Exposure duration to study drug was 79 days for tadalafil and 93 cumulative doses for both tadalafil and placebo. The table below summarizes the adverse events in Study LVHS.

Table 55: Overview Adverse Events Study LVHS

Adverse Event	Placebo N=160	Tadalafil 5 mg N=158
	n (%)	n (%)
Deaths	0(0.0)	0(0.0)
Serious Adverse Events	3(1.9)	3(1.9)
Adverse Events Leading to Discontinuation	6(3.8)	7(4.4)
Treatment Emergent Adverse Events	53(33.1)	66(41.8)
Adjunct Therapy-Related Adverse Events	7(4.4)	9(5.1)

Source: Table LVHS 12.2, Study Report LVHS, page 109.

There were no deaths in the study.

Serious adverse events (SAEs) were reported in 6 subjects (tadalafil: 3 subject; placebo: 3 subjects).

LVHS Subject 109-1801 is a 64 year-old US male who was randomized to placebo and 49 days after initiating blinded therapy developed non-cardiac chest pain. The investigator indicated that the non-cardiac chest pain was due to exertion. Study therapy was discontinued 48 days after initiating blinded therapy.

LVHS Subject 119-2812 is a 79 year-old US male who was randomized to placebo. Two months after receiving study drug, he fell over a cinder block in his yard and broke his left hip. The investigator reported that "the patient did not see the block and tripped." The event did not appear to be related to orthostasis. The patient completed the study despite having undergone a hip fracture pin placement. The patient reported urinary retention at the study visit (Visit 6) following hospital discharge. His post void residual urine at Visit 3 was 142 mL and at Visit 6 it was 87 mL. He was receiving tamsulosin at Visit 1 and at Visit 6 was also receiving bethanechol.

LVHS Subject 128-3707 is a 65 year-old US male who was randomized to placebo. Approximately one month later he suffered injury during an automobile collision which resulted in a pacemaker lead dislodgement. He was seen originally in the emergency room and released. Over subsequent days, he started having syncope and near syncope and was hospitalized. Via pacemaker interrogation it was determined that dislodgement of a lead had occurred as a result of this accident.

LVHS Subject 121-3029 is an 80 year old Caucasian US male. Past medical history included atrial fibrillation and cardiac ablation. Concomitant medications included: furosemide, quinapril, and potassium (for hypertension), warfarin sodium and diltiazem hydrochloride (for atrial fibrillation), multivitamin, calcium with vitamin D, fish oil and red yeast rice (as supplementation therapy). The patient entered the placebo lead in phase for the trial on 05 August 09. On (b) (6) the patient was admitted to the hospital for cellulitis. The placebo was held on 27 August 09. No other information has been provided. In the opinion of the study investigator the event of cellulitis was not related to the placebo, study drug or protocol procedures.

> *Reviewer's Comment: While randomized to tadalafil, the subject did not start treatment until 4 September, 2009. I agree with the opinion of the study investigator.*

LVHS Subject 127-3607 is a 56 year old Caucasian US male randomized to tadalafil. Past medical history included: hypercholesterolemia, heartburn, hiatal hernia, far-sightedness, tinnitus of the left ear, insomnia, occasional testicular pain, premature ejaculation, distal esophagitis, duodenitis, and Peyronie's disease. The patient entered the placebo lead in period of the study on 17Jul09. The placebo lead in ended on 30Jul09 and the patient entered the blinded therapy phase on 31Jul09. On 14Sep09 that patient was eating potato salad at home and he began to choke. He felt a lump and pain in his chest but could still breathe. He began to forcefully try and vomit for a 40 minute time frame. The (b) (6) the patient found blood in his stool and he went to the emergency room. He was diagnosed with an 8 cm mid esophageal tear and internal bleeding. The tear was identified as a classic Mallory Weiss tear. Study drug was held on 15Sep09. He was admitted on (b) (6) and underwent corrective surgery. The event was considered recovered on (b) (6). He was released on (b) (6). Study therapy was restarted on 17Sep09. The events were due to the patient trying to self induce vomiting. The tear was a classic Mallory Weiss tear.

Reviewer's Comment: In my opinion, it is unlikely that the study drug was related to the adverse event. The negative rechallenge further supports this opinion.

LVHS Subject 128-3701 is a 50 year-old US male patient of unspecified origin. Medical history included chronic knee pain, GERD, insomnia, and benign prostatic hypertrophy (BPH) since 2005. Concomitant medications included: alfuzosin hydrochloride, zolpidem tartrate, celecoxib, esomeprazole magnesium, and metoclopramide. On 23 April 09, the patient entered the placebo lead in treatment period of the study. On 11 May 09 the patient was randomized to blinded study drug for the treatment of erectile dysfunction and the signs and symptoms of benign prostatic hypertrophy. On 06 July 09, the patient suffered a work related injury to his right knee, specifically he fell off of a street curb as the result of a misstep. The patient has no history or concurrent visual disturbance, lethargy, inattention, syncope or presyncope. There no orthostatic blood pressures or signs of orthostasis on any study visit. On 07 July 09 magnetic resonance imaging (MRI) was completed. Results revealed a complete tear of quadriceps tendon, probable complete tear of medial retinaculum with sprain extending into anterior superficial medial collateral ligament, mild contusion medial femoral condyle, mild patellar chondromalacia, moderate joint effusion with diffuse subcutaneous edema. Blinded study drug was stopped on 13Jul09 and the patient was discontinued from the study. On (b) (6) approximately (b) (6) after starting blinded study drug, the patient was admitted to the hospital for surgical repair of the knee. Surgery consisted of suture repair with augmentation with semitendinosus graft repair reconstruction on right leg, quadriceps tendon, and complete avulsion. The patient was discharged the following day on (b) (6) and his condition is recovering. Patient's last study visit was on 13 July 09.

Reviewer's Comment: Looking at EVENTS.XPT there were 11 subjects in SOCTERM Injury, Poisoning and Procedural Complications category. 1 suffered from insect bites. Of the remaining 10, 7 were in the placebo group and 3 were in the tadalafil group. There does not seem to be a proclivity for injury in the tadalafil group. Overall, there is no detectable trend or safety signal in these SAEs.

There were 13 adverse events leading to study discontinuation. They are summarized in the table below.

Table 56: Adverse Events Leading to Discontinuation Study LVHS

Preferred Term	Placebo N=160	Tadalafil 5 mg N=158
	n (%)	
Subjects with >= 1 AE	6 (3.9)	7 (4.4)
Headache	0 (0.0)	2 (1.3)
Abdominal Pain Upper	0 (0.0)	1 (0.6)
Atrial Fibrillation	0 (0.0)	1 (0.6)
Back Pain	0 (0.0)	1 (0.6)
Blood Creatinine Phosphokinase Increased	0 (0.0)	1 (0.6)
Chest Discomfort	0 (0.0)	1 (0.6)
Lead Dislodgement	1 (0.6)	0 (0.0)
Non-cardiac Chest Pain	1 (0.6)	0 (0.0)
Pollakiuria	1 (0.6)	0 (0.0)
Upper Respiratory Tract Infection	1 (0.6)	0 (0.0)
Vision Blurred	1 (0.6)	0 (0.0)
Visual Acuity Reduced	1 (0.6)	0 (0.0)

Source: Table LVHS 12.5, LVHS Study Report, page 124.

LVHS Subject 120-2913 is a 74 year-old US male randomized to placebo and taking terazosin. He started treatment on 22 July 2009 and discontinued treatment on 27 August 2009 due to blurred vision. He also reported the AE of conjunctivitis on 15 August 2009.

LVHS Subject 128-3707 a placebo subject taking alfuzosin has been discussed in SAEs.

LVHS Subject 101-1003 a placebo patient taking terazosin is a 56 year-old black US male who discontinued secondary to an upper respiratory tract infection. He was randomized to placebo on 3 June 2009 and stopped treatment on 5 August 2009. He has hypertension and autoimmune thyroiditis.

LVHS Subject 135-4403 a placebo patient taking tamsulosin is an 82 years-old white US male. He was randomized to placebo on 10 September 2009 and discontinued on 15 October 2009 due to pollakiuria. His post void residual urine at Visits 3 and 5 were 22 and 16 mL respectively. There were no urinalysis findings indicative of infection. At Visit 1, the creatinine was elevated at 1.69 mg/dL and the calculated creatinine clearance was low at 42 mL/min. By Visit 3, the creatinine was 1.79 mg/dL.

LVHS Subject 101-1001 is 76 year-old Puerto Rican male who was using doxazosin and was randomized to tadalafil on 3 June 2009. On 4 June 2009, he noted the onset of headache and "swollen left eye." Treatment was stopped 8 June 2009. He was treated with paracetamol for headache from 5 June 2009 until 12 June 2009. There were no signs of orthostasis. There were no concurrent medical conditions predisposing to headache.

LVHS Subject 121-3016 is a 64 year-old white US male taking doxazosin who was randomized to tadalafil on 22 June 2009. Treatment was stopped on 7 July 2009 due to the adverse event of atrial fibrillation and dehydration with increased heart rate. The patient has a history of two mitral valve replacements. He has been on warfarin since 2001. There is no mention of prior atrial fibrillation and it is not listed in History.XPT dataset.

LVHS Subject 121-3016 is a 56 year-old white US male taking doxazosin who was randomized to tadalafil on 7 June 2009. Treatment was stopped 24 July 2009 due to the AE of back pain. The patient has a pre-existing history of arthritis and peripheral neuropathy (feet).

LVHS Subject 108-1718 is a 51 year-old black US male taking tamsulosin who was randomized to tadalafil on 22 May 2009. Treatment was stopped 27 May 2009 due to the adverse event of creatinine phosphokinase (CPK) increased. The patient does not have a history of cardiac disease, muscle disorders, or recent muscle injury. His CPK at Visit 1 was 658 IU/L (18-198 normal range). At Visit 3 the CPK was 1990 IU/L. At Visit 4, the CPK was 972 IU/L.

> *Reviewer's Comment: This subject at baseline had an elevated CPK and at randomization (Visit 3), it was even higher. While elevated at Visit 4, it was actually lower than before he started taking tadalafil. I cannot attribute causality to tadalafil.*

LVHS Subject 115-2403 is a 62 year-old white US male taking doxazosin who was randomized to tadalafil on 29 May 2009. Treatment was stopped 31 May 2009 due to the adverse event of headache. He also noted myalgia. There is a history of hypertension. The blood pressure was well controlled during the study. There were no signs of orthostasis noted.

LVHS Subject 119-2807 is a 68 year-old white US male taking doxazosin who was randomized to tadalafil on 14 July 2009. Treatment was stopped due to the adverse event of chest discomfort, dizziness and vision blurred. The events are possibly related to hypotension, dizziness and fatigue. The patient has a history of presbyopia and astigmatism. There is also a history of hypertension, peripheral edema and aortic arteriosclerosis. In addition to acetylsalicylic acid he takes hydrochlorthiazide. At Visit 3, the supine and standing SBP was 118 and 120 mmHg, respectively, and the supine and standing DBP was 66 and 74 mmHg respectively. At Visit 4, the supine and standing SBP was 122 and 108 mmHg, respectively, and the supine and standing DBP was 78 and 64 mmHg respectively. There were no significant changes in pulse rate and the patient was able to remain standing for orthostatic testing.

> *Reviewer's Comment: While the patient did have signs of orthostasis which may be related to dizziness and fatigue he noted, I cannot relate the chest pain to orthostasis based on the data. It is noted that there was no increase of CPK.*

LVHS Subject 104-1301 is a 76 year-old white Puerto Rican male taking terazosin who was randomized to tadalafil on 25 August 2009. Treatment was stopped 28 August 2009 due to the adverse event of upper abdominal pain. The patient also reported diarrhea on the same day.

LVHS Subject 117-2602 is a 69 year-old white US male taking terazosin randomized to tadalafil on 3 June 2009. Treatment was discontinued due to the adverse event of visual acuity reduced on 12 June 2009. The subject also reported dizziness on 8 June 2009, nausea 5 June 2009 and headache (prior to randomization on 1 June 2009). He has a history of hypertension, diabetes mellitus and arrhythmia. His medications include lisinopril, acetylsalicylic acid, finasteride, and omeprazole. At Visit 1 his BUN was elevated at 24 mg/dL. At Visit 4, the supine and standing SBP was 119 and 106 mmHg, respectively, and the supine and standing DBP was 72 and 62 mmHg respectively. At Visit 2, the supine and standing SBP was 133 and 116 mmHg, respectively, and the supine and standing DBP was 66 and 68 mmHg respectively.

> *Reviewer's Comment: Dizziness, with or without fatigue and in association with a decrease in systolic blood pressure occurred in 2 tadalafil subjects one of which noted dizziness prior to randomization. The current Cialis labeling does advise caution in patients taking alpha blockers and using tadalafil for ED. The Cialis label will advise against concomitant use of tadalafil and alpha blockers for the treatment of BPH.*

Treatment-emergent adverse events occurring in with a 1% greater frequency in tadalafil subjects versus placebo subjects are summarized below.

Table 57: Treatment-Emergent Adverse Events with >= 1% Greater Incidence in Tadalafil Subjects Study LVHS

Preferred Term	Placebo	Tadalafil 5 mg
	N=160	N=158
	n (%)	n (%)
Subjects with >= 1 TEAE	53 (33.1)	66 (41.8)
Dizziness	8 (5.0)	10 (6.3)
Dyspepsia		8 (5.1)
Diarrhea	2 (1.3)	5 (3.2)
Back Pain	2 (1.3)	4 (2.5)
Gastroesophageal reflux disease	1 (0.6)	4 (2.5)
Fatigue	1 (0.6)	3 (1.9)
Dyspnea	0 (0.0)	2 (1.3)
Eye infection	0 (0.0)	2 (1.3)
Neck pain	0 (0.0)	2 (1.3)
Oropharyngeal pain	0 (0.0)	2 (1.3)
Rash	0 (0.0)	2 (1.3)

Source: Table LVHS 12.3, LVHS Study Report, page 112

Table 58: Adverse Events Occurring on Visit 3 Date Following First Dose of Double-Blind Treatment

Subject	Treatment Group	Alpha Blocker/Dose	AE
104-1303	Tadalafil 5 mg	Terazosin/10 mg	Rhinorrhea, Pyrexia, Cough
107-1603	Placebo	Tamsulosin/0.4 mg	Dyspepsia, Malaise
109-1801	Placebo	Terazosin/5 mg	Diarrhea
115-2403	Tadalafil 5 mg	Doxazosin/8 mg	Bronchitis Viral, Myalgia, Headache
116-2501	Placebo	Alfuzosin/10 mg	Epistaxis
125-3407	Tadalafil 5 mg	Doxazosin/4 mg	Headache
131-4006	Tadalafil 5 mg	Tamsulosin/0.4 mg	Arthralgia
134-4305	Placebo	Tamsulosin/0.4 mg	Headache, Diarrhea

Source: Table LVHS 14.24, LVHS Study Report, page 318

Reviewer's Comment: The pattern of TEAEs in the first day of dosing does not seem to indicate tendency to increased AEs in the tadalafil group. Throughout the study there was a modest increase in dizziness in tadalafil patients and an increase in gastrointestinal complaints. Headache occurred more frequently in

placebo subjects as did myalgia. One report of syncope occurred in a placebo subject. It is also of note that no subject required downward titration of their alpha blocker therapy during the study. This titration was allowed at any time during the study for safety purposes.

Notable Adverse Events

Hypotension

Two (2) separate analyses of TEAEs possibly related to hypotension were conducted.

- A focused analysis included the following 7 MedDRA preferred terms: dizziness, dizziness postural, procedural dizziness, hypotension, orthostatic hypotension, syncope, and presyncope.
- An expanded analysis of TEAEs possibly related to hypotension including headache, asthenia, and fatigue.

Table 59: Treatment-Emergent Adverse Events Possibly Related to Hypotension Study LVHS

Preferred Term	Placebo (N=160)	Tadalafil 5 mg (N=158)
	n (%)	
Subjects with >= 1 TEAE (focused review)	10 (6.3)	11 (7.0)
Subjects with >= 1 TEAE (expanded analysis)	15(9.4)	16 (10.1)
Dizziness	8 (5.0)	10 (6.3)
Fatigue *(expanded analysis term)*	1 (0.6)	3 (1.9)
Headache *(expanded analysis term)*	3 (1.9)	2 (1.3)
Blood Pressure Decreased	0 (0.0)	1 (0.6)
Dizziness Postural	1 (0.6)	1 (0.6)
Asthenia *(expanded analysis term)*	3 (1.3)	0 (0.0)
Orthostatic Hypotension	1 (0.6)	0 (0.0)
Syncope	1 (0.6)	0 (0.0)

Source: Table LVHS 12.7, LVHS Study Report, page 133.

Reviewer's Comment: Similar proportions of subjects in each treatment group experienced at least 1 TEAE possibly related to hypotension in both the focused and expanded analysis groups.

An analysis of TEAEs reported during orthostatic vital sign assessments was conducted by the Sponsor. This analysis consisted of those events which were first reported during orthostatic vital sign assessment or worsened in severity after randomization. A greater proportion of placebo subjects than tadalafil subjects had such events.

Table 60: Treatment-Emergent Adverse Events Reported Upon Standing during Orthostatic Vital Sign Assessments Study LVHS

Preferred Term	Placebo (N=160)	Tadalafil 5 mg (N=158)
	n (%)	
Subjects with >= 1 TEAE	4 (2.5)	3 (1.9)
Dizziness	4 (2.5)	3 (1.3)
Dizziness Postural	0 (0.0)	1 (0.6)
Orthostatic Hypotension	1 (0.6)	0 (0.0)

Source: Table LVHS 12.8, LVHS Study Report, page 134.

Of the 14 tadalafil subjects with medical summaries for TEAEs possibly related to hypotension (from the expanded analysis and excluding 2 subjects with headache), most subjects (9 of 14) were taking nonselective alpha blockers. Of the 9 subjects taking nonselective alpha blockers, 6 subjects were <75 years of age. In addition, only 6 of the 14 tadalafil subjects also met at least 1 of the criteria for a treatment-emergent positive orthostatic test. Of the 15 placebo subjects reporting at least 1 TEAE possibly related to hypotension, 2 subjects reported headache with no other concurrent events suggestive of hypotension. In addition, 1 subject reported syncope which was secondary to pacemaker lead dislodgement. Of the 12 remaining placebo subjects with events suggestive of hypotension (from the expanded analysis and excluding 2 subjects with headache and 1 with syncope), half of the subjects (6 of 12) were taking nonselective alpha blockers. Of the 6 subjects taking nonselective alpha blockers, 5 subjects were <75 years of age. In addition, only 4 of the 12 placebo subjects also met at least 1 of the criteria for a treatment-emergent positive orthostatic test.

Dizziness (Only narratives for tadalafil randomized subjects shown)

LVHS Subject 107-1604 is a 58-year-old black male taking doxazosin 4 mg who reported vertigo, nausea, and dizziness ("lightheadedness") 10 days post-randomization, which lasted for 4 days. These same events were reported as intermittent a few days later, with the dizziness and nausea continuing for 25 days, and the vertigo for 16 days. The subject had pre-existing hypertension treated with amlodipine and lisinopril. He met the criterion for a positive orthostatic test at Visit 5 (HR increase from 64 to 86 bpm), but did not report any symptoms during orthostatic testing. This subject completed the study.

LVHS Subject 108-1729 is a 57-year-old white male taking alfuzosin 10 mg who reported dizziness 2 days after taking the first dose of randomized study drug, which lasted for 4 days. Upon further follow-up, it was reported that the event occurred upon standing up from a sitting position. The subject had pre-existing hypercholesterolemia and hypertension and was being

treated with atorvastatin and quinapril. His SBP and HR were above normal throughout the study; the AE was not reported during orthostatic testing and no vitals were taken during the event. No positive orthostatic test criteria were met at any visit. The subject continued study drug for approximately 2 months before discontinuing early due to subject decision (no longer wishes to participate). Site reported (upon follow-up request from sponsor) that the subject discontinued due to desire to obtain study drug via prescription as treatment rather than continue in the study.

LVHS Subject 109-1802 is a 59-year-old white male taking 8 mg doxazosin who reported dizziness upon standing during orthostatic testing at Visits 4 and 5. He reported pre-existing hypercholesterolemia. The subject did not meet any positive orthostatic test criteria at any visit. This subject completed the study.

LVHS Subject 112-2108 is a 75-year-old white male taking doxazosin 2 mg who reported dizziness approximately 5 weeks post-randomization which lasted 1 month. He had no pertinent medical history or concomitant medications and no further AEs were reported. No positive orthostatic test criteria were met at any visit. The subject completed the study.

LVHS Subject 113-2205 is a 61-year-old white male taking alfuzosin 10 mg who reported dizziness ("dizziness" and "lightheadedness occasional") approximately 1.5 months after randomization which ended at study completion. He reported pre-existing seasonal allergies which were treated with loratadine. The site indicated "low BP [blood pressure]" related to event, which was recorded as 105/70 mmHg for Visit 5 supine vitals. This event was reported during Visit 5 orthostatic vital sign assessment. The subject did not meet any criteria for a positive orthostatic test at any visit. He completed the study.

LVHS Subject 116-2508 is a 56 year-old black male taking alfuzosin 10 mg who reported dizziness and nausea for a single day, 1 day prior to study completion. The subject had preexisting intervertebral disc protrusion for which he took an oxycodone and acetaminophen combination medication. Follow-up from the site indicated the subject reported waking at 7:00 AM with the symptoms which resolved by 3:00 PM the same day. No additional AEs were reported and the subject did not meet criteria for a positive orthostatic test at any visit. The subject completed the study.

LVHS Subject 119-2807 is a 69-year-old white male taking doxazosin 2 mg who reported dizziness ("lightheadedness"), along with fatigue, nausea, vision blurred, chest discomfort and diarrhea all commencing 11 days post-randomization. In addition, the subject reported a mild tension headache commencing 3 days post-randomization. The subject reported pre-existing conditions of hypoesthesia ("transient left arm numbness") beginning approximately 2 months prior to randomization, blood cholesterol increased, aortic arteriosclerosis, hypertension, hyperglycemia, and edema peripheral with concomitant medications including hydrochlorothiazide and acetylsalicylic acid. Follow-up from the site indicated that the vision blurred and dizziness occurred upon waking, prior to taking medications. The subject did not meet criteria for a positive orthostatic test at any visit. He was discontinued from the study due to chest discomfort at Visit 4 at which time he was instructed to see his primary care physician

regarding his symptoms. It is stated "The primary care physician was not concerned with his symptoms."

LVHS Subject 125-3407is a 54-year-old black male taking doxazosin 4 mg who reported dizziness on 2 occasions approximately 1 month post-randomization. He reported pre-existing conditions of hypercholesterolemia and hypertension with concomitant medications including amlodipine, clonidine, Hyzaar, and metoprolol. Follow-up from the site indicated that both instances of dizziness occurred after exertion (running up stairs) and lasted for only 1 day. In addition, the subject reported worsening headaches commencing on the day of randomization and continuing for 3 days, however, the headaches were not reported simultaneously with dizziness. The subject did not meet criteria for a positive orthostatic test at any visit and no events were reported upon standing during orthostatic testing. The subject completed the study.

LVHS Subject 127-3601 is a 78-year-old white male taking terazosin 1 mg who reported dizziness ("lightheadedness") beginning the day after randomization, which was ongoing at the time of study completion. His medical history included cardiac stent placement, hypercholesterolemia, neuropathy peripheral, and deafness bilateral (since 1999). In addition to the reported dizziness, his TEAEs included nasopharyngitis, epistaxis, pneumonia, hypoacusis, and middle ear effusion. He was taking gabapentin, simvastatin, Omnicef (an antibiotic used to treat middle ear conditions), and an unknown antibiotic. Follow-up with the site indicated that the dizziness was reported as occurring when the subject bent to tie his shoes, but he did not report any symptoms upon standing during orthostatic testing. The subject met criteria for positive orthostatic tests, including for HR at all pre-randomization and post-randomization visits (Visit 2 to Visit 6) and for SBP at Visit 5. All blood pressures were within normal limits; standing HR was >100 bpm at Visits 2, 4, and 5. The subject completed the study.

LVHS Subject 128-3705 is a 72-year-old white male taking alfuzosin 10 mg who reported dizziness ("dizzy spells") that began 2 days post-randomization and continued intermittently throughout the study. He reported pre-existing conditions of type 2 diabetes mellitus, hypercholesterolemia, hypertension, and restless leg syndrome. Concomitant medications included lisinopril, aliskiren and hydrochlorothiazide, and pramipexole. Follow-up with the site indicated the dizziness was associated with changing from "a bent to erect position." However, the subject did not report any AEs during orthostatic vital sign assessments. This subject met the criterion for a positive orthostatic test for DBP at Visit 3 (baseline) and for SBP at Visit 5. The subject completed the study.

> *Reviewer's Comment: Many of the events of dizziness seemed to occur with a rapid change of position (postural). In light of the fact that tadalafil will be used as monotherapy for BPH, this observation need not be included in labeling, in my opinion. In addition, the current labeling for Cialis contains cautions and specific guidance regarding use of tadalafil for ED in alpha blocker patients.*

Dizziness Postural

LVHS Subject 128-3712 is a 71-year-old white male taking doxazosin 8 mg who reported dizziness postural ("intermittent lightheadedness from laying to standing") approximately 9 days post-randomization which lasted almost 1 month. He reported pre-existing conditions including blood cholesterol increased and hypertension, and was taking atenolol. The subject met the criterion for a positive orthostatic test for DBP at Visit 4, and the AE of dizziness was reported upon standing during orthostatic vital sign assessment at Visit 4. The subject completed the study.

Fatigue

LVHS Subject 105-1410 is a 66-year-old white male taking tamsulosin 0.8 mg who reported fatigue ("tiredness") 1 day post-randomization which lasted 4 days. He reported pre-existing conditions of sinusitis, dyspepsia, and hypercholesterolemia. Follow-up from the site indicated that the fatigue resolved when the subject switched from morning to evening dosing with study drug. The subject did not meet any criteria for a positive orthostatic test. He was discontinued at Visit 4 (due to physician decision-site closing) with no additional AEs reported.

LVHS Subject 123-3208 is a 66-year-old white male taking terazosin 7 mg, reported fatigue approximately 1 month post-randomization which was ongoing at the time of study completion. His pre-existing conditions included anemia, depression, hyperlipidemia, rheumatoid arthritis, and pain. The subject's concomitant medications included hydrocodone and paroxetine. The subject met the criterion for a positive orthostatic test for HR at Visit 6. However, he did not report any AEs upon standing during orthostatic vital sign assessments. The subject completed the study.

LVHS Subject 119-2807 reported fatigue ("increased fatigue"); this was discussed above with the AE of dizziness.

> *Reviewer's Comment: If the incidence of asthenia and fatigue are considered together, there are similar proportions of subjects in placebo and tadalafil groups who have one or both. In my opinion, this subgroup analysis does not point to a difference related to tadalafil in association with alpha blocker medication*.

Cardiac Disorders

Two tadalafil subjects reported cardiac related TEAEs versus one placebo subject (ECG abnormal). Only the tadalafil narratives are shown here.

LVHS Subject 121-3016 is a 65-year-old white male taking tamsulosin 0.4 mg who reported events of atrial fibrillation, HR increased, and dehydration approximately 3 weeks postrandomization (to tadalafil) which lasted for 2 days. The subject had a past medical history of mitral valve replacement. The site reported that these AEs occurred from being out in the sun and the subject had to go to the emergency room due to the atrial fibrillation. The subject's last dose of study drug was approximately 4 days prior to the reported AEs. The subject discontinued at Visit 4 due to the event of atrial fibrillation.

LVHS Subject 119-2807 randomized to tadalafil reported chest discomfort; this was discussed above with the AE of dizziness.

> *Reviewer's Comment: Subject 119-2807 had other symptom in addition to chest discomfort including diarrhea which could be secondary to an intercurrent illness. Subject 121-3016 had an episode to atrial fibrillation which was associated with dehydration.*

Vision Disorders

Four subjects experienced treatment emergent vision disorders. Three subjects (2 tadalafil and 1 placebo) vision blurred was reported. In one tadalafil subject with macular degeneration (Subject 115-2409) a positive rechallenge was noted. One placebo subject reported decreased visual acuity.

Hearing Disorders

Two tadalafil subjects reported treatment-emergent hearing disorders.

LVHS Subject 126-3511 is a 66-year-old white male taking tamsulosin 0.4 mg who reported deafness approximately 2 months post-randomization, which was ongoing at the time of study completion. He reported pre-existing conditions of a positive syphilis serology in December 2008 and hypercholesterolemia, and was taking no concomitant medications aside from tamsulosin. No ED history or prior PDE5 inhibitor use was reported. The subject completed the study. There is no mention of pre-existing deafness. The hearing loss is described as mild in patient data listings. The PI assessed the subject's deafness as unrelated to study drug or adjunct therapy.

LVHS Subject 127-3601 is a 78-year-old white male taking terazosin 1 mg, who reported hypoacusis and middle ear effusion simultaneously, approximately 2 months post-randomization. This subject had pre-existing bilateral deafness since 1999. See further medical history details and concomitant medications for this subject above with his AE of dizziness. Additional TEAEs reported by this subject included nasopharyngitis, epistaxis, and pneumonia. The subject's pneumonia resolved approximately 2 weeks prior to the onset of hypoacusis and middle ear effusion. The subject completed the study.

Urinary Disorders

A total of 9 subjects (5 tadalafil, 4 placebo) reported 14 treatment-emergent urinary disorders (dysuria [1 tadalafil, 1 placebo], nocturia [1 tadalafil, 2 placebo], pollakiuria [1 tadalafil, 3 placebo], urinary retention [1 tadalafil, 1 placebo], urinary tract infection [1 tadalafil], and urine flow decreased [1 tadalafil, 1 placebo]). As dysuria, nocturia, pollakiuria, and urine flow decreased are symptoms associated with BPH and the incidence appears balanced

between placebo and tadalafil subjects narratives are not provided except for the 1 tadalafil subject who experienced a urinary tract infection.

LVHS Subject 119-2809 is a 70-year-old white male taking terazosin 4 mg who reported urinary tract infection and urinary retention approximately 3 months post-randomization (to tadalafil). The subject reported multiple pre-existing conditions, including hypertension, hypercholesterolemia, type 2 diabetes mellitus and diabetic neuropathy and was taking numerous concomitant medications. Follow-up with the site indicated the subject had experienced fever and pain which resulted in an emergency room visit. During his evaluation, he was diagnosed with urinary tract infection (culture positive for E. coli) and urinary retention. Catheterization was required to relieve the retention; he was treated with Levaquin for the infection, along with having his alpha blocker changed from terazosin to tamsulosin 0.4 mg for 10 days. One (1) day prior to his final visit he stopped tamsulosin and reinitiated terazosin 4 mg; the subject completed the study.

Orthostatic Vital Signs

Overall, 60 subjects (30 per treatment group) met at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test.

The criteria were:
1. Decrease in SBP of ≥20 mm Hg from the supine to the standing position;
2. Decrease in DBP of ≥10 mm Hg from the supine to the standing position;
3. Increase in HR of ≥20 beats per minute (bpm) from the supine to the standing position; or
4. Inability to remain standing during the orthostatic assessment (as indicated on the CRF).

Table 61: Treatment Emergent Orthostatic Tests Study LVHS

	Placebo N=160	Tadalafil N=159
	n (%)	n (%)
Subjects with >= 1 Positive Orthostatic Test	30 (18.8)	30 (19.0)
Criterion 1	16 (10.0)	10 (6.3)
Criterion 2	17 (10.6)	15 (9.5)
Criterion 3	4 (2.5)	6 (3.8)
Criterion 4	0 (0.0)	0 (0.0)

Source: Table LVHS 12.9, LVHS Study Report, page 136

Reviewer's Comment: While the subject number is equal the event number is greater for placebo.

Table 62: Orthostatic Vital Signs Test Shift from Any Pre-randomization to Any Post-randomization Visit Study LVHS

	Pre-randomization	Any Post Randomization Visit	
		Positive Test	Negative Test
Overall Orthostatic Test Result		n (%)	n (%)
Placebo (N=160, N1=159)	Positive Test	14 (8.9)	22 (13.9)
	Negative Test	21 (13.3)	101 (63.9)
	Total	35 (22.2)	123 (77.8)
Tadalafil 5 mg (N=158, N1=156)	Positive Test	16 (10.3)	15 (9.6)
	Negative Test	19 (12.2)	106 (67.9)
	Total	35 (22.4)	121 (77.6)

Source: Table LVHS 12.10, LVHS Study Report, page 137

TEAEs reported upon standing during orthostatic vital sign assessment are placebo: dizziness 1 and tadalafil: dizziness postural 1.

With respect to outliers, in the tadalafil subjects the largest changes in blood pressure were systolic blood pressure -40 mmHg and diastolic blood pressure -20 mmHg. The largest increase in heart rate was 27 bpm. In the placebo subjects the largest changes in blood pressure were systolic blood pressure -32 mmHg and diastolic blood pressure -36 mmHg. The largest increase in heart rate was 31 bpm.

Uroflowmetry and Postvoid Residual Urine

Changes from baseline (Visit 3) to endpoint in Q max for each treatment group was 0.6 mL/sec. From baseline to endpoint, there were small decreases in PVR in both treatment groups (tadalafil, -8.1 mL; placebo, -1.9 mL).

> *Reviewer's Comment: Neither of these changes is clinically significant in my opinion.*

Five subjects (3 tadalafil and 2 placebo were identified with a PVR< 300mL at baseline and PVR > 300mL at endpoint. The Sponsor states that followup with the sites as well as examination of uroflowmetry data indicate that these patients had invalid prevoid volumes.
None of these subjects (113-226, 116-2504, 121-3027, 121-3029, and 128-3703) reported any urinary AEs during the study.

> *Reviewer's Comment: While the PVR was stated to be determined by ultrasound, it appears that the bladder prevoid volume was first determined by ultrasound and then the voided volume (measured) was subtracted from the prevoid volume to determine PVR. If a postvoid bladder volume had been determined by ultrasound, the prevoid volume determined by ultrasound would not alter the*

result. Based on the similar numbers between treatment groups, I would not investigate these patients further. Details of the exact methods used are not provided in the study report.

Clinical Laboratory Evaluation

Changes between treatment groups were statistically significant for hemoglobin (p=.008) and lymphocytes (p=.009). For both parameters, within group p-values were significant for 1 of the treatment groups. The change from baseline to end point in hemoglobin for the study population was -0.0290 mmol/L (Fe) for placebo and -0.1595 mmol/L (Fe) for tadalafil. The change from baseline to end point in leucocyte count for the study population was -46.6 lymphocytes/ µL for placebo and -56.5 lymphocytes/µL for tadalafil. Most subjects in both treatment groups were within normal range at both baseline and endpoint for all hematology parameters. A total of 11 subjects (7 tadalafil, 4 placebo) had shifts from normal to low for platelet count (Table LVHS.14.55). The change from baseline to end point in platelet count for the study population was -7077 platelets/ µL for placebo and -11063platelets/µL for tadalafil. None of the tadalafil subjects reported any treatment emergent bleeding events nor did the PI record these shifts as clinically significant findings.

Reviewer's Comment: In my opinion, these changes are not clinically significant.

Changes between treatment groups were statistically significant for alkaline phosphatase (p= .009), total bilirubin (p= .016), potassium (p= .031), and urea nitrogen (p= .003). The change from baseline to end point in alkaline phosphatase for the study population was -0.5556 U/L for placebo and -2.4595 U/L for tadalafil. The change from baseline to end point in total bilirubin for the study population was -0.2403 µmol /L for placebo and 0.5680 µmol /L for tadalafil. The change from baseline to end point in potassium for the study population was 0.0248 mmol /L for placebo and -0.0660 mmol /L for tadalafil. The change from baseline to end point in urea nitrogen for the study population was -0.0187 mmol /L for placebo and 0.1839 mmol /L for tadalafil.

Reviewer's Comment: In my opinion, these changes are not clinically significant.

Approximately 40% of the subjects in both treatment groups had low creatinine clearance at baseline and endpoint, as would be expected in this study which enrolled a large number of elderly subjects with multiple co-morbidities and concurrent medications.
A total of 17 subjects (11 tadalafil, 6 placebo) had normal creatinine clearance at baseline which shifted to low at endpoint. Most tadalafil subjects with shifts from normal to low creatinine clearance had pre-existing lipid disorders, hypertension, and/or diabetes. The mean serum creatinine in the tadalafil subjects increased 2.1611 µmol/L from baseline to endpoint (90.5503 to 92.7114) compared to 1.500 µmol/L from baseline to endpoint (91.1623 to 92.6623) in placebo subjects.

Reviewer's Comment: In a study with large numbers of elderly subjects with multiple co-morbidities and concurrent medications, there can be great variability in the estimates of creatinine clearance. This was evaluated extensively in the review of Study LVHR. Additionally, some LVHR were shown to have an abnormal (low) estimated creatinine clearance at Visit 1 and Visit 2 and a normal estimate at Visit 3 making a baseline to endpoint of creatinine clearance estimate possibly misleading. Nonetheless, the difference between treatmnent groups appears not clinically significant.

One (1) subject in the placebo group met the criteria of having an AST more than 3-fold the upper limit of normal and 2 subjects (1 placebo; 1 tadalafil) met the criteria of having a total bilirubin more than 1.5-fold the upper limit of normal post baseline. A narrative for 1 tadalafil-treated patient is shown below.

Significant outliers related to hepatic function (ALT, AST, and total bilirubin) are summarized by treatment group in the table below:

Table 63: Treatment -Emergent Elevated Hepatic-Related Serum Chemistry Results Study LVHS

	Placebo N=160	Tadalafil 5 mg N=158
	n (%)	
ALT>= 3 ULN	0 (0.0)	0 (0.0)
AST >= 1.5 ULN	1 (0.6)	0 (0.0)
Total Bilirubin >= 1.5 ULN	1 (0.6)	1 (0.6)
ALT >= 3 ULN and Total Bilirubin >= 1.5 ULN	0 (0.0)	0 (0.0)
AST >= 1.5 ULN and Total Bilirubin >= 1.5 ULN	0 (0.0)	0 (0.0)

Source: Table 12.14, LVHS Study Report, page 150

LVHS Subject 124-3326 is a 61-year-old native Hawaiian male randomized to tadalafil, who with total bilirubin 2.2 mg/dL (range 0.2 to 1.2 mg/dL) at endpoint also had elevated total bilirubin (1.5 mg/dL) at baseline. This subject reported myalgia, depression and drug hypersensitivity ("Cipro") as pre-existing conditions, with gabapentin, metoprolol, acetylsalicylic acid, finasteride, and alfuzosin as concomitant therapies. The subject also had slightly elevated ALT at his screening visit (44 U/L, range 6 to 43 U/L) as well as slightly elevated hemoglobin A1c (6.5%, range 4.3 to 6.1%). His endpoint urinalysis results showed the presence of glucose. The only TEAEs reported for this subject were abdominal distention and diarrhea, with no clinically significant laboratory findings recorded by the PI. The subject completed the study.

Summary of Lab Results Subject 124-3326

AST/SGOT Int'l Units/Liter	(11.0 -36.0)	27.0	30.0	31.0
ALT/SGPT Int'l Units/Liter	(6.0 -43.0)	44.0	37.0	38.0
BILIRUBIN, milligram/deciliter	(0.2- 1.2)	1.3	1.5	2.2

Reviewer's Comment: There was no discernible trend or safety signal noted in review of laboratory data.

A total of 16 subjects (10 tadalafil, 6 placebo) had shifts from normal to abnormal for urine protein, 13 subjects (8 tadalafil, 5 placebo) for urine glucose, and 4 tadalafil subjects had urine blood present at endpoint. Most tadalafil subjects with shifts from normal to abnormal for urinalysis parameters had pre-existing lipid disorders, hypertension, and/or diabetes. None of the subjects reported notable TEAEs.

Subgroup Analysis and Overall Conclusions

There were similar proportions of subjects in each treatment group reporting a TEAE possibly related to hypotension. Repeat measurements of orthostatic vital signs showed no greater impact of tadalafil on hemodynamic signs than placebo in men on concomitant alpha blocker therapy. Assessment of symptomatic orthostatic hypotension (defined as the presence of a symptom simultaneously with a positive orthostatic test) also showed similar results between treatment groups (1 subject per group).

In the subgroup analysis of TEAEs possibly related to hypotension by age (≥75 years, <75 years), there appeared to be no difference in hypotension-related adverse events between tadalafil and placebo within the younger subgroup. There also were no major differences in the incidences of hypotension-related AEs between different age subgroups among tadalafil-treated patients. However, there was a lower incidence of hypotension-related adverse events in the elderly placebo subgroup compared to the younger placebo subgroup (5.3% and 10.7%, respectively); which apparently led to a numerically greater proportion of elderly tadalafil subjects reporting events compared to the elderly placebo subjects (12.5% versus 5.3%).

Table 64: Treatment-Emergent Positive Orthostatic Tests Patients with Age Under 75 and >= 75 Years

	Subjects <75 years		Subjects ≥75 years	
	Placebo N=122	Tadalafil 5mg N=119	Placebo N=38	Tadalafil 5mg N=40
	n (%)	n (%)	n (%)	n (%)
Subjects with >= 1 Positive Orthostatic Test	21(17.2)	19 (16.1)	9 (23.7)	11 (27.5)
Criterion 1	10 (8.2)	5 (4.2)	6 (15.8)	5 (12.5)
Criterion 2	12 (9.8)	11 (9.3)	5 (13.2)	4 (10.0)
Criterion 3	3 (2.5)	4 (3.4)	1 (2.6)	2 (5.0)
Criterion 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1. Decrease in SBP of ≥20 mm Hg from the supine to the standing position;
2. Decrease in DBP of ≥10 mm Hg from the supine to the standing position;
3. Increase in HR of ≥20 beats per minute (bpm) from the supine to the standing position; or
4. Inability to remain standing during the orthostatic assessment (as indicated on the CRF).

Source: Tables LVHS 12.19 and 12.20, LVHS Study Report, pages 159, 160.

Table 65: Adverse Events Possibly Related to Hypotension By Age Group (<75; >=75 years) Study LVHS

Preferred Tern	Subject < 75 Years Old		Subject >= 75 Years Old	
	Placebo	Tadalafil 5 mg	Placebo	Tadalafil 5 mg
	N=122	N=118	N=38	N=40
Subjects with >= 1 TEAE	13 (10.7)	11 (9.3)	2 (5.3)	5 (12.5)
Dizziness	6 (4.9)	8 (6.8)	2 (5.3)	2 (5.0)
Headache	3 (2.5)	0 (0.0)	0 (0.0)	2 (5.0)
Blood pressure decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Orthostatic hypotension	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
Fatigue	1 (0.8)	3 (2.5)	0 (0.0)	0 (0.0)
Dizziness postural	2 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)
Asthenia	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table LVHS 12.15, LVHS Study Report, page 154

Treatment-emergent AEs possibly related to hypotension were also analyzed by alpha blocker type subgroups (nonselective, selective). In this analysis, a larger proportion of subjects on nonselective alpha blockers reported these TEAEs compared to those taking selective alpha blockers, regardless of treatment group (nonselective alpha blocker: tadalafil 19.2%, placebo 15.1%; selective alpha blocker: tadalafil 5.7%, placebo 6.5%); results between treatment group within each of these subgroups were similar.

Subgroup analyses of orthostatic vital signs by age (≥75 years, <75 years) appeared to show similar proportions of subjects on tadalafil and placebo meeting at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test, regardless of age subgroup, however, a larger proportion of elderly subjects compared to placebo subjects met at least 1 of the criteria, regardless of treatment group (placebo and tadalafil similarly, see Table 64).

In the subgroup analysis of orthostatic vital signs by alpha blocker type (nonselective, selective), the combination of tadalafil and nonselective alpha blocker showed a higher proportion of subjects meeting at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test compared with placebo or compared with either treatment group taking concomitant selective alpha blocker.

The incidence of discontinuations due to adverse events was low and similar between treatment groups (tadalafil: 4.4%, placebo: 3.8%). Most TEAEs were mild or moderate in severity.

Generally, the AE profile of tadalafil subjects in this study was similar to that observed in past studies of tadalafil in men with BPH; the most commonly reported TEAEs in the tadalafil group

were dizziness, dyspepsia, diarrhoea, back pain, and GERD. Slight differences in TEAEs were observed, as anticipated, based upon a greater proportion of elderly subjects and concomitant treatment with alpha blockers; specifically, a slightly higher incidence of dizziness was reported in both treatment groups than is typical in past studies of tadalafil in men with BPH.

Safety parameters of uroflowmetry, postvoid residual, and clinical laboratory values showed no clinically adverse changes with tadalafil treatment.

A numerically greater improvement in IPSS was observed in the tadalafil group compared to placebo, but the results were not clinically significant. It is to be noted that all subjects were on concomitant BPH therapy and there was a lack of LUTS severity eligibility requirement resulting in a lower mean baseline IPSS score.

Reviewer's Comment: Alpha blockers and tadalafil both may relax smooth muscle as a means of improving the signs and symptoms of BPH. In these study patients, there is no proven advantage to combination therapy. LVHS did not result in the identification of new safety concerns related to concomitant administration of tadalafil and alpha blocker therapy. No tadalafil patients reported syncope or an SAE attributable to hypotension. A trend toward increased hemodynamic signs and symptoms in men on nonselective alpha blockers, most notably doxazosin, was noted as described in the existing Cialis USPI (2009). A greater proportion of elderly subjects reported tadalafil-related TEAEs possibly relating to hypotension; however, this appears to have been due to a lower incidence of hypotension-related adverse events in the elderly placebo subgroup compared to the younger placebo subgroup (5.3% and 10.7%, respectively); which apparently led to a numerically greater proportion of elderly tadalafil subjects reporting events compared to the elderly placebo subjects (12.5% versus 5.3%).

Study LVGC (PiLUTS): A Multicenter, Parallel-Arm, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of Tadalafil Administered Once Daily to Men with Lower Tract Symptoms Secondary to Benign Prostatic Hyperplasia

This is a proof of concept Phase 2 study submitted by Sponsor in these NDA applications and will be considered in brief.

Study LVHC was a Phase 2a, proof of concept, multicenter, parallel-arm, placebo-controlled, double-blind study to evaluate the efficacy and safety of tadalafil administered once daily to men with lower tract symptoms secondary to benign prostatic hyperplasia. Tadalafil was administered once a day for 12 weeks (5 mg for 6 weeks followed by 20 mg for 6 weeks) in men with BPH-LUTS. Subjects (n = 281) had a mean age of 61.5 years (approximately one-third >65 years) and were predominantly Caucasian (81.1%). Approximately one-fourth of subjects (23.8%) had used alpha blockers within 1 year of Visit 1; more than half of subjects (55.2%) had experienced LUTS for >3 years; and approximately one-third (tadalafil, 34.8%; placebo, 37.8%) had severe

LUTS (IPSS ≥20). At Visit 2, most subjects (81.1%) categorized themselves as sexually active, and more than half of all subjects (56.8%) had ED for ≥1 year.

The last subject completed the protocol 27 July 2005. 281 subjects (138, tadalafil; 143, placebo) were randomized and 251 subjects (125, tadalafil; 126, placebo) completed the study.

The primary objectives of the study were:

- To evaluate the efficacy of 5 mg tadalafil, when taken daily for 6 weeks, and of 20 mg tadalafil, when taken daily for an additional 6 weeks, compared with placebo in improving lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) in men, as measured by the sum total of Questions 1 through 7 of the International Prostate Symptom Score (IPSS).

- To assess the safety of 5 mg tadalafil and 20 mg tadalafil taken daily in men with LUTS secondary to BPH (BPH-LUTS).

The secondary objectives of this study were:

- IPSS Irritative Domain, defined as the sum of IPSS Questions 2, 4, and 7
- IPSS Obstructive Domain, defined as the sum of IPSS Questions 1, 3, 5, and 6
- IPSS Quality of Live (QoL) Index
- BPH Impact Index (BII)
- Lower Urinary Tract Symptoms Global Assessment Questions (LUTS GAQ)
- Uroflowmetry parameters, including peak flow rate (Qmax), mean flow rate (Qave), and voided volume (Vcomp).

Notable inclusion criteria included men 45 years of age or older with BPH-LUTS for ≥6 months, an IPSS ≥13, and bladder outlet obstruction as defined by a urinary peak flow rate (Qmax) between 4 and 15 mL/s on a voided volume of at least 125 mL.

Tadalafil treatment resulted in improvement in IPSS total score (LS mean change from baseline) at Week 6 (tadalafil, -2.8; placebo, -1.2) and at Week 12 (tadalafil, -3.8; placebo, -1.7). The Sponsor observes that the difference in mean change from baseline between the treatment groups (Week 6, -1.6; Week 12, -2.1) was similar to widely prescribed alpha-blocker medication. The Sponsor also states that tadalafil treatment resulted in clinically meaningful improvements in IPSS score regardless of baseline LUTS severity (severe, IPSS≥20; moderate, IPSS <20). Tadalafil treatment significantly improved erectile function in sexually active subjects and in the subset of sexually active subjects with ED as measured by the IEFF EF Domain. Correlation analyses suggested that improvements in IPSS were not dependent on improvements in erectile function. Tadalafil did not improve uroflowmetry measures or cause a decline relative to baseline values.

There were no deaths or SAES in the study. Treatment-emergent adverse events most commonly reported in subjects who received tadalafil were erection increased (no priapism reported in the study), dyspepsia, back pain, headache, nasopharyngitis, and upper respiratory tract infection.

Reviewer's Comment: This study showed that tadalafil was well tolerated in men with BPH at doses up to 20 mg a day. In addition, tadalafil improved symptoms of BPH independently of its effect on erectile dysfunction.

Study LVIA: A Phase 2, Randomized, Double-Blind, Placebo Controlled, Parallel-Design Study to Evaluate the Efficacy and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks followed by an Open-Label Extension to Evaluate the Long-Term Safety and Efficacy to Evaluate the Long-Term Safety and Efficacy of Tadalafil in Japanese Men with Signs and Symptoms of Benign Prostatic Hyperplasia.

Study LVIA and LVIA Open-Label Extension are non-IND foreign studies and will discussed in brief.

Study LVIA was a Phase 2, randomized, double-blind, placebo-controlled, 12-week, dose-ranging study. The double-blind period was designed to examine the efficacy and safety of tadalafil 2.5 mg and 5 mg administered once daily for 12 weeks versus placebo in Japanese men with BPH-LUTS.

The long-term safety and "persistence of efficacy" of tadalafil 5-mg once-daily dosing was assessed with a 42-week, open-label extension period of Study LVIA. Subjects who completed the double-blind treatment period were given the option to continue in the open-label extension receiving tadalafil 5 mg once daily. The double-blind period together with the open-label extension provided 54 weeks of assessments.

Study LVIA enrolled Japanese subjects ≥45 years old with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Notable inclusion criteria also included total IPSS ≥13 and Qmax ≥4 and ≤15 mL/sec at the start of the placebo lead-in period and prostate volume ≥20 mL estimated by transabdominal or transrectal ultrasound at screening. After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

Randomization was stratified by baseline (after placebo lead-in period) LUTS severity (IPSS <20 or ≥ 20) and prior alpha-blocker therapy (within 12 months of screening [yes/no]). The primary objective was to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared to placebo in improving the total IPSS in men with BPH-LUTS. Key secondary

efficacy objectives were to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared with placebo in improving the Patient SEP Q3 and BII.

In the double-blind period of LVIA, 422 patients were randomized 1:1:1 (142, tadalafil 2.5 mg; 140, tadalafil 5 mg; 140, placebo) and 394 patients completed the study (135 tadalafil 2.5 mg, 128 tadalafil 5 mg, and 131 placebo). In the open-label period of LVIA, 394 patients transferred from the double-blind period (previous treatment 135, tadalafil 2.5 mg; 128, tadalafil 5 mg; 131, placebo). 323 subjects completed the open-label period of LVIA (previous treatment 113, tadalafil 2.5 mg; 109, tadalafil 5 mg; 101, placebo).

In the primary efficacy analysis, tadalafil 5 mg treatment group showed no statistically significant change in IPSS total score from baseline to endpoint compared with placebo (-1.1 [95% CI = -2.2 to 0.1; p=0.062] ANCOVA). The LS mean changes from baseline to Week 12 were -3.8 in the placebo and -4.9 in the tadalafil 5 mg treatment group. The tadalafil 2.5 mg treatment group also showed no statistically significant change compared with placebo (-0.7 [95% CI = -1.8 to 0.4; p=0.201]). In the repeated measures analysis, IPSS total score showed increased numeric improvement at each visit, which reached a statistical significant separation from placebo at Week 12 for the tadalafil 5 mg treatment group (-1.2 [p=0.035], repeated measures analysis).

Secondary efficacy variables included IPSS obstructive and irritative subscores, IPSS QoL, OABSS and Qmax. IPSS obstructive subscore and IPSS QoL showed statistically significant changes from baseline to endpoint in the tadalafil 5 mg treatment group compared with placebo (IPSS obstructive subscore, -0.9 [p=0.033]; IPSS QoL, -0.3 [p=0.022], ANCOVA). No significant changes were seen in any of the treatment groups for the other secondary endpoints including IPSS irritative subscore, OABSS and Qmax ($p \geq 0.05$).

The tadalafil 2.5 treatment group also showed no statistically significant change from baseline compared with placebo (-0.7 [95% CI = -1.8 to 0.4; p=0.201]).

Each efficacy valuable was evaluated using subgroups of baseline BPH severity, previous α-blocker therapy, previous BPH therapy other than α-blocker, baseline age and baseline prostate volume. For both the tadalafil 2.5 and 5 mg treatment groups, subjects with severe BPH at baseline show numerically greater changes from baseline to endpoint in IPSS total score than those with mild to moderate BPH (moderate BPH symptoms at baseline: -4.0 [tadalafil 2.5 mg] and -3.8 [tadalafil 5 mg]; severe BPH symptoms at baseline: -5.9 [tadalafil 2.5 mg] and -7.9 [tadalafil 5 mg]).

The Sponsor also performed 2 post hoc analyses on IPSS total score. In the analysis using an ANCOVA model including site as one of the model effects, site effect was calculated to be statistically significant ($p<0.01$), and the IPSS total score showed statistically significant change from baseline in the tadalafil 5 mg treatment group compared with placebo (-1.4 [p=0.015]). In analysis performed with subjects who had IPSS total score of ≥ 13 at baseline, there was also statistically significant change from baseline for the tadalafil 5 mg treatment group compared with placebo (-1.4 [p=0.047]).

The Sponsor summarizes the results in the open-label period of LVIA as follows:
The total IPSS score changed over the course of the extension in a dose-dependent manner with subjects experiencing IPSS total mean score changes of -2.3. -0.9, -0.3 when continuing study medication from placebo, tadalafil 2.5 mg or 5 mg to tadalafil 5mg in the open-label extension period respectively. In subjects previously treated with either placebo, tadalafil 2.5 mg or 5 mg, the IPSS storage (irritative) subscore and IPSS QoL score improvements identified at Week 18 (Visit 9) into the open-label extension period were maintained until last visit at Week 54 (Visit 18). Subjects with severe BPH (IPSS ≥ 20) at baseline experienced dose-dependent IPSS total score mean changes of -5.2, -2.7, -0.3 when changing study medication from placebo, tadalafil 2.5 mg or 5 mg to tadalafil 5 mg in the open-label extension period, respectively. In subjects with mild to moderate BPH severity (IPSS < 20) at baseline there was less room for improvement and the IPSS total score mean changes during the open-label extension period were less pronounced.

A review of the pharmacokinetic results, collected through sparse sampling of Study LVIA revealed that the measured tadalafil concentrations were higher than observed in previous studies of 2.5 mg and 5 mg once-daily dosing and according to the Sponsor, demonstrated uncharacteristically marked intra-subject variability. The pharmacokinetic results appeared to be incongruent with the observed clinical endpoints. It is also noted that the incidence of known AEs to higher tadalafil exposures i. e. mirroring that seen after 10 to 20 mg, also did not occur. The Sponsor has concluded that the pharmacokinetic results are atypical and do not raise any concerns for tadalafil in the treatment of Japanese men with BPH.

The overall compliance rate for the double-blind treatment period of LVIA was 96.9%.

Safety evaluations were performed for 422 subjects in the safety analysis set (all randomized subjects who received study treatment grouped by the treatment actually taken). In double-blind period, all treatment groups were similar with respect to the incidence of AEs. The number of patients who had at least 1 treatment-emergent adverse event (TEAE) was 53 [37.9%] in the placebo, 54 [38.0%] in the tadalafil 2.5 mg and 54 [38.6%] in the tadalafil 5 mg treatment group. TEAEs were generally mild or moderate in severity. The most frequently occurring TEAE was nasopharyngitis (placebo, 18 [12.9%]; tadalafil 2.5 mg, 11 [7.7%]; tadalafil 5 mg, 14 [10.0%]); this event was also comparable in all treatment groups. One patient in the placebo group and one patient in the tadalafil 5 mg group experienced urinary retention. The number of subjects reporting at least 1 treatment-related AEs were 11 [7.9%] in placebo, 7 [4.9%] in the tadalafil 2.5 mg and 9 [6.4%] in the tadalafil 5 mg. Serious adverse events (SAEs) were reported in 1 subject (0.7%) in placebo, 2 subjects (1.4%) in the tadalafil 2.5 mg, and 2 subjects (1.4%) in the tadalafil 5 mg, none of which were considered to be causally related to the study drug by the investigator. AEs leading to study discontinuation were reported in 5 subjects (3.6%) in placebo, 4 subjects (2.8%) in the tadalafil 2.5 mg and 5 patients (3.6%) in the tadalafil 5 mg. No deaths were reported during placebo lead-in period and double-blind treatment period.

Generally in the double-blind period of LVIA, there were no clinically adverse changes in laboratory parameters, vital signs, or mean prostate-specific antigen (PSA). As for ALT and

AST, more subjects receiving tadalafil 5 mg had abnormal shifts from normal to high compared with those receiving placebo. However, no AEs regarding hepatic dysfunctions were reported throughout the double-blind treatment period.

PVR also showed no statistically significant changes in the tadalafil treatment groups compared with the placebo treatment group ($p \geq 0.05$).

The serious adverse events (2) noted in the tadalafil 2.5 mg group were appendicitis and bladder transitional cell carcinoma. The serious adverse events (3) in the tadalafil 5 mg group occurred in 2 unique subjects and were atrial fibrillation and cardiac failure in the same patient and femur fracture in a separate patient.

In the 6 month, open-label extension of Study LVIA there was one death. Subject 130-1314 originally randomized to placebo, approximately 8 months and 3 weeks after he was randomized died from a subarachnoid hemorrhage. An additional subject, 250-2507, at 9 months and three days after randomization to placebo, developed a bile duct stone and moderate cholestatic jaundice. He was diagnosed with pancreatic carcinoma. The subject was discontinued from the study and 7 months later died of cancer of the head of the pancreas.

There were a total of 11 SAEs (4 in placebo, 3 in tadalafil 2.5 mg, and 3 in tadalafil 5 mg patients). In the formerly placebo subjects (N=131), the SAEs were cerebral infarction (1), colonic polyp (1), pancreatic carcinoma (1) and subarachnoid hemorrhage (1). In patients formerly taking tadalafil 2.5 mg, the SAEs were cholecystitis acute (1), retinal detachment (1), and sudden hearing loss (1). In patients who were formerly taking tadalafil 5 mg in the double-blind period, the SAEs were back pain (1), jaw fracture (1), traumatic arthritis (1), and urinary retention (1).

There were 36 subjects who discontinued the open-label extension period due to AEs. When compared by the previous treatment groups, the incidence of the AEs leading to discontinuation in subjects who received the placebo in the double-blind treatment period (n=17, 13.0%) was higher than those in subjects who received the tadalafil 2.5 mg (n=12, 8.9%) and 5 mg groups (n=7, 5.5%). Back pain (n=2), palpitations (n=2) and prostatitis (n=2) were the only AEs leading to discontinuation in more than 1 subject. There were 3 subjects who discontinued due to AEs related to cardiovascular disorders (palpitations [n=2]; chest pain [n=1]). Additionally, 2 subjects discontinued due to abnormal prostate findings (prostatitis), and 3 subjects due to vascular disorders (subarachnoid hemorrhage, hot flush, varicose vein). There was 1 subject who discontinued due to ear disorder (sudden hearing loss,); and 1 subject due to eye disorder (retinal detachment).

The TEAEs with incidences of 2% or more in tadalafil 5 mg treatment group during the 1-year treatment period were nasopharyngitis (18.0%), diarrhea (8.6%), back pain (5.5%), dyspepsia (4.7%), abdominal pain upper (3.1%), dermatitis (3.1%), hematuria (3.1%), headache (3.1%), periarthritis (3.1%), reflux esophagitis (3.1%), abdominal distension (2.3%), cataract (2.3%), conjunctivitis (2.3%), dysuria (2.3%), eczema (2.3%), fall (2.3%), musculoskeletal pain (2.3%), nausea (2.3%), and prostatitis (2.3%).

Hematology did not show evidence of clinically significant changes associated with tadalafil. Few subjects showed the changes from normal to abnormal (low or high) values. There were no subjects who met the Hy's rule (defined as ALT ≥ 3-fold ULN and bilirubin levels ≥2-fold ULN). Five subjects (1.3%) had an ALT shift from normal to high, and 8 subjects (2.0%) had an AST shift from normal at baseline (Visit 3) to high at end of the therapy. Serum chemistry data did not show any evidence of clinically significant changes associated with tadalafil. There were no clinically adverse findings in the urinalysis shift tables.

The Sponsor reports no clinically significant mean changes from baseline (Visit 3) to endpoint for systolic blood pressure, diastolic blood pressure and heart rate. Sponsor also reports no clinically significant mean changes from baseline to endpoint for postvoid residual urine.

Reviewer's Comment: The overall safety findings for tadalafil 5 mg in the open-label extension period were similar to those in the double-blind period, and no new safety concerns were identified. In the LVIA open-label extension, the percentages of subjects who had treatment-related AE(s), SAE(s), and AE(s) leading to discontinuation were similar to those in Open-Label Study LVHG (57.6%).

In analyzing efficacy in the double-blind period of LVIA the Sponsor states, "In the primary efficacy analysis, tadalafil 5 mg group showed no statistically significant change in IPSS total score from baseline to endpoint compared with placebo (-1.1 [95% CI = -2.2 to 0.1; p=0.062]; ANCOVA). The LS mean changes from baseline to endpoint were -3.8 in the placebo group and -4.9 in the tadalafil 5 mg group. The tadalafil 2.5 mg group also showed no statistically significant change compared with placebo (-0.7 [95% CI = -1.8 to 0.4; p=0.201]). The LS-mean change from baseline to endpoint was -4.5." A secondary analysis performed on the per protocol set using repeated measures analysis showed statistically significant change in the tadalafil 5 mg treatment group compared with placebo treatment group (-1.2 [p=0.034], ANCOVA) but no statistically significant change for the tadalafil 2.5 mg treatment group (-0.5 [p=0.367], ANCOVA).

Secondary efficacy variables included IPSS obstructive and irritative subscores, IPSS QoL, OABSS and Qmax. IPSS obstructive subscore and IPSS QoL showed statistically significant changes at endpoint in the tadalafil 5 mg group compared with placebo (IPSS obstructive subscore, -0.9 [p=0.033]; IPSS QoL, -0.3 [p=0.022], ANCOVA). No significant changes were observed for the other secondary endpoints including IPSS irritative subscore, OABSS and Qmax (p≥0.05). In a post hoc analysis performed with subjects who had an IPSS total score of ≥ 13 at baseline, there was a statistically significant change from baseline for the tadalafil 5 mg group compared with placebo (-1.4 [p=0.047]).

The Sponsor points out there are several other factors to consider in considering the LVIA efficacy result. First in terms of IPSS change, the placebo group of Study LVIA averaged 1.6 points higher than those of Study LVHG ((study LVIA, -3.8; study LVHG, -2.2). Second, Study LVIA had fewer subjects with severe BPH than study LVHG. Subjects who had severe BPH at

baseline showed numerically greater change of IPSS total score than those with mild to moderate BPH (mild to moderate, - 4.0 [tadalafil 2.5 mg] and -3.8 [tadalafil 5 mg]; severe, -5.9 [tadalafil 2.5 mg] and -7.9 [tadalafil 5 mg]). In the post hoc analysis, subjects who had an IPSS total score of ≥ 13 at baseline showed a statistically significant change from baseline in IPSS total score for the tadalafil 5 mg treatment group compared with placebo. Third, site effect might be also one of the factors that affect the efficacy results considering that the efficacy endpoint was evaluated based on the improvement of subjective symptoms. In a post hoc analysis using an ANCOVA model that included site as one of the factors, site effect was calculated to be statistically significant ($p<0.01$).

In the Study LVIA open-label extension, subjects who were originally assigned to placebo or tadalafil 2.5 mg experienced improvement in mean total IPSS when switched to tadalafil 5mg in the open-label extension). The improvement that was observed during the double-blind period in those subjects assigned to tadalafil 5 mg persisted over the 42-week open-label extension. The mean total IPSS change from baseline of the double-blind treatment period to the end of the open-label extension treatment period comprising a total of 54 weeks with tadalafil 5 mg (-5.6±5.9; CSR LVIA Open-Label Extension Section 11.4.3.1) was similar to changes observed from baseline of the double-blind treatment period in Study LVHG to the end of the LVHG open-label extension comprising a total of 64 weeks.

> *Reviewer's Comment: In considering Study LVIA (a Phase 2 study), based on multiple analyses performed by the Sponsor, there appears to be a suggestion of efficacy for the 5 mg dose of tadalafil that needs to be evaluated in phase 3 to show efficacy in Japanese men. This is a non-IND study, and the results do not effect my decision regarding efficacy for the NDA application.*

Study LVHT: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Pilot Study to Evaluate the Efficacy and Safety of Tadalafil and Tamsulosin Once-a-Day Dosing for 12 Weeks in Asian Men with Signs and Symptoms of Benign Prostatic Hyperplasia

This non-IND pilot study performed in Korea will be discussed in brief.

Study LVHT was a Phase 2, randomized, placebo-controlled pilot study. The purpose of Study LVHT was to estimate total IPSS change from baseline and the variability of that change of tadalafil 5 mg in Asian men in order to guide design of future studies examining tadalafil effect in the treatment of BPH-LUTS in Asian men in comparison to tamsulosin. Change in total International Prostate Symptom Score (IPSS) after 12 weeks was the primary endpoint.

The secondary objectives of this study in Asian men with BPH-LUTS were as follows:

- To evaluate the change from baseline of tadalafil 5 mg QD compared to placebo in total IPSS after 4 and 8 weeks and IPSS subscores (storage, voiding, and nocturia) after 4, 8, and 12 weeks.
- To evaluate the change from baseline of tamsulosin 0.2 mg QD compared to placebo in total IPSS and IPSS subscores after 12 weeks.
- To evaluate treatment differences in change from baseline of tadalafil 5 mg QD compared to tamsulosin 0.2 mg QD in the IPSS and BPH Impact Index (BII) after 12 weeks.
- To evaluate the change from baseline of tadalafil 5 mg QD compared to placebo and tamsulosin 0.2 mg QD compared to placebo in the following measures: BII, voiding dribble diary, and uroflowmetry parameters (peak urine flow rate [Qmax], mean urine flow rate [Qmean], and voided volume [Vcomp]) after 12 weeks.
- To evaluate tadalafil 5 mg QD compared to placebo and tamsulosin 0.2 mg QD compared to placebo on Patient Global Impression of Improvement (PGI-I) and Clinician Global Impression of Improvement (CGI-I) scores assessed at end of study treatment.
- To assess the safety of tadalafil 5 mg QD and tamsulosin 0.2 mg QD as examined by the following measures: adverse events, clinical laboratory tests, electrocardiograms (ECGs), postvoid residual volume (PVR), and urinalysis for 12 weeks.

Study LVHT enrolled Korean subjects ≥45 years old with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Subjects had total IPSS ≥ 13 and Qmax ≥4 and ≤15 mL/sec at the start of the placebo lead-in period. After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

151 subjects were randomized to 1 of 3 treatment groups (placebo, tadalafil 5 mg, or tamsulosin 0.2 mg) in a 1:1:1 ratio and 143 subjects completed the study (48 tadalafil, 48 tamsulosin, and 51 placebo).

This study had 50% power to detect a 2.5 difference between 2 treatments in change from baseline in total IPSS, and 80% power to detect a 3.6 difference between 2 treatments. The dropout rates were not remarkable (tadalafil 5 mg [n=48] 3, tamsulosin 0.2 mg [n=49] 1, placebo [=51] 4). Approximately 2/3 of all randomized subjects (103/151 [68.2%]) had lower urinary tract symptoms (LUTS) of moderate severity (International Prostate Symptom Score [IPSS] <20), with the remainder (48 subjects [31.8%]) having LUTS defined as severe (IPSS ≥20) at baseline; reported LUTS severity was similar for all treatment groups. Mean postvoid residual volume (PVR) at baseline was 35.7 mL (range of 0 to 262 mL); mean PVR ranged from 30.9 mL in the tadalafil group to 42.0 mL in the tamsulosin group. Previous alpha blocker therapy was similar for all treatment groups. Overall, 90 (59.6%) subjects reported having been diagnosed with ED; of these, 52 (57.8%) subjects had ED of mild severity, and 70 (77.8%) subjects had ED of ≥1 year duration.

The primary objective was to evaluate the change from baseline of tadalafil 5 mg once daily compared to placebo in total IPSS score after 12 weeks.

While numerically superior, once-a-day dosing of tadalafil 5 mg did not result in a statistically significant improvement of total IPSS score as compared to placebo at 12 weeks (tadalafil , -5.8; placebo, -4.2; p=.073). Notably, once-a-day dosing of tamsulosin 0.2 mg also did not result in a statistically significant improvement in total IPSS as compared to placebo (tamsulosin -5.4; placebo -4.2; p=.186).

With respect to secondary efficacy measures, total IPSS decrease from baseline to endpoint for subjects taking tamsulosin versus placebo in the ITT population in least-squares (LS) mean was numerically greater in the tamsulosin treatment group (-5.4) than in the placebo group (-4.2); however, the change in the tamsulosin group was not statistically significant compared to placebo (p=.186). Similar results were observed for the per-protocol population. Change for total IPSS from the beginning of placebo run-in (Visit 2) to endpoint, comparing the tamsulosin treatment group with placebo in the ITT and per-protocol populations show similar results for both populations (-6.6, -6.4 respectively for tamsulosin, -5.9, -5.9 respectively for placebo). In comparing subjects taking tadalafil versus those taking tamsulosin in total IPSS change from baseline after 12 weeks in the ITT population, the decrease from baseline in LS mean was numerically greater in the tadalafil group (-5.8) than in the tamsulosin group (-5.4), but the difference between the 2 groups was not statistically significant (p=.682). Similar results were observed in the per-protocol population. Repeated measures analysis of total IPSS at Weeks 4, 8, and 12 for the ITT population reveal LS mean changes similar in the tadalafil and tamsulosin treatment groups, both of which demonstrated numerically greater but non-statistically significant decreases when compared to placebo at any timepoint. Similar results were observed for the per-protocol population. Repeated measures results for total IPSS change from beginning of placebo run-in (Visit 2) to endpoint comparing the tadalafil and tamsulosin treatment groups with placebo in the ITT and per-protocol populations, respectively, reveal results of the analyses of similar changes from baseline (Visit 3) for both populations. The Patient Global Impression of Improvement did not show statistically significant differences in the tadalafil (p=0.176) or tamsulosin (p=0.921) treatment groups compared to placebo at the end of the study.

Changes in uroflowmetry were not significantly changed at endpoint compared to baseline as compared to placebo for either tadalafil or tamsulosin.

> *Reviewer's Efficacy Analysis: Tamsulosin at 0.2 mg a day is an approved treatment for men in Korea for LUTS (lower tract urinary symptoms). This study may be underpowered to detect a clinically significant treatment effect for either of the two active treatments (tadalafil or tamsulosin). The placebo response was a decrease of 4.2 in total IPSS which was larger than seen in the US pivotal studies (e. g. LVHG, -2.3). I recognize this is a non-IND pilot study and will not be applied to efficacy considerations for this NDA.*

A brief review of safety was conducted. During the treatment period, 7 (13.7%) of the tadalafil-treated subjects, 13 (26.5%) of the tamsulosin-treated subjects, and 2 (3.9%) of the placebo-treated subjects reported experiencing at least 1 treatment-emergent adverse event. There were no deaths in the study. Two subjects each in the tadalafil (3.9% [metastatic lung carcinoma,

back pain from lumbar spinal stenosis]) and tamsulosin (4.1%) treatment groups reported serious adverse events during the treatment period; no placebo-treated subjects reported serious adverse events. Two subjects (3.9%) in the tadalafil treatment group and 1 subject (2.0%) in the tamsulosin treatment group discontinued due to an adverse event during the treatment period.

The most commonly reported treatment-emergent adverse event in the tadalafil treatment group was myalgia (3 [5.9%]); compared to 1 ([2.0%]) in the tamsulosin group and none in the placebo group). In the tadalafil treatment group, flushing, headache, intentional overdose, lumbar spinal stenosis, metastatic lung adenocarcinoma, nasopharyngitis, pleural effusion, and pruritis were each reported by 1 (2%) subject; there were no treatment-emergent reports of dyspepsia or back pain.

No clinically adverse changes were observed in laboratory values, urinalysis parameters, vital signs, ECG abnormalities, ECG intervals, or PVR with tadalafil or tamsulosin.

> *Reviewer's Comment: The safety findings for tadalafil were comparable to those in other studies of once daily treatment in men with benign prostatic hyperplasia (BPH). No new trends or concerns were identified*.

Study LVHB: A Phase 3, Randomized, Double-Blind, Placebo and Tamsulosin Controlled, Parallel Design, Multinational Study to Evaluate the Efficacy and Safety of Tadalafil Once a day Dosing for 12 weeks in Asian Men with Signs and Symptoms of Benign Prostatic Hyperplasia.

Study LVHB is a non-IND Phase 3 foreign study and will be considered in brief.

Study LVHB was a Phase 3, randomized, placebo-controlled, four group (including one active-control arm-tamsulosin 0.2 mg daily) comparison study in Asian men in Japan, Republic of Korea, and Taiwan. The primary objective of Study LVHB was to compare the IPSS total score change of tadalafil 5 mg from baseline at Week 12 versus placebo in Asian men with signs and symptoms of BPH.

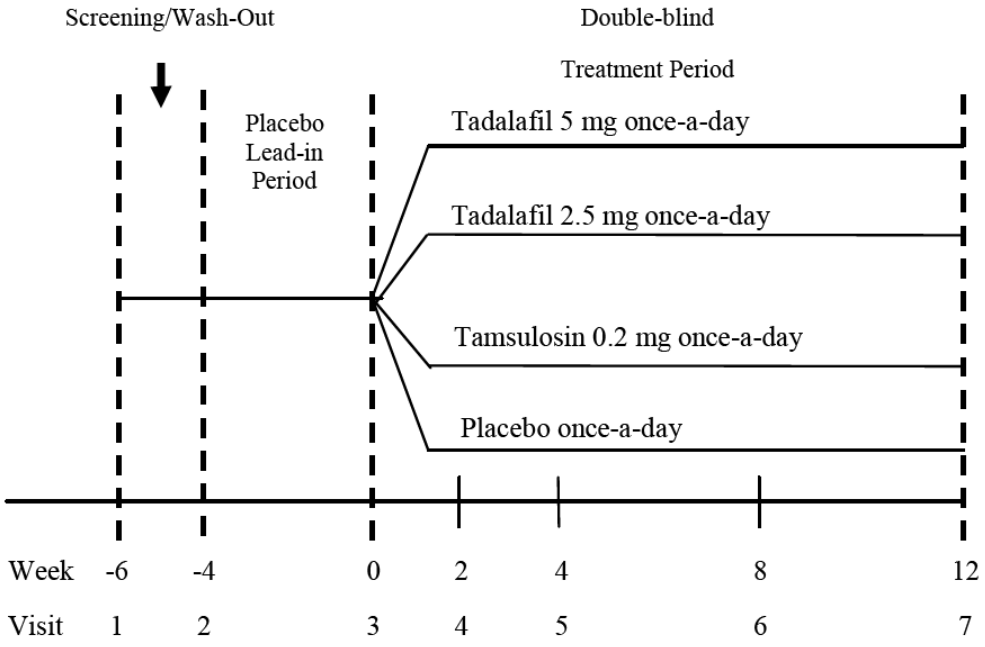
The secondary objectives were as follows:

- To compare the IPSS total score changes of tadalafil 5 mg QD from baseline at Weeks 2, 4, and 8 versus placebo and IPSS subscore (storage and voiding) changes at Weeks 2, 4, 8, and 12.
- To compare the IPSS total score and IPSS subscore (storage and voiding) changes of tadalafil 2.5 mg QD from baseline at Weeks 2, 4, 8, and 12 versus placebo.
- To compare the following measure change from baseline of tadalafil 2.5 and 5 mg QD versus placebo for 12 weeks: IPSS QoL, BPH Impact Index (BII) and peak flow rate (Qmax).

- To compare the Patient Global Impression of Improvement (PGI-I) and Clinician Global Impression of Improvement (CGI-I) scores of tadalafil 2.5 and 5 mg QD versus placebo at Week 12.
- To evaluate treatment differences in change from baseline between tadalafil 2.5 and 5 mg QD and tamsulosin HCl 0.2 mg QD in the IPSS total score, IPSS subscores, IPSS QoL, BII and Qmax at Week 12.
- To assess the safety of tadalafil 2.5 and 5 mg QD and tamsulosin HCl 0.2 mg QD as examined by the following measures: adverse events, vital signs, clinical laboratory tests, prostate specific antigen (PSA), and postvoid residual volume (PVR) for 12 weeks.

Study LVHB enrolled Asian subjects ≥45 years old with BPH (as diagnosed by a qualified physician) for >6 months at screening. Subjects had an IPSS total score of ≥13 and Qmax ≥4 and ≤15 mL/sec at the start of the placebo lead in period. After screening, all eligible subjects entered a 4-week, single-blind, once-daily lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period. At the beginning of the treatment period, eligible subjects were randomly assigned on a 1:1:1:1 ratio to one of four treatment groups: placebo, tadalafil 2.5 mg, tadalafil 5 mg, and tamsulosin 0.2 mg once daily for 12 weeks. Approximately 560 subjects (140 per treatment group) were to be randomized. 612 patients were randomized with the number of subjects in each treatment group as follows: placebo, N=154; tadalafil 2.5 mg, N=151; tadalafil 5 mg, N=155; and tamsulosin 0.2 mg, N=152. 561 subjects (91.7%) completed the study; 51 subjects (8.3%) discontinued early.

Figure 2: LVHB Study Design



Source: Figure LVHB.9.1, H6D-MC-LVHB Clinical Study Report, page 32

The primary objective was to compare the IPSS total score change from baseline for tadalafil 5 mg QD versus placebo in Asian men with signs and symptoms of BPH.

98.7% of all randomized of all randomized subjects were at least 70% compliant. All efficacy analyses were performed on an ITT basis.

Overall, 33.0% of all randomized subjects were between 65 to 75 years of age, and 6.5% were at least 75 years of age or older. The majority of subjects (55.9%) were from Japan. One-third of subjects (33.3%) were categorized as having severe BPH (IPSS $\geq$ 20) with the remainder (66.7%) having a total IPSS <20 at randomization (Visit 3). Mean duration of having BPH was 3.7 years. At screening, 54.7% of all randomized subjects had α-blocker therapy within 12 months of Visit 1, and 19.4% had taken other BPH therapy.

The primary efficacy outcome measure was the differences in mean change in total IPSS from baseline (Visit 3, Week 0) to endpoint (Visit 7, Week 12) for subjects taking tadalafil 5 mg once daily versus placebo. The primary efficacy measure was analyzed using an ANCOVA model with LOCF data imputation methodology to compare tadalafil 5 mg to placebo. The LS mean changes from baseline to endpoint were -3.0 for the placebo group and -4.7 for the tadalafil 5 mg. The LS mean difference of these changes (-1.7) was statistically significant for the tadalafil 5 mg treatment group compared with the placebo (p=.004, 95%CI -2.9 to -0.6). As for the tadalafil 2.5 mg group, the LS mean change from baseline to endpoint was -4.8. The LS mean differences (-1.8) was statistically significant for the tadalafil 2.5 mg treatment group compared with the placebo (tadalafil 2.5 mg, p=.003, 95%CI -3.0 to -0.6).

Table 66: Total IPSS Change from Baseline to Endpoint-Full Analysis Dataset Study LVHB

Treatment Group	Time Point	n	Mean (SD)	p-value
Placebo				
(N=154)	Baseline	154	16.8 (6.1)	
	Endpoint	154	13.6 (7.0)	
	Change	154	-3.1 (5.6)	
Tadalafil 2.5 mg	Baseline	151	16.6 (6.5)	0.003
N=151	Endpoint	151	11.7 (6.6)	
	Change	151	-4.9 (5.0)	
Tadalafil 5 mg	Baseline	154	17.2 (6.0)	0.004
N=155	Endpoint	154	12.2 (7.1)	
	Change	154	-5.0 (5.9)	
Tamsulosin	Baseline	152	16.6 (6.4)	<.001
0.2 mg	Endpoint	152	11.0 (6.2)	
N=152	Change	152	-5.6 (5.8)	

Source: Table LVHB.11.6, H6D-MC-LVHB Clinical Study Report, page 80.

With respect to secondary efficacy analysis, there were statistically significant LS mean differences in the changes from baseline to Weeks 2, 4, 8, and 12 for the tadalafil 5 mg group compared with placebo (p=.007 [95%CI -2.2 to -0.3], p<.001 [95%CI -2.9 to -0.8], p=.002 [95%CI -2.9 to -0.6], and p=.001 [95%CI -3.2 to -0.8], respectively), while statistically significant differences in the changes to Weeks 8 and 12 for tadalafil 2.5 mg group compared with placebo (p=.015 [95%CI -2.6 to -0.3] and p=.002 [95%CI -3.2 to -0.7], respectively). Analysis of the total IPSS change from baseline (Visit 3) to endpoint using ANCOVA with effects for treatment, α-blocker, investigator (site), and baseline IPSS value produced results consistent with the primary analysis. The LS mean changes from baseline to endpoint were -3.2 for the placebo group, -4.9 for the tadalafil 2.5 mg and -4.9 for the tadalafil 5 mg. The LS mean differences of these changes (tadalafil 2.5 mg, -1.7; tadalafil 5 mg, -1.7) were statistically significant for the tadalafil 2.5 mg and 5 mg treatment groups compared with the placebo (p=.005 [95%CI -2.9 to -0.5] and p=.005 [95%CI -2.9 to -0.5], respectively).

For secondary measures, once daily dosing of tadalafil 5 mg, but not 2.5 mg appeared to demonstrate a statistically significant improvement in the IPSS irritative (storage) subscore after 12 weeks of treatment compared with placebo. Once daily dosing of tadalafil 2.5 mg and 5 mg did not appear to result in a statistically significant change in the BII score after 12 weeks of treatment compared to placebo.

The LS mean changes from baseline to endpoint for IPSS QoL score were -0.5 for the placebo group, -0.8 for the tadalafil 2.5 mg and -0.8 for the tadalafil 5 mg. The LS mean differences of these changes (tadalafil 2.5 mg, -0.3; tadalafil 5 mg, -0.3) were statistically significant for the tadalafil 2.5 mg and 5 mg treatment groups compared with the placebo (p=.031 [95%CI -0.6 to -0.0] and p=.013 [95%CI -0.6 to -0.1], respectively).

> *Reviewer's Comment: This adequately powered phase 3 study does demonstrate efficacy in Asian men of once a day tadalafil for reducing BPH symptoms compared to placebo. The use of an active comparator also affirms that the metrics utilized are appropriate. The p-value for analysis by country was 0.335, suggesting no effect related to specific country. In addition the Sponsor conducted an additional analysis to identify the site effect by exchanging country with site in the statistical model. The results were consistent with the primary analysis (Table LVHB, 14.11). The secondary efficacy measures largely support the primary efficacy analysis.*

Regarding safety during the double-blind treatment period, 24 subjects (15.6%) reported at least 1 TEAE in the placebo group; 42 subjects (27.8%) in the tadalafil 2.5 mg group; 42 subjects (27.1%) in the tadalafil 5 mg group; and 35 subjects (23.0%) in the tamsulosin HCl 0.2 mg group. Ten subjects (6.5%) reported AEs which the investigator indicated as being treatment-related in the placebo group; 16 subjects (10.6%) in the tadalafil 2.5 mg group; 21 subjects (13.5%) in the tadalafil 5 mg group; and 12 subjects (7.9%) in the tamsulosin HCl 0.2 mg group. One severe TEAE was reported in placebo; 3 in tadalafil 2.5 mg; and 1 in tadalafil 5 mg groups. No severe TEAE was observed in tamsulosin HCl 0.2 mg group. A total of 5 SAEs were reported in the double-blind treatment period: 1 in the placebo and 4 in the tadalafil 2.5 mg groups. No death was reported. Fifteen subjects discontinued the study due to AEs: 1 (0.6%) in the placebo group; 5 (3.3%) in the tadalafil 2.5 mg, 7 (4.5%) in the tadalafil 5 mg and 2 (1.3%) in the tamsulosin HCl 0.2 mg groups. One subject had an SAE identified within 30 days of the last treatment.

Table 67: Overview Adverse Events Treatment Period Study LVHB

Adverse Events	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg	Tamsulosin 0.2 mg
	N=154	N=151	N=155	N=152
	n (%)			
Subject >= 1 TEAE	40(26.0)	49(32.5)	53(34.2)	42(27.6)
Adverse Event (AE)	24(15.6)	42(27.8)	42(27.1)	35(23.0)
Serious Adverse Event	1(0.6)	4(2.6)	0(0.0)	0(0.0)
Death	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AE Leading to Discontinuation	1(0.6)	5(3.3)	7(4.5)	2(1.3)

Source: Table LVHB 12.2, LVHB Study Report, page 121.

The four SAEs in the tadalafil 2.5 mg group were: metastatic colon cancer, hospitalization due to injury not otherwise specified, hospitalization due to hypertension (pre-existing hypertension), and hospitalization for lumbar spinal stenosis. The one SAE in a placebo patient was stage IV lymphoma.

At total of 15 subjects discontinued due to an adverse event. The adverse events in the tadalafil 2.5 mg group were: injury NOS (also an SAE), myalgia (muscular weakness), orthostatic hypotension, colon cancer and lumbar spinal stenosis. The adverse events in the tadalafil 5 mg group were: blood creatine phosphokinase increased, myalgia (3), calculus ureteric, angina pectoris, and liver injury. In the tamsulosin HCl 0.2 mg group there were two discontinuations secondary to adverse events: arrhythmia and hepatitis A.

The TEAEs with incidence ≥ 2% in any treatment group were: myalgia (placebo, 0.0%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 3.9%; tamsulosin HCl 0.2 mg, 0.0%), headache (placebo, 0.6%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 1.9%; tamsulosin HCl 0.2 mg, 0.7%), back pain (placebo, 0.6%; tadalafil 2.5 mg, 0.7%; tadalafil 5 mg, 2.6%; tamsulosin HCl 0.2 mg, 0.7%), nasopharyngitis (placebo, 1.9%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 1.3%; tamsulosin HCl 0.2 mg, 0.7%), and dizziness (placebo, 0.0%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 0.0%; tamsulosin HCl 0.2 mg, 1.3%). For myalgia, there was statistically significant difference in the tadalafil 5 mg (p=.030) group compared with placebo.

Three subjects noted fatigue (1 placebo, 1 tadalafil 2.5 mg and 1 tamsulosin). 2 subjects had orthostatic hypotension, 1 subject was in the tadalafil 2.5 mg group, and 1 subject was in the tamsulosin HCl 0.2 mg. A total of 8 subjects had headache during the double-blind treatment period: 1 in the placebo group; 3 in the tadalafil 2.5 mg; 3 in the tadalafil 5 mg; and 1 in the tamsulosin HCl 0.2 mg groups. None of these subjects reported additional events possibly related to hypotension except for 1 subject. Subject 180-1807 had fatigue with headache. Both headache and fatigue had onset 29 days after randomization and both symptoms stopped 33 days after randomization.

A total of 6 subjects experienced at least one TEAE which was possibly related to cardiovascular disorders: palpitations, n=3; chest pain, n=2; and arrhythmia, n=1. Of 6 subjects, 2 subjects

were in the tadalafil groups (palpitations, tadalafil 2.5 mg; palpitations, tadalafil 5 mg); 1 subject in the placebo (palpitations); and 3 subjects in the tamsulosin HCl 0.2 mg (chest pain [2], arrhythmia).

No tadalafil subject experienced urinary retention. There were no clinically significant increases in post void residual in any treatment group.

With respect to clinical laboratory results, a total of 12 subjects shifted from normal at baseline to low at endpoint for platelet count: 2 subjects in placebo; 2 in tadalafil 2.5 mg; 4 in tadalafil 5 mg; and 4 in the tamsulosin 0.2 mg groups. The range of the low platelet counts was 104 to $129x10^3\mu/L$ (reference range 130-394 $x10^3\mu/L$). No subjects met Hy's rule (defined as ALT ≥ 3-fold ULN and bilirubin levels ≥ 2-fold ULN). A total of 16 subjects shifted normal at baseline to high at end of therapy for AST: 8 subjects in the placebo; 2 in the tadalafil 2.5 mg; 2 in the tadalafil 5 mg; and 4 the in tamsulosin HCl 0.2 mg. For ALT, 17 subjects shifted normal at baseline to high at the end of therapy: 7 subjects in the placebo; 3 in the tadalafil 2.5 mg; 1 in the tadalafil 5 mg; and 6 in the tamsulosin HCl 0.2 mg.

Although statistically significant changes were seen in the tadalafil 2.5 mg group, there were no clinically significant mean changes for sitting and standing systolic blood pressure, sitting and standing diastolic blood pressure and sitting heart rate in all treatment groups.

> *Reviewer's Comment: The safety findings for tadalafil once daily treatment are comparable to other non-Japanese studies as well as to phase 2 Study LVIA. No new safety concerns are identified.*

6 Review of Efficacy

6.0 Efficacy Summary

The primary efficacy measure in the pivotal BPH analysis set (Study LVHG and Study LVHJ) was the change from baseline to endpoint as compared to placebo. Treatment with tadalafil 5 mg in the pivotal BPH analysis set resulted in statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -2.3; p<.001). In the additional analysis set of all BPH patients the IPSS change from baseline to endpoint compared to placebo was the same (mean difference: -2.3; p<.001). Treatment with tadalafil 5 mg in the additional BPH analysis set of subjects without ED resulted in a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -1.8, p=.021). Consistent with pivotal BPH analysis set results, treatment

with tadalafil 5 mg statistically significantly improved total IPSS change from baseline to endpoint compared to placebo in Study LVHG and Study LVHJ (p<.001[-2.6] and p=.004 [-1.9]), respectively.

In the pivotal BPH/ED analysis set, the prespecified alpha level for evaluating the statistical significance of the change from baseline to endpoint for the two co-primary endpoints(IPSS and IIEF EF Domain) in Study LVHR for each dose of tadalafil (2.5 and 5 mg) was p=.027, established by the gatekeeping procedure. There was a statistically significant difference in mean change from baseline to endpoint in total IPSS for the tadalafil 5 mg group compared to placebo (p<.001;-2.3). Treatment with tadalafil 2.5 mg did not result in a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -0.8).

Treatment with tadalafil 5 mg and 2.5 mg in Study LVHR resulted in a statistically significant improvement in IIEF EF Domain score from baseline to endpoint compared to placebo (mean difference tadalafil 5 mg: 4.7; mean difference tadalafil 2.5 mg: 3.4, both p<.001). Treatment with tadalafil 5 mg in Study LVHR resulted in a statistically significant improvement in the Total IPSS score from baseline to endpoint compared to placebo (mean difference tadalafil 5 mg: -2.3, p<.001). Treatment with tadalafil 2.5 mg in Study LVHR did not result in a statistically significant improvement in the Total IPSS score from baseline to endpoint compared to placebo (mean difference tadalafil 2.5 mg: -0.8, p<.181).

(b) (4)

The tadalafil 5 mg dose successfully met the criteria for statistical significance for SEP Q3 as a secondary endpoint for patients with BPH/ED in Study LVHR. This endpoint was the mean difference in changes in the percentage of "Yes" responses to SEP Q3 tadalafil 5 mg versus placebo (mean difference: 19.7%, p<.001).

In the one year open-label extension of LVHG in which all subjects received tadalafil 5 mg daily. efficacy was maintained over the course of the study period as assessed by the IPSS and IIEF-EF Domain.

For the pivotal BPH analysis set, there was no significant treatment-by-subgroup interaction observed for change in total IPSS with respect to age or severity of symptoms. Treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS regardless of ED status. Treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS for subjects regardless of previous alpha-blocker therapy. Treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS for subjects regardless of previous PDE5 therapy use.

In the pivotal BPH/ED analysis set, there was no significant treatment-by-subgroup interaction between age category, baseline IPSS, ED severity, previous alpha-blocker or PDE5 inhibitor therapy and change in total IPSS.

With respect to changes in the IIEF EF Domain in the pivotal BPH/ED analysis set, no significant interaction by subgroup was noted for age, baseline total IPSS, baseline total IIEF EF Domain score, previous alpha-blocker or PDE5 inhibitor therapy and changes in the IIEF EF Domain.

6.1 Indication

The proposed indications for the 2 sNDAs considered in this review are:

- NDA 21-368 SEI-20: Cialis is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).
- NDA 21-368 SEI-21: Cialis is indicated for the treatment of ED (erectile dysfunction) and the signs and symptoms of BPH (BPH/ED).

6.1.1 Methods

At the Pre-NDA meeting, April 13, 2010, the Division stated that submission of Studies LVHG, LVHJ, LVHR, LVHS, LVHK, LVHN, and LVIA would be acceptable to support a filing of a sNDA for the proposed indications. Studies LVHS (Phase 3), LVHK (Phase 2), and LVHN (Phase 2 PK) are primarily safety studies. LVIA is a Phase 2 non-IND Japanese study with an open-label safety extension that subjects could elect to continue in (until week 54) after completing the 12 week double-blind, placebo-controlled period of LVIA. LVHG also has a 52 week open-label safety extension in which subjects could elect to continue in after completing the 12 week double-blind, placebo-controlled period of LVHG.

Studies LVHG, LVHJ and LVHR are the pivotal Phase 3 studies for the two sNDAs considered in this submission and these studies will be the primary focus of this integrated efficacy review. In light of the BII being found by SEALD to be neither well defined nor reliable (not "validated"), it will not be included in the primary inferential analysis. In the pivotal BPH analysis set, the primary analysis will be changes in baseline to endpoint of the 12-week double-blind treatment period between placebo and tadalafil 5-mg treatment groups using ANCOVA with LOCF for missing data. Efficacy was evaluated in subgroups of subjects $\leq$ 65 years and >65 years and subjects <75 and $\geq$ 75 years. In addition, efficacy subgroup analyses by prior alpha blocker therapy, by prior PDE inhibitor therapy, and by Asian versus non-Asian were conducted.

With respect to the BPH/ED indication, the co-primary inferential analyses in Study LVHR compare the mean differences between the tadalafil 5-mg and placebo treatment groups and between the tadalafil 2.5-mg and placebo treatment groups in change from baseline to endpoint

of the 12-week double-blind treatment period in total IPSS and in IIEF EF Domain score. As presented for the BPH indication, exploratory subgroup analyses of IPSS are provided for the pivotal BPH/ED analysis set. For the BPH/ED indication, similar subgroup analyses are provided for IIEF EF Domain score also. Changes in these variables from baseline to endpoint of the 12-week double-blind treatment period are summarized for the following subgroups: age (≤ 65 year and >65 years; <75 years and ≥ 75 years), baseline LUTS severity (IPSS <20; IPSS ≥ 20), baseline ED severity (mild; moderate; severe), previous alpha-blocker usage, and previous PDE5-inhibitor usage.

An analysis of efficacy (for BPH) will be conducted in patients with BPH alone and in patients with BPH and associated ED.

6.1.2 Demographics

Pivotal BPH Analysis Set

The mean age of subjects at study entry for the pivotal BPH analysis set was 63.2 years. The mean age at study entry was similar among the pivotal BPH analysis set, Study LVHG, Study LVHJ, and the LVHG open-label extension.

Table 68: Age Category at Study Entry Pivotal BPH Studies LVHG and LVHJ

		Placebo Controlled		OL Extension
		Placebo	Tadalafil 5 mg	Tadalafil 5 mg
		N=376	N=373	N=428
	Protocol	n (%)		
Total	LVHG	212	212	428
	LVHJ	164	161	
	Integrated	376	373	
<= 65 years	LVHG	137 (64.6)	137 (64.6)	267 (62.4)
	LVHJ	86 (52.4)	86 (53.4)	
	Integrated	223 (59.3)	223 (59.8)	
> 65 years	LVHG	75 (35.4)	75 (35.4)	161 (37.6)
	LVHJ	78 (47.6)	75 (35.4)	
	Integrated	153 (40.7)	150 (40.2)	
< 75 years	LVHG	200 (94.3)	192 (09.6)	387 (90.4)
	LVHJ	129 (78.7)	131 (81.4)	
	Integrated	329 (87.5)	323 (86.6)	
>= 75 years	LVHG	12 (5.7)	20 (9.4)	41 (9.6)
	LVHJ	35 (21.3)	30 (18.6)	
	Integrated	47 (12.5)	50 (13.4)	

Source: Table 2.7.3.8, Summary of Clinical Efficacy, Current Submission, page 51

Overall Study LVHG had a higher percentage of subjects ≥ 75 years of age than Study LVHG (at the Division's request). Within Study LVHG and LVHJ, the percentages of subjects within each age category were similar between treatment groups. The race of all randomized subjects in the integrated population was Asian 0.4 %, Black 2.4%, White 87.4%, Other 7.2% (includes Hispanic in LVHG), and Native American 2.3%. Overall Hispanic or Latino was 19.2%.

Mean body mass index (BMI) at study entry was 27.9 kg/m^2 for tadalafil 5-mg subjects and 28.5 kg/m2 for placebo subjects in the pivotal BPH analysis set. Mean BMI at study entry was similar for Study LVHG, Study LVHJ, and the LVHG open-label extension. The percentage of subjects reporting current tobacco use at study entry was <14% across treatment groups in the pivotal BPH analysis set and within Study LVHG, Study LVHJ, and the LVHG open-label extension.

The majority of subjects in the pivotal BPH analysis set had total IPSS <20 (mild-moderate 64.6%) at randomization versus ≥ 20 (severe 35.4%), and the percentages were similar among Study LVHG, Study LVHJ, and the LVHG open-label extension. Within the pivotal BPH

analysis set, Study LVHG, and Study LVHJ, the percentages of subjects within each baseline LUTS severity category were similar between treatment groups.

The majority of subjects (>67%) in the pivotal BPH analysis set reported ED. The percentage of subjects who reported ED was similar among Study LVHG, Study LVHJ, and the LVHG open-label extension. Within the pivotal BPH analysis set, Study LVHG, and Study LVHJ, the percentage of subjects who reported ED was similar between treatment groups. The range of subjects reporting ED was 67.9% to 69.6% in all categories. Greater than 75% of subjects reporting ED were sexually active with an adult female partner.

Less than 20% of subjects reported diabetes mellitus at study entry. Less than 52% of subjects in any treatment group reported cardiovascular disease at entry in the pivotal BPB analysis set. Hypertension was reported at study entry in <45% of subjects.

The percentage of subjects using previous alpha-blocker therapy were <33% in any treatment group and <35% for PDE5-inhibitor therapy within the pivotal BPH analysis set, Study LVHG, Study LVHJ, and the LVHG open-label extension, and they were similar between each study.

Baseline characteristics and demographics in the additional BPH analysis set of subjects without ED were similar to those in the pivotal BPH analysis set, with the exception of medical history. In the additional BPH analysis set of subjects without ED, a smaller proportion of subjects reported a history of diabetes (tadalafil 5 mg: 7.7%; placebo: 5.9%) than the subjects in the pivotal BPH analysis set (tadalafil 5 mg: 13.1%; placebo: 12.0%).

Pivotal BPH/ED Analysis Set

Subjects in Study LVHR had a mean age of 62.6 years, with a range from 45.3 to 83.2 years. The mean age at study entry was similar between the treatment groups. Overall, 9.2% of subjects were 75 years or older.

Table 69: Subject Age All Randomized Subjects Pivotal BPH/ED Study LVHR

	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg	Total
	N=200	N=198	N=208	N=606
Mean Age (years)	62.9	62.2	62.5	62.6
Age Category	n (%)			
<=65	123 (61.5)	132 (66.7)	125 (60.1)	380 (62.7)
>65	77 (38.5)	66 (33.3)	83 (39.9)	226 (37.3)
<75	177 (88.5)	186 (93.9)	187 (89.9)	550 (90.8)
>=75	23 (11.5)	12 (6.1)	21 (10.1)	56 (9.2)

Source: Table 2.7.3.23, Summary of Clinical Efficacy, Current Submission, page 71

The race of all randomized subjects in Study LVHR was White 93.2%, Black 3.8%, Asian 2.3%, Native American 0.2%, and other (subjects reporting multiple races) 0.5%. Hispanic or Latino subjects were 15.5%.

The mean body mass index in kg/m^2 was 28.6 for placebo, 27.7 for tadalafil 2.5 mg, and 28.0 for tadalafil 5 mg. Tobacco use was reported in 15% of placebo subjects, 18.2% of tadalafil 2.5 mg subjects, and 12.5% of tadalafil 5 mg subjects.

Table 70: ED and BPH Severity All Randomized Subjects Study LVHR

	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
	N=200	N=198	N=208
Baseline LUTS Severity n (%)			
Moderate (IPSS <20)	122 (61.0)	123 (62.4)	124 (59.6)
Severe (IPSS>=20)	78 (39.0)	74 (37.6)	84 (40.4)
Erectile Dysfunction Severity n (%)			
Mild (IEFF EF Domain 17-30)	93 (46.5)	104 (52.5)	104 (52.5)
Moderate (IEFF EF Domain 11-16)	49 (24.5)	46 (23.2)	54 (26.0)
Severe (IEFF EF Domain 1-10)	58 (29.0)	48 (24.2)	55 (26.4)

Source: Tables 2.7.3.26 and 2.7.3.27, Summary of Clinical Efficacy, Current Submission, pages 74 and 75.

Approximately 14% of subjects in the pivotal BPH/ED analysis set had diabetes mellitus. The percentages of subjects with diabetes mellitus were similar between the treatment groups. 42.0-43.3% of subjects (based on study arm) in the pivotal BPH/ED analysis set had cardiovascular disease (including hypertension) at study entry; the percentages of subjects were similar between the treatment groups. 33.0-37.0 % of subjects (based on treatment arm) in the pivotal BPH/ED analysis set had hypertension at study entry; the percentages of subjects with hypertension were similar between the treatment groups. For all three categories, the placebo arm was always the lowest and the tadalafil 5 mg arm the highest.

The percentages of subjects previously using alpha-blocker therapy (20.2-26.9%) or PDE5-inhibitor therapy (24.2-28.0%) were similar between treatment groups in the pivotal BPH/ED analysis set.

The baseline characteristics and demographics of the additional BPH/ED analysis set of subjects with ED (those in Studies LVHG and LVHJ who had both BPH and ED) were similar to those of the pivotal BPH/ED analysis set.

Reviewer's Comment: Overall the baseline characteristics and demographics of the BPH and BPH/ED pivotal analysis sets and additional analysis sets are similar within dose groups and between studies.

BPH Subjects without ED

The mean age of subjects in the additional BPH analysis set of subjects without ED was 62.1 years for the tadalafil 5-mg treatment group and 60.0 years for the placebo treatment group. Both treatment groups were similar with respect to mean BMI and PSA at screening and total IPSS and Qmax at baseline.

The percentages of subjects reporting a history of diabetes mellitus, hypertension, and cardiovascular disease (including hypertension) in the additional BPH analysis set of subjects without ED were similar in both treatment groups (Table ISE.8). The majority of subjects had mild-moderate LUTS severity at baseline (tadalafil 5 mg: 64.1%; placebo: 66.4%).

Baseline characteristics and demographics in the additional BPH analysis set of subjects without ED were similar to those in the pivotal BPH analysis set, with the exception of medical history. In the additional BPH analysis set of subjects without ED, a smaller proportion of subjects reported a history of diabetes (tadalafil 5 mg: 7.7%; placebo: 5.9%) than the subjects in the pivotal BPH analysis set (tadalafil 5 mg: 13.1%; placebo: 12.0%).

6.1.3 Subject Disposition

BPH Indication

Pivotal BPH Analysis Set

In Studies LVHG and LVHJ, there were 373 subjects randomly assigned to tadalafil 5 mg once daily (N = 212, Study LVHG; N = 161, Study LVHJ) and 376 subjects assigned to placebo (N=212, Study LVHG; N = 164, Study LVHJ).

Table 71: Reason for Discontinuation BPH Pivotal Efficacy Data set

		Placebo Controlled		OL Extension
		Placebo	Tadalafil 5mg	Tadalafil 5mg
	Protocol	N=376	N=373	N=428
N	LVHG	212	212	428
	LVHJ	164	161	
	Integrated	376	373	
		n (%)		
Completed	LVHG	185(87.3)	182 (85.8)	299 (69.9)
	LVHJ	152 (92.7)	148 (91.9)	
	Integrated	337 (89.6)	330 (88.5)	
Discontinued	LVHG	26 (12.3)	30 (14.2)	129 (30.1)
	LVHJ	12 (7.3)	13 (8.1)	
	Integrated	38 (10.1)	43 (11.5)	
Reason for Discontinuation Integrated Results				
		Integrated Results		OL Extension
Abnormal PSA OLE LVHG		0 (0.0)	0 (0.0)	2 (0.5)
Adverse Event		6 (1.6)	15 (4.0)	22 (5.1)
Death		0 (0.0)	1 (0.3)	0 (0.0)
Entry Criteria not Met		3 (0.8)	11 (2.9)	0 (0.0)
Lack of Efficacy		1 (0.3)	3 (0.8)	15 (3.5)
Lost to Follow Up		8 (2.1)	0 (0.0)	16 (3.7)
Physician Decision		0 (0.0)	3 (0.8)	2 (0.5)
Protocol Violation		4 (1.1)	2 (0.5)	8 (1.9)
Sponsor Decision		3 (0.8)	0 (0.0)	4 (0.9)
Subject Decision		13 (3.5)	9 (2.4)	60 (14.0)

Source: Table 2.7.3.33, Summary of Clinical Efficacy, Current Submission, page 84.

It was noted in the Open-Label Extension of Study LVHG 60 subjects (14%) discontinued on the basis of subject decision. This was a greater percentage than discontinued for the same reason for the Open-Label extension for Study LVIA. On April 29, 2011, the Sponsor received a request for additional clarifying information concerning these patient's reasons for discontinuation, site locations, and any analysis they could provide. The response was received May 13, 2011. In their response the Sponsor made the following observations:

- Due to the electronic database set-up for Study LVHG, a data field did not exist for sites to enter additional details. For 11 patients, the Sponsor was able to identify CRF comments related to discontinuation: 5 subjects withdrew consent and/or refused to participate in the final visit, 3 subjects relocated, 1 subject was

out of the country, 1 subject stopped study drug and began taking Flomax, and 1 subject was unhappy with the results of the study drug.

- There was no apparent clustering of discontinuations due to subject decision at any investigative site.
- Discontinuations by visit were: Visit 8 (Week 16) 8, Visit 9 (Week 24) 18, Visit 10 (Week 38) 8, Visit 11 (Week 51) 19, and Visit 12 (Week 64) 7. Total equals 60.
- The counts and percents were generally similar across double-blind treatment group assignments (placebo: 13, tadalafil 2.5 mg: 13, tadalafil 5 mg: 15, tadalafil 10 mg: 10, tadalafil 20 mg: 8).
- The average age of all subjects enrolled in LVHG Open-Label Extension Study was 62.3 years of age. The average age of completers was 61.9 years of age. The average age of non-completers was 63.3 years of age, and the average age of subjects discontinuing due to 'Subject Decision was 64.8 years of age.
- The average Total IPSS all subjects enrolled in LVHG Open-Label Extension Study was 17.9. The average Total IPSS of completers was 17.9. The average Total IPSS of non-completers was 18.5 and the average Total IPSS of subjects discontinuing due to subject decision was 18.9. The total IPSS scores during the open-label extension did not appear to be related to treatment group assignment during the double-blind period.
- A plot of mean total IPSS over time showed that all non-completers and non completers due to subject decision had a higher mean IPSS at the beginning of the open-label extension and throughout their participation compared with all subjects and completers.
- The distribution of the severity of LUTS in subjects discontinuing due to subject decision was similar to all subjects in the study.
- The distribution of hypertension, diabetes and cardiovascular disease was similar to all subjects in the study.
- The percentage of subjects reporting at least 1 TEAE during the open-label extension of Study LVHG was 47.2% for all subjects, 48.2% for completers, 45.0% for non-completers (all subjects discontinuing early for any reason), and 38.3% (23) for subjects discontinuing early due to subject decision. Of the subjects discontinuing early due to subject decision and reporting at least 1 TEAE, only 2 MedDRA preferred terms were reported by more than 1 subject: arthralgia (3 subjects) and myalgia (3 subjects). Two of these 23 subjects reported SAEs during the open-label extension (one with non-cardiac chest pain and one with "cardiac arrest").

Reviewer's Comment: The details of the "cardiac arrest" case were generally inadequate for the reviewer to know what actually occurred with this event. Nonetheless, it is notable that the patient was discharged in good health 2 days after his "cardiac arrest", calling into question whether cardiac arrest actually occurred at all. While subject decision to discontinue may be associated with a higher baseline Total IPSS, the difference is too small for this reviewer to conclude that lack of efficacy was a factor.

The Sponsor's response is adequate to rule out any significant trend, concern, or safety signal.

In the additional BPH analysis set of all subjects, 88 % completed their respective study. Subject disposition of the additional BPH analysis set of all subjects was similar to that of the pivotal BPH analysis set. The percentages of subjects between treatment groups who completed their respective study were similar. The most common reason for discontinuation in the tadalafil 5 mg-treatment group was adverse event (n=21 [3.6%], N=576). The most common reason for discontinuation among subjects in the placebo treatment group was subject decision (n=21 [3.6%], N=581).

BPH/ED Indication

Pivotal BPH/ED Analysis Set

A total of 606 subjects were randomized to treatment in Study LVHR (pivotal BPH/ED analysis set; 198 to tadalafil 2.5 mg, 208 to tadalafil 5 mg, and 200 to placebo). The percentage of subjects completing Study LVHR was similar for tadalafil 2.5 mg, tadalafil 5 mg, and placebo (tadalafil 5 mg [88.5%], tadalafil 2.5 mg [86.9%], and placebo [85.0%].

Table 72: Subject Disposition Pivotal BPH/ED Study LVHR

	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
	N=200	N=198	N=208
	n (%)		
Randomized Population	200 (100.0)	198 (100.0)	208 (100.0)
Completed 12 weeks Double-Blind Treatment	170 (85.0)	172 (86.9)	184 (88.5)
Discontinued	30 (15.0)	26 (13.1)	24 (11.5)
Reason for Discontinuation			
Adverse Event	3 (1.5)	6 (2.9)	6 (2.9)
Death	0 (0.0)	1 (0.5)	0 (0.0)
Entry Criteria not Met	1 (0.5)	8 (4.0)	6 (2.9)
Lack of Efficacy	8 (4.0)	1 (0.5)	3 (1.4)
Lost to Follow Up	1 (0.5)	1 (0.5)	3 (1.4)
Physician Decision	1 (0.5)	0 (0.0)	0 (0.0)
Protocol Violation	6 (3.0)	6 (3.0)	2 (1.0)
Subject Decision	8 (4.0)	7 (3.5)	4 (1.9)

Source: Table 2.7.3.35, Summary Clinical Efficacy, Current Submission, page 89.

Additional BPH/ED analysis set of subjects with ED

The percentage of subjects in the additional BPH/ED analysis set of subjects with ED who completed the studies (88.5) was similar to that in the pivotal BPH/ED analysis set (86.8).

In the additional BPH/ED analysis set of subjects with ED, the most common reason for discontinuation in the placebo treatment groups (tadalafil 5 mg versus placebo; tadalafil 2.5 mg versus placebo) was subject decision. In the pivotal BPH/ED analysis set placebo group, the most common reasons were lack of efficacy and subject decision, reported for the same percentage of subjects.

In the additional BPH/ED analysis set of subjects with ED, the most common reason for discontinuation in the tadalafil 5-mg treatment group was adverse event. In the pivotal BPH/ED analysis set tadalafil 5-mg group, entry criteria not met and adverse event were reported as reasons for discontinuation by the same percentage of subjects.

In the additional BPH/ED analysis set of subjects with ED and the pivotal BPH/ED analysis set, the most common reason for discontinuation among subjects in the tadalafil 2.5-mg group was entry criteria not met.

Table 73: Subject Disposition Subjects with Erectile Dysfunction Integrated Studies LVHG and LVHR; Integrated Pivotal BPH and BPH/ED Studies (LVHG, LHVJ, and LVHR)

		Placebo	Tadalafil 2.5mg	Tadalafil 5mg
	Protocol	N=454	N=333	N=464
N	LVHG & LVHR	342	333	
	LVHG, LVHJ & LVHR	454	161	464
		n (%)		
Completed	LVHG & LVHR	297 (86.8)	289 (86.8)	
	LVHG, LVHJ & LVHR	404 (89.0)		414 (89.2)
Discontinued	LVHG & LVHR	45 (13.2)	44 (13.2)	
	LVHG, LVHJ & LVHR	50 (11.0)		50 (10.8)
Reason for Discontinuation Integrated Results				
Adverse Event	LVHG & LVHR	6 (1.8)	6 (1.8)	
	LVHG, LVHJ & LVHR	7 (1.5)		13 (2.8)
Death	LVHG & LVHR	0 (0.0)	1 (0.3)	
	LVHG, LVHJ & LVHR	0 (0.0)		1 (0.2)
Entry Criteria not Met	LVHG & LVHR	4 (1.2)	12 (3.6)	
	LVHG, LVHJ & LVHR	4 (0.9)		12 (2.6)
Lack of Efficacy	LVHG & LVHR	8 (2.3)	1 (0.3)	
	LVHG, LVHJ & LVHR	8 (1.8)		5 (1.1)
Lost to Follow Up	LVHG & LVHR	5 (1.5)	3 (0.9)	
	LVHG, LVHJ & LVHR	6 (1.3)		3 (0.6)
Physician Decision	LVHG & LVHR	1 (0.3)	1 (0.3)	
	LVHG, LVHJ & LVHR	1 (0.2)		2 (0.4)
Protocol Violation	LVHG & LVHR	7 (2.0)	6 (1.8)	
	LVHG, LVHJ & LVHR	9 (2.0)		3 (0.6)
Sponsor Decision	LVHG & LVHR	2 (0.6)	4 (1.2)	
	LVHG, LVHJ & LVHR	2 (0.4)		0 (0.0)
Subject Decision	LVHG & LVHR	12 (3.5)	11 (3.3)	
	LVHG, LVHJ & LVHR	13 (2.9)		12 (2.6)

Source: Table ISE 18, Integrated Summary of Efficacy, Current Submission, page 40.

Reviewer's Comment: Completion rates, common reasons for discontinuation, and distribution of reasons for discontinuation were similar between the additional BPH/ED analysis set of subjects with ED and the pivotal BPH/ED analysis set. There appear to be no significant differences between placebo and actively treated groups.

BPH Subjects without ED

Overall, 85.2% of the additional BPH analysis set of subjects without ED completed the double-blind treatment periods of Studies LVHG and LVHJ; the percentages of subjects who completed were similar between treatment groups for the integrated population (placebo; n=101 [84.9%] N=119: tadalafil 5 mg; n=100 [85.5%] =117).

The most common reason for discontinuation among subjects in the tadalafil 5-mg treatment group was adverse event n=8 (6.8%). The adverse event discontinuations for placebo were n=2 (1.7%). The most common reason for discontinuation among subjects in the placebo treatment group was subject decision (8 [6.7%] for placebo versus 1 [0.9%] for tadalafil 5 mg). Subject disposition of the additional BPH analysis set of subjects without ED was similar to that of the pivotal BPH analysis set.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy measure in the pivotal studies for BPH was change from baseline to endpoint (Week 12) in the total IPSS score.

Pivotal BPH Analysis Set

Baseline total IPSS values were similar between treatments within the pivotal BPH analysis set, Study LVHG, and Study LVHJ. Treatment with tadalafil 5 mg in the pivotal BPH analysis set resulted in a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (LS mean difference: -2.3; p<.001). Consistent with pivotal BPH analysis set results, treatment with tadalafil 5 mg statistically significantly improved total IPSS change from baseline to endpoint compared to placebo in Study LVHG and Study LVHJ (p<.001 and p=.004, respectively).

Treatment with tadalafil 5 mg once daily in the pivotal BPH analysis set also resulted in a statistically significant improvement in total IPSS change from baseline to Week 4 compared to placebo (mean difference: -2.0; p<.001; Table 2.7.3.39). Similarly, statistically significant improvement in total IPSS change from baseline to Week 8 for tadalafil 5 mg compared to placebo was observed (mean difference: -1.9; p<.001).

Table 74: Total IPSS Change from Baseline to Endpoint Primary Analysis Population Pivotal BPH Studies LVHG and LVHJ

Treatment	Timepoint	n	Mean	SD	p-value
LVHG					
Placebo	Baseline	205	17.1	6.36	
N=210	Endpoint	205	14.8	7.69	
	Change	205	-2.3	6.17	
Tadalafil 5mg	Baseline	205	17.3	5.97	
N=212	Endpoint	205	12.4	7.23	
	Change	205	-4.9	6.67	<.001
			LS mean Treatment Difference -2.6		
LVHJ					
Placebo	Baseline	164	16.6	5.99	
N=164	Endpoint	164	13.0	7.22	
	Change	164	-3.6	5.78	
Tadalafil 5mg	Baseline	160	17.1	6.06	
N=161	Endpoint	160	11.4	6.71	
	Change	160	-5.7	7.18	.004
			LS mean Treatment Difference -1.9		
Integrated					
Placebo	Baseline	369	16.9	6.19	
N=374	Endpoint	369	14.0	7.53	
LVHJ	Change	369	-2.8	6.03	
Integrated					
Tadalafil 5mg	Baseline	365	17.2	6.00	
N=373	Endpoint	365	11.9	7.02	
	Change	365	-5.3	6.38	<.001
			LS mean Treatment Difference -2.3		

Source: Table 2.7.3.38, Summary of Clinical Efficacy, Current submission, page 94.

Additional BPH Analysis of All Subjects

The additional BPH analysis set of all subjects comprised all subjects from Studies LVHG, LVHJ, and LVHR. The tadalafil 5-mg treatment group included 581 subjects and the placebo treatment group included 574 subjects in the Primary Analysis Population. Treatment with tadalafil 5 mg in the additional BPH analysis set of all subjects resulted in a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -2.3; p<.001). This improvement was identical to and consistent with the statistically significant improvement observed in the pivotal BPH analysis set (LS mean difference: -2.3; p<.001).

Table 75: Total IPSS Change From Baseline in the Double-Blind Period Primary Analysis Population Integrated Pivotal BPH and BPH/ED Studies LVHG, LVHJ and LVHR

Treatment	Timepoint	n	Mean	SD	LS Mean Δ
Placebo	Baseline	563	17.3	5.94	-3.3
N=574	Endpoint	563	14.1	7.14	
	Change	563	-3.2	5.94	
Tadalafil 5mg	Baseline	571	17.7	5.95	-5.7
N=581	Endpoint	571	12.0	6.87	
	Change	571	-5.7	6.46	P=<.001

Source: Table ISE.4, Integrated Summary of Efficacy, Current Submission, page 17

Additionally, in the MMRM (mixed model repeated measures) analysis, treatment with tadalafil 5 mg in the additional BPH analysis set of all subjects resulted in a statistically significant improvement in total IPSS compared to placebo overall (treatment effect: p<.001) and at Weeks 4, 8, and 12 (all p<.001). Results from the additional BPH analysis set of all subjects set were consistent with the pivotal BPH analysis set results by MMRM analysis (overall treatment effect and Weeks 4, 8, and 12: all p<.001.

BPH Analysis Set of Subjects without ED

Subjects in the additional BPH analysis set of subjects without ED were a subset of subjects from Studies LVHG and LVHJ, representing 31.5% (236/749) of the total number of subjects randomized in Studies LVHG and LVHJ. The tadalafil 5-mg treatment group included 117 subjects and the placebo treatment group included 119 subjects. There were a smaller proportion of subjects in the additional BPH analysis set of subjects without ED reporting a history of diabetes mellitus (tadalafil 5 mg: 7.7% and placebo: 5.9% versus tadalafil 5 mg: 13.1% and placebo: 12.0%, respectively.

Treatment with tadalafil 5 mg in the additional BPH analysis set of subjects without ED resulted in a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -1.8, p=.021; Table ISE.10). This change was consistent with the statistically significant improvement in total IPSS in the pivotal BPH analysis set (mean difference: -2.3, p<.001).

Table 76: Total IPSS Change from Baseline to Endpoint in the Double-Blind Treatment Period Subjects without ED in Primary Analysis Population Integrated Pivotal BPH Studies LVHG and LVHJ.

Treatment	Timepoint	n	Mean	SD	LS Mean Δ
Placebo	Baseline	115	16.4	6.26	-3.2
N=119	Endpoint	115	13.5	7.53	
	Change	115	-2.9	-3.0	
Tadalafil 5mg	Baseline	113	17.3	6.83	-5.0
N=117	Endpoint	113	12.3	12.0	
	Change	113	-5.0	6.24	P=<.021

Source: Table ISE.10, Integrated Summary of Efficacy, Current Submission, page 25

Additionally, in the MMRM analysis, treatment with tadalafil 5 mg in the additional BPH analysis set of subjects without ED resulted in a statistically significant improvement in total IPSS compared to placebo overall (treatment effect: p=.002) and at Week 4 (p=.010), Week 8 (p<.001), and Week 12 (p=.011). Results from the additional BPH analysis set of subjects without ED were consistent with the pivotal BPH analysis set results by MMRM analysis (overall treatment effect and at Weeks 4, 8, and 12: all p<.001.

> *Reviewer's Comment: The primary efficacy endpoint showed clinically meaningful and significant differences between placebo and tadalafil 5 mg dose groups in all BPH data analysis sets*.

BPH/ED Indication Effect on Total IPSS

The tadalafil 2.5 mg dose is not discussed in analysis as it did not achieve the primary efficacy end point for BPH.

Below is a portion of Table 40 from this review, which shows the co-primary outcomes in Study LVHR. The efficacy of the tadalafil 5 mg once daily dose is supported by achieving both co-primary efficacy endpoints.

Table 77: Co-Primary and Key Secondary Efficacy Outcomes - All Randomized Subjects in the Primary Analysis Population Study LVHR

Outcome	Placebo	Tadalafil 2.5 mg (N=198)			Tadalafil 5 mg (N=208)		
	N=200	n	Treatment Difference		n	Treatment Difference	
	n LS Mean	LS Mean	LS Mean (±SE)	p-value	LS Mean	LS Mean (±SE)	p-value
Co-primary							
Total IPSS	194 -3.8	191 -4.6	-0.8 (0.59)	.181	206 -6.1	-2.3 (0.58)	<.001
IIEF EF Domain	190 1.8	190 5.2	3.4 (0.67)	<.001	203 6.5	4.7 (0.66)	<.001

Using an MMRM analysis, treatment with tadalafil 5 mg in the additional BPH/ED analysis set of subjects with ED resulted in a statistically significant improvement in total IPSS compared to placebo overall and at Weeks 4, 8, and 12 (all p<.001; Table ISE.20).

These results from the additional BPH/ED analysis set of subjects with ED (tadalafil 5 mg) were consistent with the pivotal BPH/ED analysis set results by MMRM analysis (overall treatment effect and Weeks 4, 8, and 12: p<.001).

Table 78: Total IPSS Repeated Measures Analysis in the Double-Blind Period Subjects with ED in Primary Analysis Population Integrated Studies LVHG, LVHJ and LVHR Tadalafil 5 mg Once Daily

Integrated LVHG & LVHJ & LVHR	Treatment	Time	n	Mean	SD	LS Mean Δ	P value
	Placebo (N=453)	Point					
		Baseline	446	17.6	5.84		
		Week 4	434	15.1	6.74		
		Week 8	416	13.9	6.79		
		Week 12	405	14.1	7.09		
	Tadalafil 5 mg						
	(N=464)	Baseline	458	17.7	5.72		
		Week 4	448	12.7	6.34	-2.43	<.001
		Week 8	416	12.3	6.78	-1.78	<.001
		Week 12	412	11.7	6.65	-2.61	<.001

Source: Table ISE 20, Integrated Summary of Efficacy, Current Submission, page 46

With respect to the IIEF EF domain efficacy endpoint in the integrated pivotal additional analysis data set of all patients with ED in Studies LVHG, LVHJ and LVHR the results were as follows:

- For placebo: N=339. The LS mean change from baseline to endpoint (n=339) was 1.4 (16.4 to 17.8).
- For Tadalafil 5 mg: N=N=415. The LS mean change from baseline to endpoint (n=404) was 6.4 (15.7 to 22.4).

Reviewer's Comment: The co-primary efficacy endpoints for tadalafil 5 mg daily were achieved. The co-primary efficacy endpoints for tadalafil 2.5 mg daily were not achieved.

6.1.5 Analysis of Secondary Endpoints(s)

Study LVHG: The IPSS storage and voiding domains were significantly statistically improved. These domains, however, are not validated for the context of use. The BII was marginally significantly statistically improved and nocturia domain was not significantly statistically improved. The IIEF EF domain was favorably changed in a statistically significant manner showing dose effect across all doses except tadalafil 20 mg. The reader is referred to the review of Study LVHG in this NDA review for further detail.

In Study LVHJ, the key secondary analyses comparing the changes from baseline between tadalafil 5 mg and placebo were performed in a prespecified order.

1. The IIEF EF domain was significantly statistically improved.
2. The total IPSS after 4 weeks of treatment was not significantly statistically improved.
3. The BII after 12 weeks was not significantly statistically improved. The BII has been found to be not validated for the context of use.
4. The total modified IPSS (mIPSS) after 1 week of treatment was not significantly statistically improved.
5. The BII after 4 weeks of treatment was not significantly statistically improved. The BII has been found to be not validated for the context of use.

The reader is referred to the review of Study LVHJ in this NDA review for further details.

In Study LVHR, the Key Secondary variables , SEP Question 3 and the BII were both significantly statistically improved. The BII has been found to be not validated for the context of use. The reader is referred to the review of Study LVHJ in this NDA review for further details.

Reviewer's Comment: The IIEF EF domain and SEP Questions 3 results are appropriate to include in the drug labeling.

6.1.6 Other Endpoints

See Section 6.1.5; Analysis of Secondary Endpoints.

6.1.7 Subpopulations

Efficacy Results in Subpopulations

As tadalafil 5 mg once daily is the proposed dose for both indications (BPH and BPH/ED), the analysis of subgroups for tadalafil 2.5 mg will not be discussed.

BPH Indication

Age

Treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS for subjects regardless of age category (≤ 65 years, >65 years, <75 years, and ≥ 75 years). No significant treatment-by-subgroup interaction was observed between age category and change in total IPSS.

Table 79: Total IPSS by Age Change from Baseline to Endpoint in Double-Blind Period Primary Analysis Population Pivotal BPH Studies LVHG and LVHJ (integrated results)

Integrated Data	Parameter	Placebo (N=374)			Tadalafil 5 mg (N=373)		
<=65 years (N=445)		n	mean	SD	n	mean	SD
	Baseline	218	17.0	6.52	216	17.1	6.26
	Endpoint	218	13.7	7.48	216	11.8	7.26
	Change	218	-3.3	6.03	216	-5.3	6.66
>65 years (N=302)							
	Baseline	151	16.7	5.71	149	17.3	5.62
	Endpoint	151	14.5	7.59	149	12.2	6.67
	Change	151	-2.2	6.00	149	-5.2	5.97
<75 years (N=650)							
	Baseline	322	16.7	6.21	315	17.1	6.09
	Endpoint	322	14.0	7.59	315	11.7	6.94
	Change	322	-2.8	6.13	315	-5.4	6.25
>=75 years (N=97)							
	Baseline	47	17.7	6.02	50	17.9	5.42
	Endpoint	47	14.4	7.16	50	13.4	7.37
	Change	47	-3.4	5.30	50	-5.4	6.25

N=number of subjects in each subgroup; Integrated = Studies LVHG, LVHJ
Source: Tables APP 2.7.3.11 and APP 2.7.3.12, Summary of Clinical Efficacy Appendix, pages 30, 32.

IPSS Total Score Severity

Treatment with tadalafil 5 mg led to an improvement in total IPSS for subjects with mild-moderate LUTS (IPSS <20) and for those with severe LUTS (IPSS ≥ 20). For the pivotal BPH analysis set, no significant treatment-by-subgroup interaction was observed between LUTS severity category and change in total IPSS.

Table 80: Total IPSS Score by Baseline LUTS Severity Change from Baseline to Endpoint in the Double-Blind Period Primary Analysis Population Pivotal BPH Studies LVHG and LVHJ

Integrated Data	Parameter	Placebo (N=374)			Tadalafil 5 mg (N=373)		
IPSS <20 (N=488)		n	mean	SD	n	mean	SD
	Baseline	245	13.4	4.04	233	13.8	4.09
	Endpoint	245	11.3	6.25	233	9.7	5.44
	Change	245	-2.0	5.78	233	-4.0	5.44
IPSS >= 20 (N=259)							
	Baseline	124	23.7	3.25	132	23.3	3.40
	Endpoint	124	19.3	7.01	132	15.8	7.77
	Change	124	-4.4	6.22	132	-7.5	7.28

N=number of subjects in each subgroup; Integrated = Studies LVHG, LVHJ
Source: APP Table 2.7.3.13, Summary Clinical Efficacy Appendix, page 35

Previous Alpha-blocker Therapy

Treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS for subjects regardless of previous alpha-blocker therapy. In the pivotal BPH analysis set, no significant treatment-by-subgroup interaction was observed between previous alpha-blocker therapy and change in total IPSS.

Table 81: Total IPSS by Previous Alpha-Blocker Therapy Change from Baseline to Endpoint in the Double-Blind Period Primary Analysis Population Pivotal BPH Studies LVHG and LVHJ

Integrated Data	Parameter	Placebo (N=374)			Tadalafil 5 mg (N=373)		
Yes (N=488)		n	mean	SD	n	mean	SD
	Baseline	114	17.3	6.22	107	17.6	5.61
	Endpoint	114	15.6	7.91	107	12.1	6.84
	Change	114	-1.7	6.16	107	-5.4	6.77
No (N=259)							
	Baseline	255	16.7	6.18	258	17.1	6.16
	Endpoint	255	13.3	7.26	258	11.8	7.10
	Change	255	-3.4	5.91	258	-5.2	6.23

N=number of subjects in each subgroup; Integrated = Studies LVHG, LVHJ
Source: APP Table 2.7.3.15, Summary Clinical Efficacy Appendix, page 38

Previous PDE5 Inhibitor Use

Treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS for subjects regardless of previous PDE5 therapy use. No significant treatment-by subgroup interaction was observed between previous PDE5 therapy use and change in total IPSS.

Table 82: Total IPSS by Previous PDE5-Inhibitor Therapy Change From Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population Pivotal BPH Studies LVHG and LVHJ

Integrated Data	Parameter	Placebo (N=374)			Tadalafil 5 mg (N=373)		
Yes (N=184)		n	mean	SD	n	mean	SD
	Baseline	89	16.2	5.82	94	16.6	5.78
	Endpoint	89	13.0	7.34	94	10.9	6.67
	Change	89	-3.2	5.73	94	-5.7	6.29
No (N=563)							
	Baseline	280	17.1	6.30	271	17.4	6.08
	Endpoint	280	14.3	7.57	271	12.3	7.11
	Change	280	-2.7	6.13	271	-5.1	6.42

N=number of subjects in each subgroup; Integrated = Studies LVHG, LVHJ
Source: APP Table 2.7.3.15, Summary Clinical Efficacy Appendix, page 40

Reviewer's Comment: Regardless of age category, severity of lower urinary tract symptoms, erectile dysfunction severity, previous alpha-blocker therapy, and previous PDE5-inhibitor use, treatment with tadalafil 5 mg in the pivotal BPH analysis set led to an improvement in total IPSS for subjects. No significant treatment-by-subgroup interaction was observed for any of the above sub groups.

Subgroup Analysis - ED patients considering Co-Primary Endpoints of IPSS and IIEF EF domain

Age

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects regardless of age category (≤ 65 years and >65 years, <75 years and ≥ 75 years). No significant treatment-by subgroup interaction was observed between age category and change in total IPSS.

Table 83: Total IPSS Score by Age Change from Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population Pivotal BPH/ED Study LVHR

Study LVHR	Parameter	Placebo (N=200)			Tadalafil 5 mg (N=198)		
<=65 years (N=380)		n	mean	SD	n	mean	SD
	Baseline	118	18.4	5.80	127	19.1	6.08
	Endpoint	118	15.0	6.73	127	12.6	6.94
	Change	118	-3.4	5.58	127	-6.6	6.85
>65 years (N=226)							
	Baseline	76	18.0	4.51	83	17.4	5.18
	Endpoint	76	13.4	5.66	83	11.5	6.09
	Change	76	-4.6	5.71	83	-6.0	6.15
<75 years (N=550)							
	Baseline	171	18.3	5.49	185	18.7	5.84
	Endpoint	171	14.5	6.48	185	12.4	6.69
	Change	171	-3.8	5.78	185	-6.3	6.62
>=75 years (N=56)							
	Baseline	23	17.7	3.93	21	15.9	4.56
	Endpoint	23	13.0	5.36	21	9.6	5.46
	Change	23	-4.6	5.51	21	-6.3	6.29

N=number of subjects in each subgroup
Source: Table APP 2.7.3.18, Summary of Clinical Efficacy Appendix, pages 42, 43.

Severity of Lower Tract Symptoms

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects with mild-moderate LUTS (IPSS <20) of -4.6 for tadalafil 5 mg compared to -2.8 for placebo and in severe LUTS (IPSS ≥ 20) of -8.9 for tadalafil 5 mg compared to -5.6 for placebo (SCE Table APP.2.7.3.19). No significant treatment-by-subgroup interaction was observed between LUTS severity category and change in total IPSS.

Erectile Dysfunction Severity

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects regardless of ED severity. No significant treatment-by-subgroup interaction was observed between ED severity and change in total IPSS (SCE Table APP.2.7.3.20). In severe ED (IEFF EF 1-10), the changes in IPSS were -4.3 for placebo (n=55) compared to -7.6 for tadalafil (n=54) 5 mg. In moderate ED (IEFF EF 11-16), the changes in IPSS were -4.5 for placebo (n=48) compared to -6.8 for tadalafil 5 mg (n=53). In mild ED (IEFF EF 17-30), the changes in IPSS were -3.3 for placebo (n=91) compared to -5.4 for tadalafil 5 mg(n=99).

Previous Alpha Blocker Therapy

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects regardless of previous alpha-blocker therapy. No significant treatment-by subgroup interaction was observed between previous alpha-blocker therapy and change in total IPSS (SCE Table APP.2.7.3.21). In patients who had had previous alpha blocker therapy (N=142), the change in IPSS in the placebo subjects (n=45) was -3.8 as compared to the tadalafil 5 mg subjects (n=55) which was -6.1. In patients who had not had prior alpha-blocker therapy (N=464), the change in IPSS in the placebo subjects (n=149) was -3.9 as compared to the tadalafil 5 mg subjects (n=151) which was -6.4.

Previous PDE5-Inhibitor Use

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects regardless of previous PDE5 therapy use. No significant treatment-by subgroup interaction was observed between previous PDE5-inhibitor use and change in total IPSS (SCE Table APP.2.7.3.22). In those subjects having had previous PDE5 therapy (N=161), the change in IPSS for placebo (n=54) was -3.9 and for tadalafil 5 mg (n=56) the change was -6.4. In those subjects not having had previous PDE5 therapy (N=445), the change in IPSS for placebo (n=140) was -3.9 and for tadalafil 5 mg (n=150) the change was -6.3.

> *Reviewer's Comment: Regardless of age category, severity of lower urinary tract symptoms, erectile dysfunction severity, previous alpha-blocker therapy, and previous PDE5-inhibitor use, treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects. No significant treatment-by-subgroup interaction was observed for any of the above sub groups*.

BPH/ED Indication - Changes in IEFF EF Domain by Subgroup

As the tadalafil 2.5 mg dose did not meet the efficacy endpoint in BPH patients, it is not considered in this analysis.

Age

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in the IIEF EF Domain score for subjects regardless of age category (≤ 65 years and >65 years, Table APP.2.7.3.23; <75 years and ≥ 75 years). No significant treatment-by subgroup interaction was observed between age category and change in IIEF EF Domain score.

Table 84: IIEF EF Domain by Age Change from Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population Pivotal BPH/ED Study LVHR

Study LVHR	Parameter	Placebo (N=200)			Tadalafil 5 mg (N=208)		
<=65 years (N=380)		n	mean	SD	n	mean	SD
	Baseline	115	17.0	6.54	122	17.6	6.94
	Endpoint	115	18.8	8.29	122	23.7	7.00
	Change	115	1.8	7.25	122	6.1	7.43
>65 years (N=226)							
	Baseline	75	13.8	7.06	81	15.0	7.36
	Endpoint	75	15.8	8.98	81	21.7	8.36
	Change	75	2.0	6.75	81	6.7	6.97
<75 years (N=550)							
	Baseline	167	16.3	6.78	182	16.9	7.18
	Endpoint	167	18.4	8.39	182	23.1	7.55
	Change	167	2.1	7.04	182	6.2	7.20
>=75 years (N=56)							
	Baseline	23	11.4	6.47	21	13.6	6.89
	Endpoint	23	11.4	8.34	21	20.9	8.04
	Change	23	-0.0	6.90	21	7.3	7.66

N=number of subjects in each subgroup
Source: Tables APP 2.7.3.23 and 2.7.3.24, Summary of Clinical Efficacy Appendix, pages 48, 49.

Severity of Lower Urinary Tract Symptoms

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in the IIEF EF Domain score for subjects with mild-moderate LUTS (IPSS <20) and severe LUTS (IPSS ≥ 20). No significant treatment-by-subgroup interaction was observed between LUTS severity category and change in the IIEF EF Domain score.

Table 85: IIEF EF Domain by Baseline LUTS Severity Change from Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population Pivotal BPH/ED Study LVHR

Study LVHR	Parameter	Placebo (N=200)			Tadalafil 5 mg (N=208)		
IPSS <20 (N=369)		n	mean	SD	n	mean	SD
	Baseline	117	16.5	7.06	122	17.8	7.45
	Endpoint	117	17.6	8.92	122	23.2	7.68
	Change	117	1.2	6.75	122	5.4	6.89
IPSS >= 20 (N=236)							
	Baseline	73	14.6	6.55	81	14.6	6.41
	Endpoint	73	17.5	8.32	81	22.4	7.54
	Change	73	2.9	7.40	81	7.7	7.56

N=number of subjects in each subgroup; Integrated = Studies LVHG, LVHJ
Source: APP Table 2.7.3.25, Summary Clinical Efficacy Appendix, page 49

Erectile Dysfunction Severity

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in the IIEF EF Domain score for subjects regardless of baseline ED severity. No significant treatment-by-subgroup interaction was observed between ED severity and change in the IIEF EF Domain score. However the Sponsor notes, the mean change from baseline in IIEF EF Domain score was greater for subjects who were classified as having moderate or severe ED at baseline than in those with mild ED at baseline.

Table 86: IEFF EF Domain by Baseline Severity Change from Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population Pivotal BPH/ED Study LVHR

Protocol LVHR	Parameter	Placebo (N=200)			Tadalafil 5 mg (N=208)		
		n	mean	SD	n	mean	SD
IIEF EF 17-30 (N=296)	Baseline	88	22.1	3.68	97	23.1	3.61
	Endpoint	88	22.4	6.90	97	26.2	4.61
	Change	88	0.3	6.71	97	3.1	4.73
IIEF EF 11-16 (N=149)	Baseline	48	13.5	1.73	53	13.6	1.66
	Endpoint	48	17.0	7.78	53	22.7	6.61
	Change	48	3.5	7.97	53	9.1	6.93
IIEF EF 1-10 (N=161)	Baseline	54	7.4	1.85	53	7.5	1.77
	Endpoint	54	10.4	6.72	53	17.1	9.35
	Change	54	2.9	6.22	53	9.5	8.75

N=number of subjects in each subgroup
Source: APP Table 2.7.3.26, Summary Clinical Efficacy Appendix, page 51

Previous Alpha-Blocker Therapy

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS for subjects regardless of previous alpha-blocker therapy. No significant treatment-by-subgroup interaction was observed between previous alpha-blocker therapy and change in total IPSS.

Table 87: Total IPSS Score by Previous Alpha-blocker Therapy Change from Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population Pivotal BPH/ED Study LVHR

Study LVHR	Parameter	Placebo (N=200)			Tadalafil 5 mg (N=208)		
Yes (N=142)		n	mean	SD	n	mean	SD
	Baseline	45	18.1	5.38	55	19.8	6.32
	Endpoint	45	14.3	7.03	55	13.7	6.48
	Change	45	-3.8	6.86	55	-6.1	6.27
No (N=464)							
	Baseline	149	18.3	5.33	151	18.0	5.51
	Endpoint	149	14.4	6.18	151	11.5	6.58
	Change	149	-3.9	5.34	151	-6.4	6.69

N=number of subjects in each subgroup
Source: APP Table 2.7.3.21, Summary Clinical Efficacy Appendix, page 46

Previous PDE5 Inhibitor Use

Treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in the IIEF EF Domain score for subjects regardless of previous PDE5 therapy use. No significant treatment-by-subgroup interaction was observed between previous PDE5-inhibitor use and change in the IIEF EF Domain.

Table 88: IIEF EF Domain by Previous PDE5-Inhibitor Therapy Change from Baseline to Endpoint in the Double-Blind Treatment Period Primary Analysis Population BPH/ED Study LVHR

Study LVHR	Parameter	Placebo (N=200)			Tadalafil 5 mg (N=208)		
Yes (N=161)		n	mean	SD	n	mean	SD
	Baseline	52	14.2	7.14	56	14.7	6.64
	Endpoint	52	15.9	8.81	56	21.6	8.47
	Change	52	1.8	8.23	56	6.9	8.23
No (N=445)							
	Baseline	138	16.3	6.76	147	17.3	7.30
	Endpoint	138	18.2	8.57	147	23.4	7.23
	Change	138	1.9	6.57	147	6.1	6.84

N=number of subjects in each subgroup
Source: APP Table 2.7.3.28, Summary Clinical Efficacy Appendix, page 53

Reviewer's Comment: Regardless of age category, severity of lower urinary tract symptoms, erectile dysfunction severity, previous alpha-blocker therapy, and previous PDE5-inhibitor use, treatment with tadalafil 5 mg in the pivotal BPH/ED analysis set led to an improvement in total IPSS and IIEF for subjects. No significant treatment-by-subgroup interaction was observed for any of the above sub groups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Treatment with tadalafil 5 mg dosed once daily demonstrated statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo in subjects with BPH-LUTS in Studies LVHG and LVHJ. Increasing the dose to tadalafil 10 mg daily resulted in a small increase in total IPSS as compared to tadalafil 5 mg once a day. There was no increased effect with tadalafil 20 mg. The LUTS-GAQ response assessing overall improvements in LUTS during therapy produced results showing statistically significant improvements in urinary symptoms in the tadalafil 5 mg, 10 mg and 20 mg groups but not in the tadalafil 2.5 mg group.

In Study LVHR, the tadalafil 2.5 mg dose failed to show statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo in subjects with BPH-LUTS and ED. In addition, in Study LVHR, tadalafil 5 mg but not tadalafil 2.5 mg showed statistically significant improvement in PGI-I and CGI-I both of which are global questions relating to clinical improvement of LUTS. With respect to the IIEF EF domain, clinically and statistically significant changes compatible with dose effect occurred across all doses except tadalafil 20 mg in Study LVHG.

Reviewer's Comment: Therefore, for both indications (BPH-LUTS and BPH-LUTS/ED), the efficacy data support tadalafil 5 mg once daily.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the 1 year safety extension of Study LVHG, the efficacy of tadalafil 2.5 mg and tadalafil 5 mg once daily for the treatment of men with BPH was maintained at 52 weeks. The tadalafil 2.5 mg once daily dose in Study LVHR, did not improve the IPSS in men with both ED and BPH in a statistically significant manner. Below are Tables 17 and 18 from this review (Study LVHG) which illustrate the persistence of efficacy for tadalafil 5 mg once daily in the treatment of men with BPH and men with BPH/ED.

Table 89: IPSS from Baseline to Endpoint LVHG Open-Label Extension

IPSS Total		Previous Double-Blind Therapy					
		Placebo N=91	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71	Total N=427
Visit 3	Week 0	n=91	n=95	n=83	n=85	n=71	n=425
IPSS Mean (SD)		17.5(5.7)	17.6(6.0)	18(6.2)	19(5.5)	17.7(6.2)	18.0(5.9)
Visit 6	Week 12	n=92	n=96	n=83	n=85	n=71	n=427
IPSS Mean (SD)		15.6(6.4)	14.5(6.4)	12.7(7.1)	13.6(7.3)	12.4(6.4)	13.9(6.8)
Endpoint	Week 64	n=89	n=95	n=82	n=81	n=69	n=416
IPSS Mean (SD)		13.4(7.1)	11.9(6.6)	13.0(7.8)	13.2(6.7)	13.1(7.5)	12.9(7.1)
Change From Visit 3 to Endpoint							
		n=89	n=95	n=82	n=81	n=69	n=416
IPSS Mean (SD)		-4.1(6.8)	-5.7(5.4)	-5.0(7.2)	-5.7(6.4)	-4.6(7.7)	-5.0(6.7)
Change From Visit 6 to Endpoint							
		n=89	n=95	n=82	n=81	n=69	n=416
IPSS Mean (SD)		-2.2(5.3)	-2.5(5.1)	0.2(5.4)	-0.2(5.8)	0.8(6.4)	-0.9(5.7)

IC=tadalafil Source: Table LVHG 11.7 H6D-MC-LVHG Abbreviated Study Report, page 642

Table 90: IEFF EF Domain Scores Open-Label Extension Period Sexually Active Patients with History of ED

International Index of Erectile Function EF Domain Score		Previous Double-Blind Therapy					
		Placebo N=51	IC 2.5 mg N=53	IC 5 mg N=47	IC 10 mg N=43	IC 20 mg N=41	Total N=235
Visit 3	Week 0	n=51	n=53	n=47	n=42	n=41	n=234
IIEF EF Mean (SD)		16.3(8.8)	16.3(9.0)	15.8(8.7)	15.9(8.5)	16.0(8.9)	16.1(8.7)
Visit 6	Week 12	n=51	n=52	n=47	n=42	n=41	n=233
IIEF EF Mean (SD)		16.6(8.9)	20.8(7.9)	21.1(9.2)	22.7(8.1)	23.3(8.4)	20.7(8.8)
Visit 8	Week 16	n=47	n=53	n=43	n=42	n=38	n=223
IIEF EF Mean (SD)		23.2(8.2)	22.4(7.4)	24.0(6.7)	21.7(8.2)	23.9(7.1)	23.0(7.5)
Endpoint	Week 64	n=40	n=39	n=32	n=31	n=28	n=170
IIEF EF Mean (SD)		24.6(6.3)	24.4(7.0)	22.1(9.5)	22.5(7.8)	25.6(5.7)	23.9(7.6)

Source: Table LVHG 11.21, H6D-MC-LVHG Abbreviated Study Report, page 669

Reviewer's Comment: In patients with BPH, the efficacy of tadalafil 5 mg once daily for the treatment of BPH and BPH/ED is maintained at 64 weeks.

6.1.10 Additional Efficacy Issues/Analyses

Non-IND Studies Conducted in Asian Countries

The percentages of subjects among treatment groups in the non-IND studies conducted in Asian countries analysis set were similar for LUTS severity (total IPSS), history of hypertension, diabetes mellitus, and cardiovascular disease, and previous alpha blocker therapy. The majority of subjects presented with mild-moderate LUTS severity. In comparison to baseline characteristics and demographics in the pivotal BPH analysis set, the Asian subjects in the non-IND studies conducted in Asian countries analysis set had a smaller mean BMI, less history of cardiovascular disease (including hypertension), and more often had previously been treated with alpha-blocker therapy. The baseline LUTS severity was lower (milder) in subjects in the non-IND studies conducted in Asian countries analysis set than in the pivotal BPH analysis set

With respect to the smaller Study LVIA and its open-label extension, in the primary efficacy analysis for the double-blind period, the tadalafil 5 mg group showed numerical improvement over placebo but no statistically significant change in IPSS total score from baseline to endpoint compared with placebo (-1.1 [95% CI = -2.2 to 0.1; p=0.062]; ANCOVA). The LS mean changes from baseline to endpoint were -3.8 in the placebo group and -4.9 in the tadalafil 5 mg group. The tadalafil 2.5 mg group also showed no statistically significant change compared with placebo (-0.7 [95% CI = -1.8 to 0.4; p=0.201]).

The Sponsor points out there are several factors to consider regarding the LVIA efficacy result. First in terms of IPSS change, the placebo group of Study LVIA averaged 1.6 points higher than those of Study LVHG (study LVIA, -3.8; study LVHG, -2.2). Second, Study LVIA had fewer subjects with severe BPH than study LVHG. Subjects who had severe BPH at baseline showed numerically greater change of IPSS total score than those with mild to moderate BPH (mild to moderate, - 4.0 [tadalafil 2.5 mg] and -3.8 [tadalafil 5 mg]; severe, -5.9 [tadalafil 2.5 mg] and -7.9 [tadalafil 5 mg]). In the post hoc analysis, subjects who had an IPSS total score of ≥ 13 at baseline (which is the usual inclusion criteria for U.S. BPH trials) showed a statistically significant change from baseline in IPSS total score for the tadalafil 5 mg treatment group compared with placebo. Third, site effect might be also one of the factors that affect the efficacy results considering that the efficacy endpoint was evaluated based on the improvement of subjective symptoms. In a post hoc analysis using an ANCOVA model that included site as one of the factors, site effect was calculated to be statistically significant ($p<0.01$).

In the Study LVIA open-label extension, subjects who were originally assigned to placebo or tadalafil 2.5 mg experienced improvement in mean total IPSS when switched to tadalafil 5mg in the open-label extension. The improvement that was observed during the double-blind period in those subjects assigned to tadalafil 5 mg persisted over the 42-week open-label extension. The mean total IPSS change from baseline of the double-blind treatment period to the end of the open-label extension treatment period comprising a total of 54 weeks with tadalafil 5 mg (-5.6±5.9; CSR LVIA Open-Label Extension Section 11.4.3.1) was similar to changes observed from baseline of the double-blind treatment period in Study LVHG to the end of the LVHG open-label extension comprising a total of 64 weeks.

Study LVHT was a small Korean protocol. In this study, once-a-day dosing of tadalafil 5 mg was numerically better than placebo, but this did not result in a statistically significant improvement of total IPSS score as compared to placebo at 12 weeks (tadalafil , -5.8; placebo, -4.2; p=.073). Notably, once-a-day dosing of tamsulosin 0.2 mg also did not result in a statistically significant improvement in total IPSS as compared to placebo (tamsulosin -5.4; placebo -4.2; p=.186).

> *Reviewer's Comment: Tamsulosin at 0.2 mg a day is an approved treatment for men in Korea for LUTS (lower tract urinary symptoms). However, it is a lower dose than that approved in the United States (0.4 mg daily). Study LVHT may be underpowered to detect a clinically significant treatment effect for either of the two active treatments (tadalafil or tamsulosin). The placebo response was a decrease of 4.2 in total IPSS which was larger than seen in the US pivotal studies (e. g. LVHG, -2.3). Both LVIA and LVHT were Phase 2 studies and appeared to have flaws. They studies are not of sufficient quality, in my opinion, to be used to form an opinion as to the efficacy of tadalafil 5 mg daily in treating men with BPH.*

In the Phase 3 Asian Study, LVHB, the primary efficacy outcome measure was the differences in mean change in total IPSS from baseline (Visit 3, Week 0) to endpoint (Visit 7, Week 12) for subjects taking tadalafil 5 mg once daily versus placebo. The primary efficacy measure was analyzed using an ANCOVA model with LOCF data imputation methodology to compare tadalafil 5 mg to placebo. The LS mean changes from baseline to endpoint were -3.0 for the

placebo group and -4.7 for the tadalafil 5 mg. The LS mean difference of these changes (-1.7) was statistically significant for the tadalafil 5 mg treatment group compared with the placebo (p=.004, 95% CI -2.9 to -0.6). As for the tadalafil 2.5 mg group, the LS mean change from baseline to endpoint was -4.8. The LS mean differences (-1.8) was statistically significant for the tadalafil 2.5 mg treatment group compared with the placebo (tadalafil 2.5 mg, p=.003, 95%CI -3.0 to -0.6).

> *Reviewer's Comment: This adequately powered phase 3 study does demonstrate efficacy in Asian men of once a day tadalafil for reducing BPH symptoms compared to placebo. The use of an active comparator also affirms that the metrics utilized are appropriate. The p-value for analysis by country was 0.335, suggesting no effect related to specific country. In addition the Sponsor conducted an additional analysis to identify the site effect by exchanging country with site in the statistical model. The results were consistent with the primary analysis. The secondary efficacy measures largely support the primary efficacy analysis.*
>
> *In my opinion, this is the only Asian study I consider credible upon which to base an efficacy decision regarding Asian subjects with BPH. The number of Asian men in Studies LVHG, LVHJ, and LVHR was quite small and insufficient to adequately support an efficacy in Asian men with BPH claim. At this time, I would not include any statement in the drug label citing either efficacy or lack thereof in Asian men with signs and symptoms of BPH.*

Efficacy Benefit of Adding Tadalafil to BPH Patients Taking Alpha-Blockers

While the Sponsor has stated that tadalafil as treatment for signs and symptoms of BPH is to be used only as monotherapy, Study LVHS assessed the safety of adding tadalafil to the BPH treatment regimen in patients taking alpha-blockers. As part of the study, the efficacy endpoints of change from baseline to endpoint in total IPSS, change in storage (irritative) symptoms, voiding (obstructive) symptoms, nocturia symptoms, and QoL were assessed. The LS mean change from baseline to endpoint in total IPSS was not significantly different (p = 0.13) for the tadalafil 5 mg treatment group (-2.20) compared with placebo (-1.33). Tadalafil 5 mg once daily did not result in statistically significant improvement in storage (irritative) symptoms, voiding (obstructive) symptoms, nocturia symptoms, or QoL when compared with placebo (all p>.169). A complete discussion of Study LVHS is present in this review for further detail.

A sensitivity analysis of total IPSS using an ANCOVA model, including effects for treatment and IPSS centered-baseline, as well as stratification factors for region, age group, and alpha blocker type provided results similar to those presented above.

Table 91: Total IPSS Symptom Score Double-Blind Period Primary Analysis Population Study LVHS

Treatment	Time Point	n	mean	SD	LS Mean Δ
Placebo (N=159)	Baseline	156	13.30	6.57	
	Endpoint	156	11.81	6.26	
	Change	156	-1.49	5.29	-1.33
Tadalafil 5 mg (N=158)	Baseline	156	13.87	7.15	
	Endpoint	156	11.60	6.69	
	Change	156	-2.28	5.65	-2.20
					p=0.130

Source: Table LVHS 11.10, LVHS Study Report, page 94

Reviewer's Comment: The addition of tadalafil 5 mg once daily as part of a treatment regimen for BPH in men already taking alpha-blockers adds no demonstrable clinical efficacy benefit in this study (LVHS).

7 Review of Safety

Safety Summary

The studies performed by the Sponsor for BPH and BPH/ED, and the additional data provided for subjects ≥75 years of age obtained from previous clinical studies for daily ED treatment and for PRN ED treatment, are adequate to assess the safety of tadalafil used once a day for the treatment of BPH in patients with BPH alone and in patients with BPH in association with ED. The data below include information from the June 23, 2011, sNDA amendments. In the pivotal and additional analysis sets supporting the BPH and BPH/ED indications:

- ***1448 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in the BPH and BPH/ED studies, with a total exposure of 624.5 subject years.***
- ***363 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.***
- ***296 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.***
- ***There were 160 subjects ≥75 years of age. The Sponsor was able to provide data on an additional 240 subjects ≥75 years of age. Of the total of 403 subjects ≥75 years of age, 173 had been exposed to tadalafil for at least 6 months and 102 had been exposed for 1 year.***

There were no deaths reported during the double-blind or open-label extension periods of Study LVHG, during BPH safety Study LVHS, or during the clinical pharmacology Study LVHN. One death (Subject LVHJ-303-3316-myocardial infarction) was reported in Study LVHJ in a patient with pre-existing coronary artery disease. One death in a placebo subject (Subject LVHK-117-2705) was reported in Study LVHK. One death (Subject LVHR-208-2806) was reported during Study LVHR. The cause of this subject's death remains undetermined. These events are not indicative of a safety concern or discernible pattern.

The adverse event profile for tadalafil in this study population is similar to the adverse events profiles noted in trials conducted for ED prn and once daily use for ED.

With respect to SAEs, there appeared to be no discernible repetitive occurrence pattern in the overall population, in men with BPH alone and in men with BPH/ED. In the open-label safety extension, one incidence of global amnesia 4 days following study completion, was associated with vigorous physical exercise, and therefore, cannot be attributed to tadalafil).

For the pivotal BPH analysis set, the percentage of subjects discontinuing due to an AE was significantly greater in the tadalafil 5 mg group compared to the placebo group (4.0% versus 1.6%). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5 mg group (1.1%). The most commonly reported adverse events leading to discontinuations, including headache, will be noted in labeling. All other AEs leading to discontinuation were less than 1%. In the long-term open label extension of Study LVHG, dyspepsia and stomach discomfort were the only AEs leading to discontinuation that occurred in more than 1 subject. In the additional BPH analysis set of all subjects, the percentage of subjects discontinuing due to an AE was significantly greater in the tadalafil group compared to placebo (3.6% versus 1.6 %). Headache was again the most frequently reported AE leading to discontinuation in the tadalafil 5 mg group and was the only event reported by a significantly greater percentage of subjects in the tadalafil group compared to placebo (0.9% versus 0.0%). In all randomized subjects with ED and BPH, for the tadalafil 5 mg group, headache leading to discontinuation occurred in 0.6% of patients while occurring in 0.0% of placebo subjects. All other AEs leading to discontinuation occurred at the rate t 0.2% or less. SAEs did not have a repetitive occurrence pattern with the exception of headache, dyspepsia and stomach discomfort. These AEs are part of the known safety profile of tadalafil.

The incidence of TEAEs reported was similar compared to placebo and all dose levels of tadalafil with the exception of subjects < 65 years of age. In subjects < 65 years of age and across all doses of tadalafil, there was an approximate 30% increase in TEAEs with a possible relationship to dose.

With respect to TEAEs that were possibly related to hypotension including headache, asthenia and fatigue, the data do not suggest an age-related or an antihypertensive-therapy-related decrease in tolerability with tadalafil therapy. Headache is the most commonly reported AE and is known to be associated with tadalafil treatment. Headache following tadalafil administration is not typically associated with hypotension in the populations studied in these NDAs.

A significantly greater percentage of subjects in the tadalafil 5 mg group compared to placebo reported at least 1 TEAE each in the Gastrointestinal disorders SOC (driven mainly by dyspepsia and gastroesophageal reflux disease) and the Musculoskeletal and connective tissue disorders SOC (driven by pain in extremity and myalgia). These events are known to be associated with tadalafil.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The studies/clinical trials used to evaluate safety in this NDA review are shown in Table 3 of this review.

Safety evaluation includes data from the following studies:

- Three Phase 3 efficacy and safety studies using utilizing tadalafil 2.5 mg, 5 mg, 10 mg, and 20 mg once-a-day dosing in men with BPH (Studies LVHG, LVHJ; 1383 randomized and 1106 subjects completed studies) and tadalafil 2.5 mg and 5 mg once-a-day dosing in men with BPH/ED (Study LVHR; 606 randomized and 526 subjects completed study).
- A long term 1 year open-label safety extension (Study LVHG OLE) utilizing tadalafil 5 mg once-a-day dosing in men with BPH (428 randomized; 299 subjects completed).
- A Phase 2 proof of concept study, LVGC (PiLUTS) assessing the safety and efficacy of tadalafil 5 mg and tadalafil 20 mg in men with BPH-LUTS (281 randomized and 251 subjects completed).
- Three safety studies:
    1. Study LVHN, a Phase 1, clinical pharmacology study assessing pharmacokinetic differences in young versus older men taking tadalafil 20 mg once-a-day (27 enrolled and 27 subjects completed).
    2. Study LVHS, a study primarily assessing the safety of concomitant use of tadalafil 5 mg in patients taking alpha-blockers (318 randomized and 280 subjects completed).
    3. Study LVHK, a study to evaluate possible detrimental urodynamic effects of tadalafil 20 mg once-a-day in men with BPH (200 randomized and 181 subjects completed).
- Four foreign Non-IND studies
    1. Study LVIA, a phase 2 study to evaluate the safety and efficacy of tadalafil 2.5 mg and tadalafil 5 mg once-a-day in Japanese men with BPH (422 randomized and 394 subjects completed).

2. Study LVIA OLE, a 42 week open-label safety extension to evaluate the long term safety and efficacy of tadalafil 5 mg once-a-day in Japanese men with BPH (394 randomized and 323 subjects completed).
3. Study LVHT, a phase 2 study to evaluate the safety and efficacy of tadalafil 5 mg and tamsulosin 0.2 mg administered in Korean men with BPH (151 randomized and 143 subjects completed).
4. Study LVHB, a phase 3 study to evaluate the safety and efficacy of tadalafil 5 mg in Asian men with BPH (612 randomized and 561 completed).

Analyses supporting the BPH indication use data from the placebo and 5-mg tadalafil treatment groups of Studies LVHJ and LVHG. These data define the **pivotal BPH analysis set.**

Additional analyses for BPH were conducted using integrated data from **subjects without ED,** and from the placebo and tadalafil 5-mg treatment groups of studies LVHG, LVHJ, and LVHR (referred to as the **additional BPH analysis set of all subjects**). Data from the LVHG open-label extension study comprise the primary long-term exposure analysis set. In this open-label extension, subjects previously assigned to placebo, 2.5 mg tadalafil, 5 mg tadalafil, 20 mg tadalafil, or 20 mg tadalafil treatment groups in the double-blind treatment period were administered tadalafil 5 mg.

In a separate analysis, data from the placebo and tadalafil 5 mg treatment groups from two, phase 2, placebo-controlled studies conducted in Asian countries (Studies LVHT and LVIA) were integrated to evaluate the efficacy and safety of tadalafil in subjects in Asian countries **(**referred to as the **non-IND studies conducted in Asian countries analysis set).** Asian phase 3 study LIHB is analyzed separately. Safety in Asian non-IND studies is briefly described in this review.

The safety results from the open-label safety extension of LVIA are considered briefly. In the LVIA open-label extension, subjects were administered tadalafil 5 mg.

Analysis Sets Supporting the BPH/ED Indication

Analyses supporting the BPH/ED indication use the **pivotal BPH/ED analysis set** from placebo, 2.5 mg, and 5 mg tadalafil treatment groups of Study LVHR. Study LVHR enrolled subjects presenting with BPH-LUTS and ED.

Additional analyses for the BPH/ED indication are conducted using integrated data from subjects with ED from the placebo and tadalafil treatment groups of Studies LVHG and LVHR, and integrated data from subjects with ED from the placebo and tadalafil 5 mg treatment groups of Studies LVHG, LVHJ and LVHR (referred to as the **additional BPH/ED analysis set of all subjects with ED).**

7.1.2 Categorization of Adverse Events

The adverse events were analyzed in the following categories:

- Deaths
- Other serious adverse events
- Dropouts
- Adverse events
- Adverse events in the following situations
    - Co-administration and prior use of alpha-blocker therapy
    - AEs by prior PDE5 Inhibitor Therapy
    - Ethnicity
    - Diabetes (as an intrinsic factor)
    - Renal Impairment (as an intrinsic factor)
    - Hepatic Impairment
    - Subgroups based on age (as an intrinsic factor), disease severity,
- Other adverse events of interest, which include:
    - Bleeding Events
    - Cardiovascular Events
    - Ear Disorders
    - Eye Disorders
    - Event Possibly Related to Hypotension, including Headache, Asthenia and Fatigue
    - Myalgias and Back Pain
    - Seizures
    - Transient Global Amnesia
- Extrinsic Factors
    - Concomitant Antihypertensive Drug Use
    - CYP3A4 Inhibitor Use
    - Previous Phosphodiesterase Type 5 Inhibitor Use
    - Prior Use of Alpha-Blocker Therapy

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events were analyzed separately for each study listed in these sNDA submissions and data is pooled for the defined integrated data analysis sets.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 92: Number of Subjects Exposed and Subject-Year Exposure to Tadalafil All Randomized Subjects- Placebo Controlled Studies LVHG, LVHG Open-Label Extension, LVHJ, LVHR, LVHK and LVHS

			Tadalafil				
Indication	Study Type	Protocol	2.5 mg n subj. yrs.	5 mg n subj. yrs.	10 mg n subj. yrs.	20 mg n subj. yrs.	>=5mg n subj. yrs.
BPH	Long-term Open-label	LVHG		427 347.6			427 347.6
BPH	Pivotal Placebo-controlled	LVHG	208 47.6	212 47.6	216 47.1	209 45.1	637 139.2
BPH		LVHJ		161 36.6			161 36.6
BPH/ED		LVHR	197 43.3	208 45.3			208 45.3
BPH	Special Safety - Placebo-Controlled	LVHK				96 22.3	96 22.3
BPH		LVHS		158 34.3			158 34.3
Totals							
Subjects			405	1083	216	305	1448
Subject Years			90.9	510.4	47.1	67.4	624.5

Source: Table 2.7.4.4, Summary of Clinical Safety, page 28

Table 93: Duration of Exposure to Tadalafil by Dosage All Randomized Subjects-Placebo Controlled Studies LVHG, LVHG Open-Label Extension, LVHJ, LVHR, LVHK and LVHS

Duration	Tad 2.5 mg	Tad 5 mg	Tad 10 mg	Tad 20 mg	Tad=>5 mg
	n	n	n	n	n
>= 3 mos	355	951	174	251	1450
>= 6 mos		357			352
>= 12 mos		283			280

Source: Table 2.7.4.5, Summary of Clinical Safety, page 29. This table includes corrections from the June 23, 2011 NDA amendment.

Demographics and other baseline characteristics were well balanced between the tadalafil 5-mg and placebo groups of the pivotal BPH analysis set, with no clinically relevant treatment group

differences observed in subject demographics or in clinical characteristics. Overall, the subject population in the pivotal BPH analysis set was representative of the general BPH population with regard to demographics and comorbidities. The mean age in the tadalafil 5-mg and placebo groups was 63.3 years and 63.0 years, respectively; 40.2% of subjects in the tadalafil group and 40.7% of subjects in the placebo group were older than 65 years of age; 13.4% of the subjects in the tadalafil 5-mg group and 12.5% of subjects in the placebo group were 75 years of age or older. The predominant race was White in both treatment groups. Mean body mass index (BMI), mean prostate-specific antigen (PSA), mean PVR volume, and Qmax categories (<10 mL/sec, 10-15 mL/sec, or >15 mL/sec) were generally similar between the tadalafil 5-mg and placebo groups. Additionally, baseline medical history relevant to cardiovascular disease risk was well balanced between treatment groups. Demographics and other baseline characteristics in the open-label extension were generally similar with those of the pivotal BPH analysis set. In the additional BPH analysis set of all subjects, demographics/other baseline characteristics and subject disposition were generally similar between the tadalafil 5-mg and placebo groups, and were consistent with those of the pivotal BPH analysis set.

For BPH safety Studies LVHK and LVHS, in general, demographics and other baseline characteristics were balanced within each study and consistent with those of the pivotal BPH analysis set, with a few exceptions. In Study LVHK, mean PVR volume was numerically lower in the tadalafil treatment group compared with placebo (45.7 mL versus 59.3 mL, respectively). Additionally, baseline mean Qmax was slightly higher in Study LVHK than in other tadalafil studies, as the study population included subjects with and without urodynamic evidence of bladder outlet obstruction at baseline. In Study LVHK, baseline medical history of overall cardiovascular, cardiac, cerebrovascular, and other vascular disorders were balanced between treatment groups, although fewer subjects in the tadalafil group reported ischemic heart disease at baseline. In Study LVHS, subjects tended to be slightly older than subjects in the pivotal BPH analysis set, as would be anticipated given the predefined population consisting of at least 20% of subjects 75 years of age or older. In Study LVHS, a significantly greater percentage of subjects in the placebo group reported baseline cardiovascular disorders compared to the tadalafil 5-mg group, which was primarily driven by a numerically greater percentage of subjects in the placebo group reporting hypertension at baseline compared with the tadalafil group.

Demographics and other baseline characteristics were well balanced across the tadalafil 5-mg, tadalafil 2.5-mg, and placebo groups in the pivotal BPH/ED analysis set, with no clinically relevant treatment group differences observed in subject demographics or in clinical characteristics. Overall, the subject population in the pivotal BPH/ED analysis set was representative of the general BPH/ED population with regard to demographics and comorbidities. The mean age was 62.6 years; 37.3% of subjects were older than 65 years of age, and 9.2% of subjects were 75 years of age or older. The predominant race was White. Mean BMI, mean PSA, mean PVR volume, and Qmax categories were generally similar across treatment groups. Additionally, baseline medical history relevant to cardiovascular disease risk was well balanced across treatment groups.

Reviewer's Comment: Overall, the studies submitted in this submission have data documenting acceptable overall exposure at appropriate doses and durations to support

both sNDA applications. The demographics of the populations included in these studies are appropriate for the intended population of use.

7.2.2 Explorations for Dose Response

BPH-LUTS: The Sponsor conducted study LVGC (PiLUTS), a phase 2a, proof-of-concept study in men with BPH-LUTS, to explore the safety and efficacy of once-daily tadalafil in this population. The study was a dose-escalation study of tadalafil 5 mg dosed once daily for 6 weeks followed by tadalafil 20 mg dosed once daily for 6 weeks compared to placebo in 281 subjects. The primary efficacy endpoint was the total IPSS after 6 weeks of treatment compared with placebo. Two pivotal, placebo-controlled studies were conducted (LVHG and LVHC) to support the BPH indication. Study LVHG assessed dose response to tadalafil dosage strengths 2.5 mg, 5 mg, 10 mg and 20 mg once daily. The primary efficacy parameter was change in total IPSS from baseline to endpoint (after 12 weeks). Study LVHG randomized 1058 subjects who were at least 45 years of age and who presented with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. All observations, whether secondary efficacy variables, vital signs, clinical chemistry, or BMI, were analyzed by dose group. The incidence of subjects with 1 or more TEAE increased with increasing tadalafil dose. Below is Table 10 of this review illustrating this result.

Table 94: Overview of Adverse Events Study LVHG

Adverse Events	Placebo (N=212)	IC 2.5 mg (N=209)	IC 5 mg (N=212)	IC 10 mg (N=216)	IC 20 mg (N=209)	Tadalafil (N=846)
	n (%)					
Deaths	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SAEs	6(2.8)	3(1.4)	1(0.5)	2(0.9)	5(2.4)	11(1.3)
Discontinuation AE	5(2.4)	1(1.9)	12(5.7)	11(5.1)	14(6.7)	41(4.8)
≥ 1 TEAE	18(8.5)	56(26.8)	65(30.7)	75(34.7)	83(39.7)	279(33.0)

IC=tadalafil **Source:** Table LVHG 12.2, H6D-MC-LVHG Study Report, page 132.

Below is part of Table 8 of this review showing doses used in evaluating efficacy.

Table 95: Efficacy Outcomes All Randomized Subjects in the Primary Analysis Population Study LVHG

	Placebo N=210	Tadalafil 2.5mg N=208	Tadalafil 5mg N=212	Tadalafil 10mg N=216	Tadalafil 20mg N=208
Outcome	n LS Mean	Treatment Difference LS Mean p-value	Treatment Difference LS Mean p-value	Treatment Difference LS Mean p-value	Treatment Difference LS Mean p-value
Total IPSS	205 -2.23	-1.58 .005	-2.60 <.001	-2.90 <.001	-2.94 <.001

Source: Table 2.7.3.3, Summary of Clinical Efficacy, Current Submission, page 38

Study LVHJ randomized 325 subjects to either placebo or tadalafil 5 mg once daily for 12 weeks and confirmed the efficacy of tadalafil 5 mg.

Reviewer's Comment: The Sponsor has adequately evaluated the dose response for tadalafil once daily in the treatment of men with BPH-LUTS to allow a risk benefit assessment of the various doses. Tadalafil 5 mg once daily is supported as the dose for men with BPH.

BPH/ED: To assess the efficacy and safety of tadalafil in the treatment of men with both BPH and ED, the Sponsor performed pivotal, phase 3 Study LVHR which was a randomized, double-blind, placebo-controlled, parallel-design, multinational study to evaluate the efficacy and safety of tadalafil 2.5 mg or 5 mg dosed once daily for 12 weeks for men with BPH-LUTS and ED. Tadalafil 2.5 mg or 5 mg dosed once daily for men with ED have been previously approved for the treatment of male ED, starting at the tadalafil 2.5 mg daily dose. Study LVHR randomized 606 subjects ≥ 45 years of age who presented with BPH-LUTS for >6 months and ED for ≥ 3 months. The co-primary efficacy outcomes were the change in total IPSS and the International Index of Erectile Function (IIEF) − Erectile Function (EF) Domain score from baseline to Week 12. Below is a portion of Table 40 from this review:

Table 96: Co-Primary and Key Secondary Efficacy Outcomes - All Randomized Subjects in the Primary Analysis Population Study LVHR

Outcome	Placebo	Tadalafil 2.5 mg (N=198)			Tadalafil 5 mg (N=208)		
	N=200	n	Treatment Difference		n	Treatment Difference	
	n LS Mean	LS Mean	LS Mean (±SE)	p-value	LS Mean	LS Mean (±SE)	p-value
Co-primary							
Total IPSS	194 -3.8	191 -4.6	-0.8 (0.59)	.181	206 -6.1	-2.3 (0.58)	<.001
IIEF EF Domain	190 1.8	190 5.2	3.4 (0.67)	<.001	203 6.5	4.7 (0.66)	<.001

Reviewer's Comment: In study LVHR, the tadalafil 2.5 mg did not show efficacy for BPH. There was modest increase of AEs in the tadalafil 5 mg dose as compared to tadalafil 2.5 mg once daily. This is similar to the findings in once-daily ED studies. Dose response explorations for BPH/ED are adequately evaluated.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *in vitro* testing was performed

7.2.4 Routine Clinical Testing

The safety assessments included: AEs, clinical laboratory measurements (hematology, urinalysis, chemistry and PSA), vital signs (sitting vital signs, including diastolic blood pressure (DBP), systolic blood pressure (SBP), and heart rate, post-void residual urine volume and urodynamics, physical examination including digital rectal examination (DRE), International Prostate Symptom Score (IPSS), and the International Index of Erectile Function Erectile (IIEF) Function Domain (EF). . These were recorded at each study visit in the double-blind periods of each study and in the open-label extension period of Study LVHG

7.2.5 Metabolic, Clearance, and Interaction Workup

Drug interaction studies were done with selective and non-selective $alpha_1$ blocking agents and co-administration of 5 mg tadalafil was without significant changes in blood pressure. The Sponsor conducted an open-label clinical pharmacology study, Study LVHN, to assess PK in elderly patients (70 to 80 years of age) versus young patients (≤ 60 years of age). Three of the younger patients had mild renal impairment, which is an expected finding in some older men. There appeared to be no differences in tolerability profile between the age groups in Study LVHN using tadalafil 20 mg for 10 days of once daily dosing.

The Sponsor notes a trend toward increased hemodynamic signs and symptoms in men on non-selective alpha blockers, most notably doxazosin, as described in the existing Cialis USPI (2009.) In the original once-a-day sNDA application for ED, a study assessing the interaction of tadalafil and digoxin was submitted. Review of this study by the Office of Clinical Pharmacology showed no interaction with digoxin. Studies to assess drug metabolism, drug interaction and clearance were not done for these sNDAs, as these aspects of tadalafil were evaluated in the original NDA.

> *Reviewer's Comment: Tadalafil in the treatment of BPH is to be used as monotherapy at this time.*

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There were no new trends in drug-related adverse events as compared to the original NDA and as compared to the daily dosing sNDA. The safety profile has been detailed in the individual study reports, the Integrated Summary of Safety and the Appendices. The daily dosing of tadalafil as outlined in these two applications is a safe drug regimen.

7.3 Major Safety Results

Findings from the required "Four Month Update of Safety Information for Cialis®" identified no new safety findings related to tadalafil.

7.3.1 Deaths

BPH Analysis Set

There were no deaths reported during the double-blind or open-label extension periods of Study LVHG, during BPH safety Study LVHS, or during the clinical pharmacology Study LVHN. One death (Subject LVHJ-303-3316) was reported in Study LVHJ. One death in a placebo subject (Subject LVHK-117-2705) was reported in Study LVHK. The placebo patient was admitted to the hospital with pneumonia, a nodular infiltrate in the upper lober of the right lung, and pleurisy.

LVHJ-303-3316: The LVHJ subject was an 81-year old white male in the tadalafil 5-mg group who had preexisting conditions of hyperlipidemia and hypertension (BP 140/90 mm Hg while on lisinopril and study drug). The patient was characterized as having a moderate sexual dysfunction and was sexually active with a female partner. Concomitant medications included lisinopril and simvastatin. The patient also had degenerative arthritis and polyneuropathy. Approximately 2.5 months after receiving the first dose of study drug (tadalafil 5 mg), the subject was hospitalized with chest pain and diagnosed with an acute posterior myocardial infarction (MI) and third degree atrioventricular block; study drug was discontinued. Cardiac catheterization was performed and demonstrated 75%, 90%, and 90% occlusion of the LAD, circumflex and right coronary arteries, respectively. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequent intra-aortic balloon pump. The subject's condition worsened and he died 3 days later.

> *Reviewer's Comment: This patient had significant coronary artery disease that is highly likely to have been pre-existing. He also had hypertension and hyperlipemia.*

BPH/ED Analysis Set

One death (Subject LVHR-208-2806) was reported during Study LVHR.

LVHR 208-2806: The patient was a 67-year old Caucasian male. The patient's medical history included back pain, sinusitis, and orthopedic surgery on his ankle (all in 1984). Concomitant medications included tiaprofenic acid, a multivitamin, ascorbic acid, vitamin B, and ergo calciferol. On 14-APR-2009, the patient began the placebo lead-in period of the study and stopped on 14-MAY-2009. On 15-MAY-2009, the patient began the treatment period with study drug for erectile dysfunction with signs and symptoms of benign prostatic hypertrophy. The patient was last seen at visit 6 on 10-JUL-2009 and was on study drug at that time. The patient's last dose of study drug prior to the event was 13-JUL-2009. On (b) (6) the investigator received a telephone call from the patient's wife who informed him that the patient had died. She said she had found him dead in his house on (b) (6), and he had probably been dead for two to three days. There is no witness report to provide medical details at and around the time of death. Immediate cause of death per medical certification of death document was myocardial infarction, and date of death was documented as (b) (6). I t is also noted by the patient's primary care physician that the patient had a cardiac arrhythmia. What role this may have played

in the patient's death is uncertain. Other significant conditions contributing to the death included impaired glucose tolerance, sleep apnea, mild mitral valve prolapse, and episodic atrial fibrillation. An autopsy was not performed. The investigator stated that he did not believe that the myocardial infarction was related to drug or protocol.

> *Reviewer's Comment: In the absence of observation of the acute episode, the lack of autopsy findings, as well as an unclear history of cardiac disease, I am unable to conclude that this death is related to tadalafil.*
>
> *In sum, I do not discern any safety concern from these deaths.*

7.3.2 Nonfatal Serious Adverse Events

BPH Analysis Sets

The table below presents a summary of SAE's for the pivotal BPH analysis set. 7 subjects reported 12 SAEs. The number of subjects reporting at least 1 SAE was not significantly different between treatment groups. Subject LVHJ-303-3316 experienced an SAE that resulted in death and is described above. The episode of pancreatitis (Subject LVHG-600-1081) appears to be related to biliary obstruction secondary to cholelithiasis and the narrative is presented in the review of Study LVHG.

Table 97: Serious Adverse Events by Decreasing Frequency in the Tadalafil 5-mg Group, All Randomized Subjects-Pivotal BPH Studies LVHG and LVHJ Double-Blind Treatment Group

Preferred Term	Placebo N=376	Tad 5 mg N=373
	n (%)	n (%)
Subjects with >=1 SAE	4(1.1)	3(0.8)
Acute MI	0(0.0)	1(0.3)
Cholecystitis	0(0.0)	1(0.3)
Endocarditis	0(0.0)	1(0.3)
Pancreatitis	0(0.0)	1(0.3)
Cartilage Injury	1(0.3)	0(0.0)
Cerebrovascular Accident	1(0.3)	0(0.0)
Coronary Artery Stenosis	1(0.3)	0(0.0)
Indwelling Catheter	1(0.3)	0(0.0)
Renal Colic	1(0.3)	0(0.0)
Rheumatoid Arthritis	1(0.3)	0(0.0)
Ureteral Catheterization	1(0.3)	0(0.0)
Urinary Retention	1(0.3)	0(0.0)

Source: Table 2.7.4.25. Summary of Clinical Safety, page 80

The SAEs in the long-term open-label extension of Study LVHG are summarized below:

Table 98: Serious Adverse Events by Decreasing Frequency in the Total Tadalafil Group, All Subjects Enrolled in the Open-Label Extension Period LVHG

Preferred Term	Previous Therapy				
	Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg
Patients with >=1 SAE	N=92	N=96	N=83	N=85	N=71
Arthritis	0 (0.0)	0 (0.0)	1 (1.2)	1(1.2)	0(0.0)
Knee arthroplasty	1 (1.1)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Non-cardiac chest Pain	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Basedow's disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Bladder neoplasm	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac congestive failure	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Coronary artery stenosis	1 (1.1)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)
Fibula fracture	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GERD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Global Amnesia	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Hip arthroplasty	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Meniscus lesion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Osteoarthritis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Sinus polyp	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

IC=tadalafil
Source: Table 2.7.4.26., Clinical Summary of Safety, page 81.

In the Additional BPH analysis of all subjects, 9 subjects reported 14 SAEs.

Table 99: Serious Adverse Events in the Additional BPH Analysis of all BPH Subjects Studies LVHG, LVHJ and LVHR Double-Blind Treatment Period.

	Placebo (N=576)	Tadalafil 5 mg (N=581)
Preferred Term	n (%)	
Subjects with >= 1 SAE	5 (0.9)	4 (0.7)
Acute Myocardial Infarction	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)
Endocarditis	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	1 (0.2)
Cartilage Injury	1 (0.2)	0 (0.0)
Cerebrovascular Accident	1 (0.2)	0 (0.0)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Indwelling Catheter Management	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)
Renal Colic	1 (0.2)	0 (0.0)
Rheumatoid Arthritis	1 (0.2)	0 (0.0)
Ureteral Catheterization	1 (0.2)	0 (0.0)
Urinary Retention	1 (0.2)	0 (0.0)

Source: Table ISS.7, Integrated Summary of Safety, page 34.

In the Additional BPH Analysis set of subjects without ED, 3 subjects in the placebo group reported 4 SAEs (2.5%) and no subjects in the tadalafil 5 mg group reported SAEs.

> *Reviewer's Comment: The individual SAEs in no case had a greater frequency than 1 for any preferred term. This is true for all BPH analysis sets. I cannot discern any pattern of SAEs raising a safety concern. Some of the SAEs are compatible with the age of the study subjects and others are part of the known safety profile for tadalafil.*

BPH/ED Analysis Sets

In the pivotal BPH/ED analysis set, four subjects reported SAEs.

Table 100: Serious Adverse Events All Randomized Subjects Pivotal BPH/ED Study LVHR Double-Blind Treatment Period

Preferred Term	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
	N=200	N=198	N=208
	n (%)		
Subject with >= 1 SAE	1 (0.5)	2 (1.0)	1 (0.5)
Pancreatitis Hemorrhagic	0 (0.0)	0 (0.0)	1 (0.5)
Intervertebral Disc Protrusion	0 (0.0)	1 (0.5)	0 (0.0)
Myocardial Infarction	0 (0.0)	1 (0.5)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.5)	0 (0.0)	0 (0.0)

Source: Table 2.7.4.27, Summary of Clinical Safety, page 83

LVHR Subject 401-4104: SAE: a 69-year-old Caucasian male patient. The patient had no relevant medical history. Concomitant medications included ramipril for hypertension, fluticasone propionate/salmeterol xinafoate for chronic obstructive bronchopneumopathy and pantoprazole sodium. On 27-Oct-2009, the patient started the placebo lead-in period of the study and completed this phase on 30-Nov-2009 for the treatment of erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. On 01-Dec-2009, the patient commenced the treatment period with blinded therapy (tadalafil 5 mg). The last dose of blinded study medication prior to the event onset was on 25-Dec-2009 and therapy was then stopped. On [redacted] (b) (6) the patient was admitted initially to hospital for acute pancreatitis. This was [redacted] (b) (6) post the first dose of blinded study therapy, the patient required prolonged hospitalization due hemorrhagic pancreatitis. There were no laboratory data, examination findings or corrective treatments specified. On [redacted] (b) (6) a cholecystectomy was performed and on [redacted] (b) (6) an endoscopic retrograde cholangio-pancreatography was performed. At the time of the report, the patient had recovered from the event, but was not discharged from hospital. Study drug was permanently discontinued in response to the event and the patient was withdrawn from the study.

Reviewer's Comment: The fact that the patient underwent a cholecystectomy and at a later date an endoscopic procedure to possibly assess the patency of the hepatobiliary duct system raises the question of an obstructive etiology of the patient's pancreatitis. There is no discussion of the findings or indications for the cholecystectomy as well as the endoscopy findings. I am therefore not able attribute the pancreatitis to the study drug.

In the additional BPH/ED analysis set of subjects with ED, the number of subjects reporting at least 1 SAE was not significantly different for either tadalafil group when compared to placebo. All individual SAEs were reported with a frequency of less than 1%.

Table 101: Serious Adverse Events All Randomized Subjects With ED Studies LVHG, LVHJ, and LVHR Double-Blind Treatment Period.

Preferred Term	Placebo (N=342)	Tadalafil 2.5 mg (N=333)	Placebo (N=454)	Tadalafil 5 mg (N=464)
	n (%)			
Subjects with >= 1 SAE	2 (0.6)	6 (1.8)	2 (0.4)	4 (0.9)
Acute Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Indwelling Catheter Management	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Renal Colic	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Ureteral Catheterization	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Urinary Retention	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Atrial Tachycardia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Bladder Neoplasm	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Intervertebral Disc Protrusion	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Myocardial Infarction	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Nephrolithiasis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Acute Renal Failure	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Ureteral Stent Insertion	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Ureteric Rupture	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)

Source: Table ISS 13, Integrated Summary of Safety, page 66

LVHG patient 123-3320 (tadalafil 2.5 mg) had the following SAEs: renal failure, nephrolithiasis, ureteric rupture, ureteral stent insertion and bladder neoplasm. LVHG patient 406-6610 (placebo) had the following SAEs: urinary retention, renal colic, ureteral catheterization, and indwelling catheter management.

> *Reviewer's Comment: There are two cases of pancreatitis noted in the BPH/ED additional analysis set: LVHR 401-4104 (hemorrhagic pancreatitis) and LVHG 110-2027. Both patients were receiving tadalafil 5 mg. Both patients underwent a cholecystectomy as part of their treatment. Detailed narratives are present in the respective study reports in this submission. My interpretation is that in both*

cases an obstructive causation cannot be ruled out. This confounding factor does not allow me to attribute the SAEs of pancreatitis to the study drug.

Across 68 clinical pharmacology studies with doses ranging from 2.5 to 100 mg, there have been 3 SAEs (angina, pneumothorax, spinal laminectomy) in a total of 2080 tadalafil-treated subjects versus 6 SAEs in a total of 1283 placebo-treated subjects.

7.3.3 Dropouts and/or Discontinuations

BPH Analysis Sets

For the pivotal BPH analysis set, the percentage of subjects discontinuing due to an AE was significantly greater in the tadalafil 5-mg group compared to the placebo group (4.0% versus 1.6%, p=.045). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5-mg group (1.1%), and was the only event that was reported by a significantly greater percentage of subjects in the tadalafil group compared with placebo (p=.045). In Study LVHJ, there was an acute myocardial infarction resulting in death. This event has been reviewed previously and narratives furnished earlier in this review. All other AEs leading to discontinuation were reported with a frequency of less than 1 percent.

Reviewer's Comment: The incidence of discontinuations due to adverse events is listed in the label. The most commonly reported advers events leading to discontinuation, including headache, will be added to labeling.

Table 102: Adverse Events Reported as Reason for Study Discontinuation in the Tadalafil 5 mg Group Pivotal BPH Studies LVHG and LVHJ Double-Blind Treatment Period

Preferred Term	Placebo N=376	Tadalafil 5 mg N=373
	n (%)	
Subjects Discontinued due to AE	6 (1.6)	15 (4.0)
Headache	(0.0)	4 (1.1)
Acute Myocardial Infarction	(0.0)	1(0.3)
Abdominal Pain Upper	2 (0.5)	3 (0.8)
Dyspepsia	(0.0)	1 (0.3)
Myalgia	(0.0)	1 (0.3)
Pain	(0.0)	1 (0.3)
Pain in Extremity	(0.0)	1 (0.3)
Pancreatitis	(0.0)	1 (0.3)
Retinal Tear	(0.0)	1 (0.3)
Rotator Cuff Syndrome	1 (0.3)	(0.0)
Coronary Artery Stenosis	1 (0.3)	(0.0)
Dizziness	1 (0.3)	(0.0)
Eye Pain	1 (0.3)	(0.0)

Source: Table 2.7.4.29, Summary of Clinical Safety, page 87.

In the long-term open-label extension of Study LVHG, 22 subjects (5.2%) discontinued due to AEs. Dyspepsia (2 subjects) and stomach discomfort (2 subjects) were the only AEs leading to discontinuation that occurred in more than 1 subject.

Table 103: Adverse Events Reported as Reason for Study Discontinuation in Total Tadalafil Group Open-Label Extension Period Study LVHG

Preferred Term	Previous Placebo	Total
	N=92	N=427
	n (%)	
Patients with >= 1 AE leading to Discontinuation	6 (6.5)	22 (5.2)
Dyspepsia	1 (1.1)	2 (0.5)
Stomach discomfort	1 (1.1)	2 (0.5)
Acute coronary syndrome	0 (0.0)	1 (0.2)
Arrhythmia	0 (0.0)	1 (0.2)
Bladder Neoplasm	1 (1.1)	1 (0.2)
Carpal Tunnel Syndrome	0 (0.0)	1 (0.2)
Coronary Artery Disease	0 (0.0)	1 (0.2)
Deafness Unilateral (see narrative below)	0 (0.0)	1 (0.2)
Gastroesophageal Reflux Disease	0 (0.0)	1 (0.2)
Hepatic Enzyme Increased	0 (0.0)	1 (0.2)
Hepatic Function Abnormal	1 (1.1)	1 (0.2)
Hot Flush	0 (0.0)	1 (0.2)
Muscle Tightness	1 (1.1)	1 (0.2)
Esophagitis	0 (0.0)	1 (0.2)
Pollakiuria	0 (0.0)	1 (0.2)
Prostate Cancer	0 (0.0)	1 (0.2)
Prostatic Intraepithelial Neoplasia	0 (0.0)	1 (0.2)
Residual Urine	0 (0.0)	1 (0.2)
Seasonal Allergy	0 (0.0)	1 (0.2)
Visual Disturbance	1 (1.1)	1 (0.2)

Source: Table 2.7.4.30, Summary of Clinical Safety, page 88.

LVHG Subject 106-1604 a 48-year-old who received tadalafil 2.5 mg in the double-blind phase, reported deafness unilateral at Visit 11 which lasted 17 days. According to the subject's otolaryngologist the subject had previously experienced neurosensory hearing loss (October 2006). The event occurred 2 months after a previous check-up and the otolaryngologist replied that there was minimal progression. The subject discontinued the study due to this event. Prior to the event of deafness unilateral the subject reported vertigo positional which occurred prior to Visit 10 and lasted for 63 days. One month after the deafness unilateral the subject reported tinnitus which lasted approximately 2 weeks. To treat the tinnitus, the patient used hydrogen peroxide ear drops. Concomitant medications were ascorbic acid and fluticasone for allergy.

Reviewer's Comment: This appears to be an exacerbation of a pre-existing condition.

In the additional BPH analysis set of all subjects, the percentage of subjects discontinuing due to an AE was significantly greater in the tadalafil 5-mg group compared to the placebo group (3.6% versus 1.6%, p=.028). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5-mg group and was the only event that was reported by a significantly greater percentage of subjects in the tadalafil group compared to placebo (0.9% versus 0.0%, p=.025). All AEs leading to discontinuation were reported with a frequency <1%. Acute MI was reported as an SAE that resulted in death (1 subject) – previously described.

Table 104: Adverse Events Reported as Reason for Study Discontinuation in the Tadalafil 5 mg Group Studies LVHG, LVHJ, and LVHR Double-Blind Treatment Period

Preferred Term	Placebo (N=576)	Tadalafil (N=581)
	n (%)	
Subjects Discontinued due to AE	9 (1.6)	21 (3.6)
Headache	0 (0.0)	5 (0.9)
Abdominal Pain Upper	2 (0.3)	3 (0.5)
Myalgia	0 (0.0)	2 (0.3)
Back Pain	1 (0.2)	1 (0.2)
Dyspepsia	0 (0.0)	1 (0.2)
Muscle Spasms	0 (0.0)	1 (0.2)
Pain	0 (0.0)	1 (0.2)
Pain in Extremity	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	1 (0.2)
Retinal Tear	0 (0.0)	1 (0.2)
Rotator Cuff Syndrome	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)
Abdominal Discomfort	1 (0.2)	0 (0.0)
Blood Creatine Phosphokinase Increased	1 (0.2)	0 (0.0)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Dizziness	1 (0.2)	0 (0.0)
Eye Pain	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)

Source: Table ISS.8, Integrated Summary of Safety, page 36. (The episode of syncope occurred in tadalafil 2.5 mg subject LVHG 123-3320.)

In the additional BPH analysis set of subjects without ED, the percentage of subjects with discontinuations due to AEs was numerically greater in the tadalafil 5-mg group compared to the placebo group (6.8% versus 1.7%), but this difference was not statistically significant. A numerically greater percentage of subjects in the tadalafil 5-mg group reported discontinuations due to AEs, compared with tadalafil-treated subjects in the pivotal BPH analysis set. In this

analysis set (tadalafil 5 mg N=117), 3(2.6%) tadalafil subjects discontinued due to abdominal pain upper, 2 (1.7%) tadalafil subjects discontinued due to headache, and 1 (0.9%) tadalafil subject discontinued due to myalgia or retinal tear (1 each).

> *Reviewer's Comment: Analysis of all BPH data analysis sets does not present a new safety concern or signal. There appear to be no meaningful differences between the various data analysis groups.*

BPH/ED Analysis Sets

In the pivotal BPH/ED analysis set, twelve subjects discontinued the study due to AEs: 3 subjects (1.5%) in the placebo group, 6 subjects (2.9%) in the tadalafil 5 mg group, and 3 subjects (1.5%) in the tadalafil 2.5 mg group. No AE leading to discontinuation was reported by more than 1 subject. The table below summarizes adverse events leading to discontinuation in all patients with ED in the double-blind treatment of studies LVHG, LVHJ, and LVHR.

Table 105: Adverse Events Reported as Reason for Study Discontinuation in the Tadalafil 5 mg Group All Randomized Subjects with ED Studies LVHG, LVHJ and LVHR Double-Blind Treatment Period

Preferred Term	Placebo (N=342)	Tadalafil 2.5mg (N=333)	Placebo (N=454)	Tadalafil 5mg (N=464)
	n (%)			
Subjects Discontinued due to AE	6 (1.8)	6 (1.8)	7 (1.5)	13 (2.8)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)
Acute Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Back Pain	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Muscle Spasms	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myalgia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pain in Extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatitis Hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Rotator Cuff Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Syncope (narrative below)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Abdominal Discomfort	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Abdominal Pain Upper	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Creatine Phosphokinase Increased	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Dizziness	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
Eye Pain	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Non-Hodgkin's Lymphoma	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Myocardial infarction	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Nocturia	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Ureteric Rupture	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Source: Table ISS.14, Integrated Summary of Safety, page 68.

Reviewer's Comment: The two episodes of pancreatitis have been discussed as SAEs and found, in the reviewer's opinion, not to be related to the study drug. The three episodes of myocardial infarction were considered in narratives in their respective study reports. Brief narratives are presented below:

- *In one of these subjects (Subject LVHR-208-2806, tadalafil 2.5 mg), the patient was found dead in his house by his wife 4 days after his last dose of study drug. No autopsy was performed. Myocardial infarction was presumed to be his cause of death.*

- *In another of these subjects (Subjects LVHG-101-1166, tadalafil 2.5mg), the patient was a 93 year old man who took study drug for two weeks, then suffered a myocardial infarction when performing "heavy manual labor, including digging out tree roots".*
- *In the last of these patients (Subject LVHJ-303-3316, tadalafil 5mg), the patient was an 80 year male with hypertension (140/90 mmHg while on lisinopril and study drug), hyperlipidemia, degenerative arthritis, and polyneuropathy who suffered a myocardial infarction approximately 10 weeks after initiating study medication. His cardiac cath revealed 75%, 90%, and 90% occlusion of the LAD, circumflex and right coronary arteries. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequently an intra-aortic balloon pump. He died 4 days after his MI.*

In each case there were confounding elements, and the overall incidence of cardiovascular events was not significantly different between drug and placebo in the overall study population(s).

LVHR Subject 207-2710 is a 57-year-old Hispanic male randomized to tadalafil 5 mg, reported mild syncope with an event start date of 19 September 2009, which was 33 days postrandomization, and an end date of 6 October 2009; last dose of study drug was taken on 25 September 2009. Concurrent with the syncope, the subject also reported headache of the same duration. Follow-up with the site indicated that the subject had episodic events of lightheadedness over the period of time between the event start and end dates. The subject did not have one isolated episode of syncope (i.e., loss of consciousness) lasting 18 days nor did he have any isolated syncopal episode, but rather intermittent episodes of headache and lightheadedness. The subject's medical history included emphysema and asthma. His SBP was elevated at the randomization visit, but otherwise all BP measurements were within normal limits. He met the criterion for a treatment emergent positive orthostatic test (supine heart rate was 82 bpm and standing was 106 bpm) at Visit 6 (approximately 2 months after randomization). The subject discontinued at Visit 6 due to syncope.

Reviewer's Comment: While initially classified as syncope, it does not appear that syncope occurred, but at a later date the subject did have a positive orthostatic test.

Reviewer's Comment: The percentage of subjects in the additional BPH/ED analysis set of subjects with ED with discontinuations due to AEs was similar to that of the overall BPH study population. Analysis of this data set does not present a new safety concern or signal. There appear to be no meaningful differences between the various data analysis groups either with or without ED.

7.3.4 Adverse Events of Interest

Based on the known safety profile of tadalafil established in the ED PRN use populations and the ED daily use populations, special safety topics were agreed upon during the 13 April 2010 pre-NDA meeting. These topics define adverse events of interest in terms of this review, and include: bleeding events, cardiovascular events, ear disorders (including sudden hearing loss), eye disorders (including nonarteritic anterior ischemic optic neuropathy [NAION]), TEAEs possibly related to hypotension (including headache, asthenia, and fatigue), myalgias and back pain, seizures, and transient global amnesia. Definitions for these special safety topic TEAEs were derived primarily from existing Standard MedDRA queries when one or more appropriate queries for the special safety topic was available. The Sponsor has provided summaries of TEAEs associated with special safety topics for the pivotal BPH analysis set, additional BPH analysis set of all subjects, the long term safety extension period of LVHG, and the pivotal BPH/ED analysis set. The Sponsor has also calculated incidence rates adjusted for the time of exposure for the tadalafil 5 mg groups of the pivotal BPH analysis set and for the long term open-label extension period of LVHG. The focus of review will be on the 5 mg tadalafil dose versus placebo.

The Sponsor has also performed a separate analysis across 68 clinical pharmacology studies for special safety topics. These results will not be the primary focus of review.

Bleeding Events: In the **pivotal BPH analysis set** (**tadalafil** 5 mg N=373, placebo N=376), 4 subjects (1.1%) reported a total of 4 bleeding AEs versus 0 for placebo. The AEs were epistaxis 2, hemorrhoidal hemorrhage 1 and rectal hemorrhage 1. In the **additional BPH analysis set of all BPH** (tadalafil 5 mg N=581, placebo N=576), 6 subjects (1.0%) reported a total of 6 bleeding TEAEs compared to none for placebo. These AEs were epistaxis 3, pancreatitis hemorrhagic, hemorrhoidal hemorrhage 1 and rectal hemorrhage 1. None of these events were SAEs or led to study discontinuation.

In the **Open-Label Extension** of Study LVHG, a total of 9 subjects (2.1%) reported at total of 9 bleeding TEAEs. None of the bleeding events were SAEs or led to study discontinuation.

Table 106: Bleeding Adverse Events Open-Label Extension LVHG

Preferred Term	Total N=427
Subjects >= 1 TEAE	
Hematuria	3 (0.7)
Contusion	2 (0.5)
Ecchymosis	1 (0.2)
Eye Hemorrhage	1 (0.2)
Hematoma	1 (0.2)
Intra-Abdominal Hematoma	1 (0.2)

Source: Table APP 2.7.4.72, Summary Clinical Safety Appendix, page 542

LVHG patient 138-4801 was hospitalized for a cardiac arrhythmia and received coronary ablative intervention and anticoagulants. While not described in narrative, intra-abdominal hematoma-mild is listed as one of the diagnoses. LVHG patient 117-2720 was noted to have a mild "bruise" and LVHG patient 104-143 is listed as having had a "bicycle accident" with AEs of "chest wall injury and head contusion."

When adjusted for time of exposure, the incidence rate for subjects with bleeding TEAEs in the long-term **open-label extension** period of Study LVHG was 2.6 subjects per 100 person-years, which is numerically lower than the incidence rate observed in the **pivotal BPH analysis set** (4.8 subjects per 100 person-years).

In the **BPH/ED analysis set**, two subjects (1.0%) in the tadalafil 5 mg group (N=208) reported 2 bleeding episodes compared to none in the placebo group (N=200). One subject (LVHR-401-4104) reported an SAE of hemorrhagic pancreatitis that led to discontinuation. The narrative for this subject has been previously presented. The second patient reported epistaxis as an AE.

> *Reviewer's Comment: Despite no demonstrated effects of tadalafil on bleeding time, a caution for patients with baseline bleeding disorders is reflected in the drug labeling (**5.12 Effect on Bleeding).** The case of hemorrhagic pancreatitis was confounded by biliary obstruction and in my opinion; I would not include this bleeding episode in labeling. However, it is not possible to exclude the role of tadalafil in the other 4 bleeding adverse events in the pivotal BPH analysis set (epistaxis x 2, hemmorhoidal hemorrhage, and rectal hemorrhage). The cases of epistaxis are reflected in the label by the adverse event term "epistaxis" in adverse events reported infrequently in clinical trials where a causal relationship is uncertain. It would be appropriate to add the terms "hemorrhoidal and rectal hemorrhage" to that section as well.*

Cardiovascular Events: For the analysis of the cardiovascular disorder special safety topic, the total number of subjects reporting at least 1 cardiovascular disorder TEAE was compared between treatment groups. In addition, the following categories and subcategories were compared between treatment groups: cardiac disorders (cardiac arrhythmias, cardiac failure, cardiomyopathy, ischemic heart disease, and other cardiac disorders), cerebrovascular disorders (hemorrhagic cerebrovascular disorders and ischemic cerebrovascular disorders), and other vascular disorders (hypertension, embolic and thrombotic events, renovascular disorders, vasculitis, and other vascular disorders).

For the **pivotal BPH analysis set**, the Sponsor reported that there were no significant differences between treatment groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs. Twenty-two subjects (2.9%) reported a total of 24 cardiovascular disorder TEAEs. In the placebo group there were 9 (2.4%) cardiovascular TEAEs. In the tadalafil 5 mg group there were 13 (3.5%) cardiovascular TEAEs. Three events were SAEs: 1 SAE (Subject LVHJ- 303-3316, tadalafil 5 mg) of acute MI in an 80 year old man with documented triple vessel occlusive disease that resulted in discontinuation/death, 1 SAE (Subject

LVHG-309-1952, placebo) of coronary artery stenosis that led to study discontinuation, and 1 SAE (Subject LVHG-600-1084, placebo) of cerebrovascular accident. No other cardiovascular TEAEs led to study discontinuation.

Table 107: Treatment-Emergent Cardiovascular Adverse Events in the Tadalafil 5 mg Group Pivotal BPH Studies LVHG and LVHJ Double-Blind Period

	Placebo (N=376)	Tadalafil 5 mg (N=373
Cardiovascular Disorders n (%)	9 (2.4)	13 (3.5)
Preferred Terms		
Tachycardia	1 (0.3)	1 (0.3)
Atrioventricular block first degree	1 (0.3)	0 (0.0)
Bundle branch block right	1 (0.3)	0 (0.0)
Cardiomegaly	0 (0.0)	1 (0.3)
Edema Peripheral	1 (0.3)	1 (0.3)
Acute Myocardial Infarction	0 (0.0)	1 (0.3)
Coronary Artery Stenosis	1 (0.3)	0 (0.0)
Cardiac Murmur	1 (0.3)	0 (0.0)
Cerebrovascular Accident	1 (0.3)	0 (0.0)
Hypertension	4 (1.1)	8 (2.1)
Blood Pressure Fluctuation	0 (0.0)	1 (0.3)
Hypotension	0 (0.0)	1 (0.3)

Source: Table APP 2.7.4.75, Appendix Clinical Summary of Safety, page 545

Reviewer's Comment: 7 of 8 tadalafil subjects listed with hypertension had hypertensive blood pressure readings in Visits 1-3 as did 4 of 4 placebo subjects. It is my conclusion that these subjects did not have treatment emergent hypertension. If the hypertension AEs are not considered treatment-emergent, then there appears to be no overall increase in AEs as compared to placebo.

Twenty-five subjects in the **long-term, open-label extension of LVHG** (5.9%) reported a total of 39 cardiovascular disorder TEAEs. Six of these events were SAEs: coronary artery stenosis (Subject LVHG-118-2804), coronary artery disease (Subject LVHG-123-3315), cardiac arrest (Subject LVHG-123-3324), atrial flutter (Subject LVHG-138-4801), congestive cardiac failure (Subject LVHG-138-4809), and acute coronary syndrome (Subject LVHG-205-8001). The SAEs of coronary artery disease, arrhythmia, and acute coronary syndrome resulted in study discontinuation. No other cardiovascular TEAEs resulted in study discontinuation. When the Sponsor adjusted the incidence of these TEAEs based on time of exposure, their conclusion the rates of incidence were lower than in the **pivotal BPH analysis set**.

Table 108: Treatment Emergent Cardiovascular Events LVHG Open-Label Extension Study

Cardiovascular Disorders Preferred Term	Total N=427
	n (%)
All Disorders	25 (5.9)
Atrial fibrillation	2 (0.5)
Arrhythmia	1 (0.2)
Atrial Flutter	1 (0.2)
Atrioventricular Block Complete	1 (0.2)
Atrioventricular Block Second Degree	1 (0.2)
Cardiac Arrest	1 (0.2)
Ventricular Arrhythmia	1 (0.2)
Peripheral Edema	5 (1.2)
Cardiac Failure Congestive	1 (0.2)
Coronary Artery Disease	3 (0.7)
Acute Coronary Syndrome	1 (0.2)
Angina Unstable	1 (0.2)
Coronary Arterial Stent Insertion	1 (0.2)
Coronary Artery Stenosis	1 (0.2)
Myocardial Infarction	1 (0.2)
Cardiac Murmur	1 (0.2)
Cardiac Pacemaker Insertion	1 (0.2)
Left Ventricular Hypertrophy	1 (0.2)
Mitral Valve incompetence	1 (0.2)
Cerebrovascular Event	1 (0.2)
Penile Vein Thrombosis	1 (0.2)
Renal Artery Occlusion	1 (0.2)
Hypertension	8 (1.9)
Blood Pressure Increased	1 (0.2)

Source: Table APP 2.7.4.76, Appendix Clinical Summary of Safety, page 548.

Reviewer's Comment: Of the 8 cases listed as treatment emergent hypertension, 7 had hypertensive blood pressure readings on Visits 1 -3, 5 of 8 had hypertensive blood pressure readings on Visits 4 through 6. Only one subject (LVHG 135-4503) appeared to have treatment emergent hypertension in the open-label period. His blood pressure was 140/90 mm Hg on Visit 9 (his last visit), and there were no other elevated blood pressures for this subject at previous visits.

In the instance of cardiac arrest, the narrative does not provide adequate data or description for this reviewer to ascertain exactly what transpired, although it was unexpected that the patient was discharged in good health 2 days after "cardiac arrest". This narrative is present in Study LVHG Open-Label review under SAEs.

In the **additional BPH analysis set of all subjects**, there were no significant differences between treatment groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs. Twenty-nine subjects (2.5%) reported a total of 31 cardiovascular disorder TEAEs.

Table 109: Treatment Emergent Cardiovascular Adverse Events Additional BPH Analysis Set

Cardiovascular Disorders	Placebo (N=581)	Tadalafil 5 mg (N=581)
	n (%)	
Total Disorders	11(1.9)	18 (3.1)
Preferred Terms		
Heart Rate Decreased	1 (0.2)	1 (0.2)
Tachycardia	0 (0.0)	1 (0.2)
Atrioventricular First Degree Block	1 (0.2)	0 (0.0)
Bundle Branch Block Right	1 (0.2)	0 (0.0)
Cardiomegaly	0 (0.0)	1 (0.2)
Edema Peripheral	1 (0.2)	1 (0.2)
Acute Myocardial Infarction	0 (0.0)	1 (0.2)
Scan Myocardial Perfusion Abnormal	0 (0.0)	1 (0.2)
Coronary Artery Stenosis	1 (0.2)	0 (0.0)
Cardiac Murmur	1 (0.2)	0 (0.0)
Cerebrovascular Accident	1 (0.2)	0 (0.0)
Hypertension	5 (0.9)	11 (1.9)
Blood Pressure Fluctuation	0 (0.0)	1 (0.2)
Hypotension	0 (0.0)	1 (0.2)
Orthostatic Hypertension	1 (0.2)	0 (0.0)

Source: Table ISS 49, Integrated Summary of Safety, page 335

> *Reviewer's Comment: The analysis of the **additional BPH analysis set of all subjects** does not indicate any new safety issue or concern. The issue of hypertension has been previously discussed – there appear to be few instances of true new-onset hypertension in these studies. If the hypertension AEs are not considered treatment-emergent, then there appears to be no overall increase of AEs in the tadalafil 5 mg group versus placebo.*

BPH/ED Analysis Set

The Sponsor notes there were no significant differences between the tadalafil 5- and 2.5-mg groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs, when

compared with placebo except for study discontinuation in the **pivotal BPH/ED analysis set**. Two subjects in the tadalafil 2.5 mg group (myocardial infarction) and one subject in the tadalafil 5 mg group (acute myocardial infarction) discontinued secondary to these adverse events versus none for placebo (Table ISS.14 page 68 ISS). Ten subjects (1.7%) reported a total of 10 cardiovascular disorder TEAEs (in 10 unique patients). One subject (LVHR-208-2806, tadalafil 2.5 mg) was found dead in his house by his wife 4 days after his last dose of study drug with a presumed cause of death related to an MI, and this case was reported as an SAE of myocardial infarction that resulted in discontinuation/death (see previous narrative and reviewer comments for this case).

Table 110: Treatment-Emergent Cardiovascular Adverse Events Pivotal BPH/ED Study LVHR

Cardiovascular Disorders	Placebo (N=200)	Tadalafil 2.5 mg (N=198)	Tadalafil 5 mg (N=208)
	n (%)		
	2 (1.0)	3 (1.5)	5 (2.4)
Preferred Terms			
Heart Rate Decreased			1 (0.5)
Palpitations		1 (0.5)	
Scan Myocardial Perfusion Abnormal			1 (0.5)
Myocardial Infarction		1 (0.5)	
Hypertension	1 (0.5)		3 (1.4)
Orthostatic Hypotension	1 (0.5)	1 (0.5)	

Source: Table APP 2.7.4.77, Summary Clinical Safety Appendix, page 551

With respect to the cases of hypertension noted in Pivotal BPH/ED Study LVHR, there were three cases of hypertension reported for tadalafil 5 mg subjects, none for tadalafil 2.5 mg subjects and 1 for placebo subjects. The reviewer assessed the Vitals.XPT subject line lisitings. Two of the three tadalafil 5 mg subjects had either or both systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥90 mmHg at Visits 1-3. In the placebo subject in LVHR with treatment emergent hypertension, the diastolic blood pressure was 92 mmHg at Visits 2 and 3.

> *Reviewer's Comment: In my opinion, there is only one LVHR patient with treatment emergent hypertension, Subject LVHR 210-2962(tadalafil 5 mg).*

In the pooled data from the double-blind periods of Studies LVHG, LVHJ, and LVHR, three subjects in the tadalafil 2.5- and 5-mg groups (N=797) reported myocardial infarctions that led to study discontinuation compared to none for placebo (N=786). This finding was identified in the 74 Day Letter as a potential review issue and the Sponsor was requested to respond. Their narratives are presented in brief below and in greater detail in the respective Study report in which these events occurred.

- Subject LVHR-208-2806, tadalafil 2.5 mg: The patient was found dead in his house by his wife 4 days after his last dose of study drug. No autopsy was performed. Myocardial infarction was presumed to be his cause of death.

- Subject LVHG-101-1166, tadalafil 2.5mg: The patient was a 93 year old man who took study drug for two weeks, then suffered a myocardial infarction when performing "heavy manual labor, including digging out tree roots".

- Subject LVHJ-303-3316, tadalafil 5mg: The patient was an 80 year male with hypertension (140/90 mmHg while on lisinopril and study drug), hyperlipidemia, degenerative arthritis, and polyneuropathy who suffered a myocardial infarction approximately 10 weeks after initiating study medication. His cardiac cath revealed 75%, 90%, and 90% occlusion of the LAD, circumflex and right coronary arteries. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequently an intra-aortic balloon pump. He died 4 days after his MI.

The Sponsor points out in their Regulatory Response of 12 April 2011, all of the above subjects had pre-existing diseases or conditions that are known risk factors for myocardial infarction. Subject LVHJ 303-3316 had hypertension and hyperlipidemia for 10 years. Subject LVHR 208-2806 had cardiac arrhythmia, impaired glucose tolerance, sleep apnea and mild mitral valve prolapse. Subject LVHG 101-1166, a 93 year old male, was performing heavy manual labor when the event occurred.

> *Reviewer's Comment: In each MI discontinuation case there were confounding elements and the overall incidence of cardiovascular events was not significantly different between drug and placebo in the overall study population(s). This is especially true if the reports of hypertension are not considered significant (see below). Discontinuations due to MI as a concern have been resolved, in my opinion.*

In the 74 Day Letter sent to Sponsor, the concern relating to TEAEs of hypertension was raised. In the Additional BPH/ED Set of Subjects with ED, 2.4% (11/464) tadalafil 5 mg subjects reported hypertension compared to 0% (0/333) in the placebo group and compared to placebo groups (2.5 mg placebo 0.6% [2/342] and 5 mg placebo 0.9%[3/454]). In response to this concern, the Sponsor identified and reviewed 14 ED subjects with the TEAE of hypertension in the three pivotal studies. Their analysis revealed that actual, evidence-based TEAEs of hypertension were few and most of the subjects reported to be hypertensive did not have recorded postrandomization increases in systolic blood pressure from those recorded prior to randomization. The Sponsor also identified and analyzed 16 additional subjects with a TEAE of treatment-emergent hypertension not included in the Additional BPH/ED Set of Subjects with ED. 3 of these patients were placebo and 12 of the remaining 13 were participating in the open-label period of LVHG. 10 of these subjects had hypertension at study entry or risk of hypertension. The Sponsor concludes "Review of subject's pre- and post-randomization serial blood pressures values finds no evidence for treatment-emergent increases in blood pressure in

subjects with TEAE of hypertension in the integrated analysis from Studies LVHG, Study LVHJ and Study LVHR."

Reviewer's Comment: The reviewer accessed the VITALS XPT data set for each Analysis set reviewed in the Cardiovascular TEAEs section. The line listings for each subject reporting the TEAE of hypertension were analyzed and the findings confirm the Sponsor's analysis results and conclusion. The review issue regarding hypertension with tadalafil use in the BPH and BPH/ED population is resolved. There are no new cardiovascular safety signals or concerns.

Ear Disorders: In the **long-term open-label LVHG extension period**, a total of 5 subjects (1.2%) reported a total of 8 ear disorder TEAEs. None of these events were SAEs, and 1 event of unilateral deafness (Subject LVHG-106-1604, previously discussed and repeated herein) led to study discontinuation.

LVHG Subject 106-1604 a 48-year-old who received tadalafil 2.5 mg in the double-blind phase, reported deafness unilateral at Visit 11 which lasted 17 days. According to the subject's otolaryngologist the subject had previously experienced neurosensory hearing loss (October 2006). The event occurred 2 months after a previous check-up and the otolaryngologist replied that there was minimal progression. The subject discontinued the study due to this event. Prior to the event of deafness unilateral the subject reported vertigo positional which occurred prior to Visit 10 and lasted for 63 days. One month after the deafness unilateral the subject reported tinnitus which lasted approximately 2 weeks. To treat the tinnitus, the patient used hydrogen peroxide ear drops. Concomitant medications were ascorbic acid and fluticasone for allergy.

Reviewer's Comment: This appears to be an exacerbation of a pre-existing condition.

In the **additional BPH analysis set** of all subjects, 5 subjects reported a total of 6 ear disorder TEAEs. Two of the ear disorder TEAEs occurred in the **pivotal BPH analysis set** (vertigo, tinnitus [neither led to discontinuation]). The additional 4 ear disorder TEAEs occurred in the **pivotal BPH/ED analysis set**, and no significant differences were observed across treatment groups.**.**

Table 111: Treatment Emergent Ear Disorder Adverse Events All Randomized Subjects Studies LVHG, LVHJ, and LVHR

Preferred Term	Placebo	Tadalafil 5 mg
	N-576	N=581
	n (%)	
Subjects with >= 1 TEAE	3 (0.5)	2(0.2)
Deafness	0 (0.0)	1 (0.2)
Vertigo	1 (0.2)	1 (0.2)
Balance Disorder	1 (0.2)	0 (0.0)
Labyrinthitis	1 (0.2)	0 (0.0)
Vertigo Positional	1 (0.2)	0 (0.0)

Source: Table ISS 50, Integrated Summary of Safety, page 339

LVHJ Subject 302-3210, as described previously , was an 82-year old white male who reported a TEAE of deafness (actual term "acute hearing loss") approximately 12 weeks postrandomization. Further follow-up with the site revealed that the subject had reported tinnitus in the left ear and an audiogram showed impaired hearing capacity. The subject received infusion therapy of pentoxifylline and prednisolone. The event was reported as resolved at the final visit. No historical diagnoses, preexisting conditions, or concomitant medications were reported. Approximately 2 months prior to the onset of the deafness, the subject received a 10-day course of doxycycline for a wound infection. The subject completed the study.

In the clinical pharmacology studies, of the subjects exposed to placebo, 0.4% (5/1289) reported a total of 5 ear and labyrinth disorder TEAEs. Of subjects receiving tadalafil at any dose, 0.2% (5/2080) of subjects reported a total of 9 ear and labyrinth disorder TEAEs. The total event rate was similar regardless of placebo or tadalafil treatment, with no more than 0.5% of subjects experiencing ≥ 1 ear and labyrinth disorder TEAE, regardless of treatment.

> *Reviewer's Comment: This data does not appear to demonstrate a treatment-related effect of tadalafil on ear disorders, although it is not possible to rule out a causal relationship in LVHJ Subject 302-3210.*

Eye Disorders: In the **pivotal BPH analysis set,** few eye disorder TEAEs were reported, and no significant differences were observed between treatment groups. Three subjects (0.4%) reported a total of 5 eye disorder TEAEs: 2 subjects (0.5%) in the tadalafil 5-mg group reported 4 events, and 1 subject (0.3%) in the placebo group reported 1 event. None of these events were SAEs. One event of retinal tear (Subject LHVG-106-1605, tadalafil 5 mg) led to study discontinuation. NAION was not reported.

In the **long-term open-label extension period** of Study LVHG, six subjects (1.4%) reported a total of 6 eye disorder TEAEs. One subject (LVHG-102-1201) reported an SAE of Basedow's disease (exophthalmic goiter).

In the **additional BPH analysis set of all subjects**, seven eye disorder TEAEs (in five patients) were reported, and no significant differences were observed between treatment groups.

For the **pivotal BPH/ED analysis set,** few eye disorder TEAEs were reported, and no significant differences were observed across treatment groups. Four subjects (0.7%) reported a total of 6 eye disorder TEAEs: 2 subjects (1.0%) in the tadalafil 5-mg group reported 2 events, and 2 subjects (1.0%) in the tadalafil 2.5-mg group reported 4 events. None of these events were SAEs or led to study discontinuation.

Table 112: Treatment Emergent Eye Disorder Adverse Events All Randomized Subjects Studies LVHG, LVHJ and LVHR

Preferred Term	Placebo	Tadalafil 5 mg
	N-576	N=581
	n (%)	
Subjects with >= 1 TEAE	1 (0.2)	4 (0.7)
Vision Blurred	1 (0.2)	3 (0.5)
Photopsia	0 (0.0)	1 (0.2)
Retinal Tear	0 (0.0)	1 (0.2)
Vitreous Floaters	0 (0.0)	1 (0.2)

Source: Table ISS 51, Integrated Summary of Safety, page 340.

Within the clinical pharmacology studies, 1.5% (19/1289) placebo subjects reported a total of 20 eye disorder TEAEs. Of the subjects receiving tadalafil at any dose, 2.3% (48/2080) subjects reported a total of 54 eye disorder TEAEs. The proportion of subjects with ≥1 eye disorder TEAE reported across all tadalafil treatment groups was generally higher (range: 1.5% [4/268] of subjects at the tadalafil 5-mg dose to 4.0% [8/202] of subjects at the 40-mg dose) than placebo at all dose levels, with the exception of the tadalafil 2.5-, 50- and 80-mg dose groups, where none of 36 subjects treated reported an eye disorder TEAE. Among subjects receiving tadalafil and with ≥1 eye disorder TEAE, the most frequent of the 54 TEAEs was vision blurred. Other eye disorder TEAEs reported in ≥2 subjects in any single tadalafil treatment group with greater incidence compared to placebo included photophobia, eye disorder, and visual impairment.

> *Reviewer's Comment: The differences between tadalafil and placebo in eye-related AEs is driven by several events of "blurred vision", which have been previously reported in clinical trials of tadaalfil, but at an incidence < 2% and where a causal relationship to tadalafil is uncertain. The term "blurred vision" in the current label appropriately reflects the cases reported in the BPH program.*

Treatment-Emergent Events Possibly Related to Hypotension, Including Headache, Asthenia, and Fatigue: Two separate analyses of TEAEs possibly related to hypotension were performed. The first analysis focused on the following 7 MedDRA preferred terms: dizziness, dizziness postural, procedural dizziness, hypotension, orthostatic hypotension syncope, and presyncope. An expanded analysis of TEAEs possibly related to hypotension was performed which included the preferred terms of headache, asthenia, and fatigue, as well as several other event terms. The Sponsor presents a complete list of MedDRA (version 13.0) preferred terms used in this expanded analysis.

BPH Analysis Sets
Using the focused list of TEAEs possibly related to hypotension, for the **pivotal BPH analysis set,** the Sponsor reports differences were noted between the tadalafil 5 mg and placebo groups in the percentages of subjects reporting at least 1 TEAE or any individual TEAE possibly related to hypotension.

Table 113: Treatment Emergent Events Possibly Related to Hypotension Pivotal BPH Studies LVHG and LVHJ

Preferred Term	Placebo	Tadalafil 5 mg
	(N=376)	(N=373)
	n (%)	
Subjects with >= 1 TEAE	1 (0.3)	5 (1.3)
Dizziness	1 (0.3)	4 (1.1)
Hypotension	0 (0.0)	1 (0.1)

Source: Table APP 2.7.4.89, Appendix Summary Clinical Summary of Safety, page 575.

For the **pivotal BPH analysis set,** with respect to TEAEs possibly related to hypotension (expanded analysis), including the terms headache, asthenia, and fatigue, no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension. Twenty-nine subjects (3.9%) reported a total of 30 events possibly related to hypotension. Of these, 19 were reports of headache (2.5%), which was the most frequently reported event in both treatment groups (tadalafil 5 mg: 3.2%; placebo: 1.9%). No events possibly related to hypotension were SAEs, and 4 events of headache (Subjects LVHG-101-1169, LVHG-522-3278, LVHG-600-1086, and LVHJ-107-1712; all tadalafil 5 mg) led to study discontinuation. Three AEs of headache (1 tadalafil 5-mg subject and 2 placebo subjects) were reported on the same day as randomization and therefore were not included in the statistical output of TEAEs possibly related to hypotension based on the definition of a TEAE. The Sponsor states that inclusion of these events would not have altered the interpretation of the analysis of TEAEs possibly related to hypotension.

Table 114: Treatment-Emergent Events Possibly Related to Hypotension Including Headache, Fatigue, and Asthenia Pivotal BPH Studies LVHG and LVHJ

Preferred Term	Placebo	Tadalafil 5 mg
	(N=376)	(N=373)
	n (%)	
Subjects with >= 1 TEAE	11 (2.9)	18 (4.8)
Headache	7 (1.9)	12 (3.2)
Dizziness	1 (0.3)	4 (1.1)
Asthenia	2 (0.5)	1 (0.3)
Fatigue	1 (0.3)	1 (0.3)
Hypotension	0 (0.0)	1 (0.3)

Source: Table APP 2.7.4.90, Appendix Summary Clinical Summary of Safety, page 576.

In the **long-term open-label extension period** of LVHG, TEAEs possibly related to hypotension, including headache, asthenia, and fatigue occurred in thirteen subjects (3.0%) who reported a total of 16 TEAEs. Of these, 7 were reports of headache (1.6%), occurring primarily (6 of 7 reports) in subjects who had been previously assigned to receive tadalafil 10 or 20 mg during the double-blind period of Study LVHG. No TEAEs possibly related to hypotension were SAEs or led to study discontinuation.

In the **additional BPH analysis set of all subjects**, no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension using both the expanded and focused list of preferred terms. Fifty-two subjects (4.5%) reported a total of 54 TEAEs possibly related to hypotension using the expanded list of terms. Of these, 30 events occurred in the **pivotal BPH analysis set.** The additional 24 events occurred in the tadalafil 5-mg and placebo groups in the **pivotal BPH/ED analysis set** along with the 8 TEAEs possibly related to hypotension occurring in the tadalafil 2.5 mg group.

Table 115: Treatment Emergent Adverse Events Possibly Related to Hypotension including Headache, Asthenia and Fatigue Studies LVHG, LVHJ and LVHR (Expanded BPH Analysis Set)

Preferred Term	Placebo	Tadalafil 5 mg
	(N=576)	(N=581)
	n (%)	
Subjects with >= 1 TEAE	20 (3.5)	32 (581)
Headache	13 (2.3)	24 (4.1)
Dizziness	3 (0.5)	6 (1.0)
Asthenia	2 (0.3)	1 (0.2)
Fatigue	1 (0.2)	1 (0.2)
Hypotension	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)
Orthostatic Hypotension	1 (0.2)	0 (0.0)

Source: Table ISS 53, Integrated Summary of Safety, page 342.

With respect to the **pivotal BPH/ED analysis set.** No significant differences were observed for either tadalafil group in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, when compared to placebo. Thirty subjects (5.0%) reported a total of 32 events possibly related to hypotension. Of these, 23 were reports of headache (3.8%), which was the most frequently reported event in all treatment groups (tadalafil 5 mg: 5.8%; tadalafil 2.5 mg: 2.5%; placebo: 3.0%). No TEAEs possibly related to hypotension were SAEs. Three TEAEs possibly related to hypotension led to study discontinuation: 1 event of headache (Subject LVHR-112-2216, tadalafil 5 mg), 1 event of syncope (LVHR-207-2710, tadalafil 5 mg), and 1 event of dizziness (LVHR-104-1404, tadalafil 2.5 mg).

Table 116: Treatment-Emergent Adverse Events Possibly Related to Hypotension Pivotal BPH/ED Study LVHR

Preferred Term	Placebo	Tadalafil 2.5 mg	Tadalafil 5 mg
	(N=200)	(N=198)	(N=208)
	n (%)		
Subject with >= 1 TEAE	9 (4.5)	7 (3.5)	14 (6.7)
Headache	6 (3.0)	5 (2.5)	12 (5.8)
Dizziness	2 (1.0)	2 (1.0)	2 (1.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic Hypotension	1 (0.5)	0 (0.0)	0 (0.0)

Source: Table APP 2.7.4.94, Appendix Clinical Summary Safety, page 580

Reviewer's Comment: The results in adverse events possibly related to hypotension in both the focused and expanded analysis groups are driven by the preferred terms headache and dizziness. Both of these events have been previously reported in clinical trials in patients taking tadalafil andwere reported in the BH program pivotal studies, but do not appear to be associated with hypotension. As is shown in the table below:

Table 117: Selected Events Possibly Related to Hypotension All Randomized Subjects Studies LVHG, LVHJ, LVHR Double-Blind Treatment Period

Preferred Term	*Placebo (N=576)*	*Tadalafil 5 mg (N=581)*
	n (%)	
Headache	*13 (2.2)*	*24 (4.1)*
Dizziness	*3 (0.5)*	*6 (1.0)*
Hypotension	*0 (0.0)*	*0 (0.0)*
Syncope	*0 (0.0)*	*1 (0.2)*
Fatigue	*1 (0.2)*	*0 (0.0)*

Source: Table ISS.53, Integrated Summary of Safety, Page 342.

In my opinion, there is not an indication that events possibly related to hypotension occur with increased frequency as compared to placebo in this study population. Dizziness and headache appear to occur independent of hypotension. Headache is listed as an adverse event for the BPH program in the Adverse Reactions section of labeling, but "dizziness" is not. Recommend adding the term 'dizziness" to the label in the BPH program section of Adverse Reactions.

Myalgias and Back Pain: Thirty-one subjects (4.1%) reported a total of 35 myalgia/back pain TEAEs in the **pivotal BPH analysis set**. The percentage of subjects reporting at least 1 myalgia/back pain TEAE was significantly greater in the tadalafil 5-mg group compared with the placebo group (6.2% versus 2.1%, p=.006). The most commonly reported myalgia/back pain TEAE in the tadalafil 5-mg group was back pain (2.1%), which was not significantly different between the tadalafil 5-mg group and placebo. Among the TEAEs that were reported in less than 2% of subjects, pain in extremity (p=.008), myalgia (p=.025), and arthralgia (p=.044) were reported by a significantly greater percentage of subjects in the tadalafil 5-mg group compared to the placebo group. No myalgia/back pain TEAEs were SAEs and 4 events led to study discontinuation: myalgia (Subject LVHG-102-1200, tadalafil 5 mg), pain in extremity (Subject LVHG-102-1206, tadalafil 5 mg), and pain (Subject LVHG 110-120-2008, tadalafil 5 mg), and back pain (Subject LVHJ-401-4101, placebo). One AE of back pain (tadalafil 5 mg) and 1 AE of myalgia (placebo) were reported on the same date as randomization and therefore were not included in the statistical output of myalgia/back pain TEAEs based on the definition of a TEAE. Inclusion of these events would not have altered the interpretation of the analysis of myalgia/back pain TEAEs in the Sponsor's opinion.

Twenty-eight subjects (6.6%) in the **long-term open-label extension** of Study LVHG reported a total of 30 myalgia/back pain TEAEs. Overall, the percentages of subjects reporting at least 1 myalgia/back pain TEAE were similar (3.1% to 6.0%) between subjects previously treated with tadalafil 2.5, 5, 10, and 20 mg, compared with a numerically greater percentage of subjects previously treated with placebo reporting at least 1 myalgia/back pain TEAE (13.0%), which was driven by a numerically greater percentage of previously treated placebo subjects reporting back pain, myalgia, and arthralgia compared to the other previous tadalafil dose groups. No myalgia/back pain TEAE were SAEs and 1 event of muscle tightness (Subject LVHG-139-4907) led to study discontinuation.

In the **additional BPH analysis set of all subjects** (tadalafil 5 mg or placebo), the percentage of subjects reporting at least 1 myalgia/back pain TEAE was significantly greater in the tadalafil 5-mg group compared with the placebo group (5.9% versus 2.4%, p=.004). Forty-eight subjects (4.1%) reported a total of 54 myalgia/back pain TEAEs. Of these, 35 events occurred in the **pivotal BPH analysis set.** The additional 12 events occurred in the tadalafil 5-mg and placebo groups in the **pivotal BPH/ED analysis set** along with the 7 myalgia/back pain events occurring in the tadalafil 2.5 group.

Table 118: Treatment Emergent Myalgias/Back Pain Adverse Events Studies LVHGH, LVHJ, and LVHR

Preferred Term	Placebo	Tadalafil 5 mg
	N-576	N=581
	n (%)	
Subjects with >= 1 TEAE	14 (2.4)	34 (2.4)
Back Pain	8 (1.4)	14 (2.4)
Pain in Extremity	0 (0.0)	8 (1.4)
Myalgia	2 (0.3)	7 (1.2)
Arthralgia	2 (0.3)	5 (0.9)
Muscle Spasms	0 (0.0)	2 (0.3)
Pain	0 (0.0)	2 (0.3)
Musculoskeletal Pain	2 (0.3)	1 (0.2)
Musculoskeletal Chest Pain	1 (0.2)	0 (0.0)

Source: Table ISS 54, Integrated Summary of Safety, page 343.

Reviewer's Comment: As expected, the incidence of myalgia/back pain events was higher in tadalafil 5mg compared to placebo, including the incidence of discontinuations due to adverse events. Myalgia/back pain events also include a number of terms other than "myalgia" and "back pain" – including "pain in extremity", " arthralgia", and "muscle spasms". While the label does mention "back pain" in the BPH program section, it does not mention myalgia, pain in extremity, muscle spasms and arthralgia, nor does it

mention discontinuations due to these events. Recommend adding the additional terms and the discontinuations to the label in the BPH program section of Adverse Reactions.

In the **pivotal BPH/ED analysis set,** no significant differences were observed in the percentage of subjects reporting at least 1 myalgia/back pain TEAE, or any individual myalgia/back pain TEAEs, in the tadalafil 5-mg or 2.5-mg groups when compared to placebo. Twenty four subjects (4.0%) reported a total of 26 myalgia/back pain TEAEs. The most commonly reported myalgia/back pain TEAE in the tadalafil 5-mg group was back pain (2.9%). No other myalgia/back pain TEAE was reported with a frequency of greater than 1 percent. No myalgia/back pain events were SAEs. Three myalgia/back pain TEAEs led to study discontinuation: 1 event of myalgia (Subject LVHR-209-2913, tadalafil 5 mg), 1 event of back pain (Subject LVHR-702-7215, tadalafil 5 mg), and 1 event of muscle spasms (Subject LVHR-704-7401, tadalafil 5 mg). One AE of muscle spasms (tadalafil 5 mg) was reported on the same date as randomization and therefore was not included in the statistical output of myalgia/back pain TEAEs based on the definition of a TEAE. Inclusion of this event would not have altered the interpretation of the analysis of myalgia/back pain TEAEs in the Sponsor's opinion.

Seizures: No seizure TEAEs were reported in the **pivotal BPH analysis set,** in the **long-term open-label extension** of Study LVHG, in the **additional BPH analysis set of all subjects,** in the **pivotal BPH/ED analysis set,** or in the combined clinical pharmacology studies.

Transient Global Amnesia: No transient global amnesia TEAEs were reported in the **pivotal BPH analysis set**, or in the **additional BPH analysis set of all subjects**.

For the **long-term open-label extension period** of Study LVHG, two subjects (0.5%) reported a total of 2 transient global amnesia TEAEs. One event was an SAE (transient global amnesia, Subject LVHG-204-1431). Neither of the transient global amnesia TEAEs led to study discontinuation. In Subject LVHG-204-143, the transient global amnesia occurred 4 days after the 12 month study period had ended and after weight lifting. In the second case, LVHG-110-2011 (a non-serious case), the event occurred after 3 months of drug exposure and the patient completed the LVHG study period. The duration of the event is unknown

No transient global amnesia TEAE's were reported in the **pivotal BPH/ED analysis set.**

Within the clinical pharmacology studies, one placebo subject reported amnesia. No amnesia TEAEs were reported in any tadalafil-treated subjects in the 68 clinical pharmacologic studies.

7.3.5 Submission Specific Primary Safety Concerns

The submission-specific primary safety concerns included:

- The safety of tadalafil use in the elderly with BPH

Reviewer's Comment: The Sponsor has conducted a thorough review by age groups for adverse events. Overall, in my opinion, no age-related safety concern or signal is detected in the review of studies submitted in the NDAs (see 7.5.3 Drug-Demographic Interaction).

- The safety of tadalafil with concomitant antihypertensive medication in men with BPH

  Reviewer's Comment: It does not appear that tadalafil presented an increased risk in any age subgroup for hypotension in patients taking concomitant antihypertensive medications (see 7.5.5 Drug-Drug interactions).

- The frequency of notable adverse events (bleeding, cardiovascular, ear disorders, eye disorders, hypotension, myalgias and back pain, seizures and transient global amnesia) in BPH patients taking tadalafil.

  Reviewer's Comment: In the additional analysis set of all BPH patients for the three pivotal studies (LVHG, LVHJ, and LVHR), there were six (1.0%) bleeding AEs in the tadalafil 5 mg group and 0 (0.0%) in the placebo group. The AEs were three episodes of epistaxis, 2 episodes of rectal or hemorrhoidal hemorrhage, and 1 episode of hemorrhagic pancreatitis (with possible obstruction from cholelithiasis). With respect to cardiovascular events (refer to Table 109), the difference between tadalafil 5 mg and placebo is driven by the differences in reported hypertension (tadalafil 11 [1.9%] versus placebo 5 [0.91%]). Hypertension in most patients was noted in the pre-randomization period and therefore was not treatment emergent. The results in adverse events possibly related to hypotension in both the focused and expanded analysis groups are driven by the preferred terms headache and dizziness. Both of these events are known to be associated with tadalafil in a dose related manner and in the pivotal studies do not appear to be associated with hypotension. There did not appear to be an increase of AEs related to hypotension. Myalgias (tadalafil 5.9% versus placebo 2.4%) and back pain were present in more tadalafil subjects than placebo as would be expected from the safety profile of tadalafil. No seizures or episodes of transient global amnesia were noted in the double-blind periods. In the open label period of LVHG, 2 subjects reported transient global amnesia. In one subject, this event occurred after weight lifting. The reader is referred to Section 7.3.5 of this review for a more detailed discussion for each of these notable adverse events.

  My review of notable adverse events did not reveal any new safety concerns relating to tadalafil use in patients with BPH.

- The safety of co-administration of tadalafil and alpha-blockers in men with BPH.

  Reviewers Comment: In Study LVHS (Section 5.3 of this review), the safety results are comparable with other tadalafil studies submitted. There were no new safety concerns or signals noted in patients concomitantly using alpha blockers and tadalafil. The non

selective alpha blockers generated 9 of 14 adverse events possibly related to hypotension (page 126 of LVHS Study Report).

- The safety of tadalafil use in men with BPH previously using either PDE5 inhibitors or alpha-blockers.

  Reviewer's Comment: The adverse events associated with alpha-blocker washout were relatively few and for the most part of modest severity. There was only 1 episode of retention in 279 men who stopped taking alpha-blockers. There is some degree of symptomatic worsening during alpha blocker washout. In my opinion, alpha-blockers can be safely stopped in men with BPH prior to using tadalafil for BPH treatment. Most of the significant adverse events, from a genitourinary standpoint, occurred in Study LVHR and usually occurred in the first 7 days of washout.

  No clinically important findings relevant to prior alpha blocker use were noted and the TEAEs observed in subjects with prior alpha-blocker use are consistent with the known safety profile of tadalafil.

  No clinically important findings relevant to prior PDE5 inhibitor use were noted and the TEAEs observed in subjects with prior alpha-blocker use are consistent with the known safety profile of tadalafil. The reader is referred to Section 7.5.5. of this review for a more detailed discussion of prior alpha-blocker and PDE5 therapy and alpha-blocker washout.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 119: Treatment-Emergent Adverse Events with >= 1% increased Frequency Tadalafil 5 mg Versus Placebo BPH Subjects With and Without ED Studies LVHG, LVHJ and LVHR

Preferred Term	Patients Without ED n (%)		Patients with ED n (%)	
	Placebo	Tadalafil 5g	Placebo	Tadalafil 5 mg
	N=119	N=117	N=454	N=464
Subjects >= 1 TEAE	24 (20.2)	41 (35.0)		
Headache	2 (1.7)	6 (5.1)		
Dyspepsia	0 (0.0)	5 (4.3)		
Diarrhea	1 (0.8)	3 (2.6)		
Myalgia	0 (0.0)	3 (2.6)		
Depression	0 (0.0)	2 (1.7)		
Insomnia	0 (0.0)	2 (1.7)		
Nocturia	0 (0.0)	2 (1.7)		
Subjects >= 1 TEAE			96 (21.1)	125 (26.9)
Headache			11 (2.4)	18 (3.9)
Back Pain			6 (1.3)	11 (2.4)
Hypertension			3 (0.7)	11 (2.4)
Dyspepsia			1 (0.2)	9 (1.9)
Pain in Extremity			0 (0.0)	7 (1.5)

Sources: Tables ISS 9 and ISS 12, Integrated Summary of Safety, pages 47 and 55.

Reviewer's Comment: The table above summarizes AE in BPH subjects with and without ED. The AE profile is similar to the known profile of tadalafil in both BPH subjects with and without ED with the exception of hypertension in patients with ED. This has been extensively studied in the analysis of each of the three pivotal studies. It was found that in most cases the subjects noted to have hypertension after receiving active treatment (post randomization), upon subject by subject line review, were hypertensive at one of the visits preceding drug exposure (Visit 1-Visit-3), and there was actually no increase in blood pressure during treatment in those patients. The review of hypertensive patients is shown in each of the individual pivotal studies within this review. It is my opinion that there does not appear to be adequate credible evidence to support the concern of hypertension in BPH/ED patients taking tadalafil.

There were no significant differences between the tadalafil 5-mg and placebo groups in the percentages of subjects with SAEs (including deaths and nonfatal SAEs) and procedure related TEAEs. There were significantly greater percentages of subjects in the tadalafil 5-mg versus the placebo groups with TEAEs (p=.003), discontinuations due to AEs (p=.028), and treatment-related AEs (possibly study drug related; p<.001).

The table below summarizes the most common treatment-emergent events in the integrated data base for all three pivotal studies.

Table 120: Common TEAEs >=2% in the Tadalafil Group and Greater than Placebo Group All Randomized Subjects Studies LVHG, LVHJ, and LVHR

Preferred Term	Placebo (N=576)	Tadalafil (N=581)
	n (%)	
Subjects with >= 1 TEAE	121 (21.0)	166 (28.8)
Headache	13 (2.3)	24 (4.1)
Back Pain	8 (1.4)	14 (2.4)
Dyspepsia	1 (0.2)	14 (2.4)
Nasopharyngitis	9 (1.6)	12 (2.1)

Source: Table ISS 4, Integrated Summary of Safety, page 24

Reviewer's Comment: These results are compatible with the known safety profile of tadalafil.

The table below summarizes TEAE by System Organ Class (SOC) in order to identify if individual AEs when considered by organ class point to a new safety signal or concern.

Table 121: Treatment-Emergent Events by System Organ Class All Randomized Subjects Studies LVHG, LVHJ and LVHR

System Organ Class	Placebo (N=576)	Tadalafil 5 mg (N=581)
	n (%)	
Subjects with >= 1 TEAE	121 (21.0)	166 (28.6)
Cardiac Disorders	3 (0.5)	3 (0.5)
Ear and Labyrinth Disorders	2 (0.3)	4 (0.7)
Endocrine Disorders	1 (0.2)	1 (0.2)
Eye Disorders	1 (0.2)	1 (0.2)
Gastrointestinal Disorders	3 (0.5)	7 (1.2)
General Disorders & Administrative Site Conditions	9 (1.6)	14 (2.4)
Hepatobiliary Disorders	1 (0.2)	1 (0.2)
Immune System Disorders	0 (0.0)	3 (0.5)
Infections and Infestations	33 (5.7)	36 (6.2)
Injury, Poisoning and Procedural Complications	8 (1.4)	7 (1.2)
Investigations	0 (0.0)	1 (0.2)
Metabolism and Nutrition Disorders	2 (0.3)	6 (1.0)
Musculoskeletal and Connective Tissue Disorders	18 (3.1)	36 (6.2)
Neoplasms Benign, Malignant, and Unspecified	3 (0.5)	1 (0.2)
Nervous System Disorders	17 (3.0)	30 (5.2)
Psychiatric Disorders	3 (0.5)	6 (1.0)
Renal and Urinary Disorders	5 (0.9)	7 (1.2)
Reproductive System and Breast Disorders	1 (0.2)	2 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	9 (1.6)	13 (2.2)
Skin and Subcutaneous Tissue Disorders	6 (1.0)	7 (1.2)
Surgical and Medical Procedures	1 (0.2)	3 (0.5)
Vascular Disorders	7 (1.2)	14 (2.4)

Source: Table ISS 47, Integrated Summary of Safety, page 324

Reviewer's Comment: The one subject who reported hearing loss (LVHJ 302-3120) had been exposed to doxycycline prior to randomization. This subject completed the study and the hearing loss resolved after treatment. The differences in gastrointestinal results were driven by 44 (7.6%) of tadalafil 5 mg subjects reporting dyspepsia and 5 subjects (0.9%) reporting gastroesophageal reflux disease versus 1 (0.2%) and 0 (0.0%) for placebo subjects respectively. This difference is a manifestation of the known safety profile of tadalafil. The differences in musculoskeletal disorders were driven by back pain (14 [2.4%] for tadalafil; 8 [1.4%] for placebo), pain in extremity (8 [1.4%] for tadalafil; 0 [0.0%] for placebo); and myalgia (7 [1.2%] for tadalafil; 2 [0.3%] for placebo). This difference is compatible with the known safety profile of tadalafil. The

differences in nervous system disorders were mainly driven by the differences in headache (24 [4.1%] for tadalafil and 13 [2.3%] for placebo). Headache is a known AE in the safety profile of tadalafil. In vascular disorders, hypertension was reported in 11 [1.9%] of tadalafil subjects and 5 [0.5%] of placebo subjects. As has been previously shown, many of the subjects identified as having hypertension after randomization, were found to have pre-existing hypertension prior to randomization, with no subsequent increase in BP post-randomization. There was only one patient in all three pivotal studies who was noted to have an increase in the prostate specific antigen. Analysis by SOC has not identified any new safety signals or concerns, in my opinion.

Table 122: Treatment-Emergent Adverse Events Occurring in >=2% of Tadalafil-Treated Subjects Open-Label Extension of Study LVHG

Preferred Term	Previous Placebo (N=92)	Total (N=427)
	n (%)	n (%)
Patients with >= 1 TEAE	50 (54.3)	256 (57.6)
Dyspepsia	4 (4.3)	17 (4.0)
Gastroesophageal Reflux Disease	2 (2.2)	17 (4.0)
Back Pain	4 (4.3)	16 (3.7)
Headache	3 (3.3)	13 (3.0)
Sinusitis	0 (0.0)	12 (2.8)
Hypertension	0 (0.0)	11 (2.6)
Cough	1 (1.1)	9 (2.1)

Source: Table LVHG, H6D-MC-LVHG Abbreviated Study Report, page 67.

Reviewer's Comment: The common AEs in the Open-Label Extension of LVHG are similar to those noted in the pivotal studies. Hypertension based on line analysis is not a treatment emergent event.

7.4.2 Laboratory Findings

Differences in laboratory parameters between the tadalafil 5 mg and placebo groups were not significant, in the Sponsor's opinion. For alkaline phosphatase, there was a statistically significant difference, but this appeared to be due to a negative mean change from baseline to last observation, and the Sponsor did not consider it clinically significant. No statistically significant findings were observed between the tadalafil 5 mg and placebo groups in any of the treatment-emergent abnormal, high or low chemistry values. There were no significant trends with regard to liver chemistries.

Table 123: Treatment-Emergent Elevated Hepatic-Related Serum Chemistry Results Studies LVHG, LVHJ and LVHR

	Placebo (N=576)	Tadalafil 5 mg (N=581)
	n (%)	
ALT >=3 ULN	3 (0.5)	3 (0.3)
AST >=3 ULN	1 (0.2)	1 (0.2)
Total bilirubin >= 1.5 ULN	5 (0.9)	1 (0.2)
ALT >= 3 ULN & Total bilirubin >=1.5 ULN	0 (0.0)	0 (0.0)
AST >= 3 ULN & Total bilirubin >=1.5 ULN	0 (0.0)	0 (0.0)

Source: Table ISS 60, Integrated Summary of Safety, page 357

Eleven subjects met the criteria of any value for AST or ALT more than 3-fold ULN or bilirubin more than 1.5-fold ULN (placebo: 8 subjects; tadalafil 5 mg: 3 subjects), although no subjects in either treatment group had elevations in both transaminase and total bilirubin levels post baseline.

Clinical sites were not instructed to measure body weight after the screening visit, thus approximately 40% of subjects in this analysis set were missing post baseline creatinine clearance calculations. Of the patients with creatinine clearances calculated, the percentage of subjects with treatment-emergent low estimated creatinine clearance (using Cockcroft-Gault formula) was numerically greater in the tadalafil 5-mg group versus placebo (33/215 [15.3%] versus 21/213 [9.9%], p=.090), but there was no statistically significant difference. None of these 54 subjects reported a TEAE related to renal impairment or failure.

> *Reviewer's Comment: Creatinine clearance decreases with aging. The Sponsor included patients > 65 and > 75 years of age in the pivotal studies to ensure a representative patient population. Therefore, some patients did not enter the pivotal studies with normal creatinine clearances. In addition, normal creatinine clearance was defined at Visit 3. By subject line review, this reviewer was able to identify 10 placebo and 20 tadalafil 5 mg subjects in Study LVHR with a creatinine clearance normal at Baseline (Visit 3). Two of the tadalafil 5 mg subjects and three of the placebo subjects had low creatinine clearances at Visit 1. In addition, the reliability of the Cockcroft-Gault formula to estimate creatinine clearance is based on the variability of the method used to measure the blood creatinine. In obese patients, this formula is less accurate than in lean patients. The Cockcroft-Gault formula underestimates the creatinine clearance in its higher ranges and underestimates the creatinine clearances in its lower ranges. The formula also does not adequately approximate the curve of creatinine clearance over age (J Int. Med, 2003:253: 563-573).*

Because of missing data for creatinine clearance (40% of subjects without body weight post screening), the Sponsor analyzed serum creatinine changes. The percentage of subjects with

treatment-emergent high creatinine, although small, was also numerically greater in the tadalafil 5-mg group versus placebo (11/524 [2.1%] versus 4/511 [0.8%], p=.077, though not statistically significantly greater). Five of these 15 subjects with treatment-emergent high creatinine had a screening (Visit 1, pre-randomization) creatinine value that was above the upper limit of normal (ULN) based on Standardized International (SI) units prior to treatment. Of the remaining 10 subjects, 4 were deemed to have clinically relevant increases in creatinine based on review of the by-visit values over the course of the study (1 in placebo [Subject LVHR-118-3952] and 3 in tadalafil 5 mg [Subjects LVHJ-400- 4002, LVHJ-500-5032, and LVHR-500-5005]). All 4 of these subjects had low estimated creatinine clearance on at least 1 pre-randomization measurement. Three of these 4 subjects (1 placebo subject and 2 tadalafil 5-mg subjects) had no relevant preexisting conditions reported, no concomitant medications, and no TEAEs reported during the study; all completed the study.

> *Reviewer's Comment: Based upon the Sponsor's analysis, 3 of 524 subjects exposed to tadalafil 5 mg in the three pivotal studies as compared to 1 of 5ll placebo subjects had treatment emergent abnormal (high) serum creatinine. These differences are too small (0.6 % for tadalafil 5 mg as compared to 0.2 % for placebo) to clinically distinguish clinical significance of one from the other.*

Changes between the tadalafil 5 mg and placebo groups in hematology values were not statistically significant, except for the mean change from baseline to last observation in lymphocytes (tadalafil 5 mg: -0.04 bill/L versus placebo: 0.02 bill/L; p=.045), which is not clinically meaningful in the Sponsor's opinion.

Seven subjects in the long-term open-label extension of Study LVHG reported a low platelet count (<130 x 109/L). None of the subjects had a platelet count consistent with thrombocytopenia (<100 x 109/L). One subject (LVHG-123-3309) had a history of leukopenia, and was taking steroids. Two other subjects (LVHG-202-1226 and LVHG-203- 1330) took steroids. One subject (LVHG-118-2829) took clopidogrel through Visit 9, which has been associated with thrombocytopenia. In addition, the patient had a course of azithromycin at Visit 6. His low platelet counts were first noted at Visit 8 or Week 16 which was the first platelet count after this antibiotic which has post-marketing reports of thrombocytopenia. One subject (LVHG-101-1127) also had laboratory abnormalities of macrocytes and anisocytosis; his concomitant medications included colchicine for gout. The remaining subjects (LVHG-100-1016 and LVHG-138-4809) had platelet counts of 188 x 109/L and 179 x 109/L, respectively, at the last visit. For these subjects, baseline values were even lower, rangingd from 127 to 227 x 109/L. One subject (LVHG-202-1226), taking tadalafil 2.5 mg per day, reported mild epistaxis throughout the treatment phase of the study (Visits 4 to 12). His lowest platelet count was 114 x 109/L at Visit 8; his platelet count was 156 x 109/L at baseline and 151 x 109/L at Visit 12. In summary, the finding of several patients with low platelet count in the oen label extension of Study LVHG appears to be coincidental to tadalafil use, and usually explainable by use of some other drug or condition.

In addition, three of the LVHG open-label extension subjects had no real change in the platelet count (203-1330, 107-1016 and 138-1409). Two subjects had sporadic low platelet counts that

were not sustained (123-3309 and 202-1226). The remaining two subjects were exposed to medications associated with thrombocytopenia (118-2829 and 101-1127). See table below.

Given that there were 7 subjects in the open-label extension period of Study LVHG with treatment-emergent low platelet counts, none consistent with thrombocytopenia (<100 x 109 /L), relevant data were reviewed for the additional BPH analysis set of all subjects. The changes from baseline in platelet counts between the tadalafil 5-mg and placebo groups were -10.76 versus 6.77 bill/L, respectively. The individual subjects with treatment-emergent low platelet counts were reviewed (tadalafil 5 mg: 6 [1.2%] subjects versus placebo: 3 [0.6%] subjects). There were no subjects for whom platelet counts ever dropped to a level considered to be thrombocytopenia (<100 x 109/L), with the lowest values ranging from 112 to 127 x 109/L.

> *Reviewer's Comment: There is no data reflecting thrombocytopenia (<100x 10^9/L) associated with tadalafil 5 mg in a long-term study.*

In the additional BPH analysis set of all subjects, no clinically adverse or statistically significant differences were observed between the tadalafil 5-mg and placebo groups in treatment-emergent abnormal results in urinalysis tests.

> *Reviewer's Comment: Overall, there were no clinically significant changes noted in clinical laboratory values in any of the pivotal data analysis sets.*

7.4.3

Vital Signs

Vital signs are reviewed in detail within the individual study analyses submitted. In the double-blind period of LVHG, there were no statistically significant mean changes from baseline to endpoint in the tadalafil groups when compared to placebo for heart rate, SBP, or DBP. Similar findings were present in the open-label extension period of Study LVHG. In LVHK, no statistically significant or clinically adverse changes from baseline to endpoint in mean heart rate, SBP, or DBP were observed between the tadalafil 20-mg group and placebo groups.

In Studies LVHJ, LVHR, and LVHS testing for orthostasis was performed.

- In Study LVHJ, the percentage of subjects with at least 1 treatment-emergent positive orthostatic test was similar between treatment groups (tadalafil 5 mg: 19.3%, placebo: 23.2%). No treatment-emergent adverse events were reported upon standing during orthostatic vital sign assessment.
- In Study LVHR, a similar proportion of subjects in each treatment group met at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test; neither the tadalafil 5-mg group (18.3%; p=.534 versus placebo) nor the tadalafil 2.5-mg group (20.7%; p=1.00 versus placebo) were statistically significantly different from placebo (21.0%).
- Study LVHS involved coadministration of tadalafil 5 mg or placebo with alpha blocker therapy. In this study, the percentage of subjects with at least 1 treatment-emergent positive test was similar between treatment groups (tadalafil 5 mg: 19.0%, placebo: 18.8%). An assessment of symptomatic orthostatic hypotension (presence of a clinical symptom simultaneously with a positive orthostatic test) also showed similar overall results between treatment groups (1 subject per group).

At the time of the filing review, a concern was raised regarding the increased incidence of hypertension (2.4% in the tadalafil 5 mg group compared to 0.6% in the placebo group). This concern has since been resolved through a detailed review of the individual cases, showing elevated BP at baseline with no further increases from baseline in most of the incident subjects.

> *Reviewer's Comment: The incidence of vital sign changes was similar between tadalafil 5 mg and placebo subjects. This was true even for patients coadministering tadalafil with alpha-blocking agents and was also true considering subgroup analysis by age. Vital sign changes in patients coadministering antihypertensive agents with tadalafil 5 mg versus placebo also did not exhibit any clinically significant differences even when analyzed by age subgroups. In addition, the incidence of hypertension has been extensively reviewed. It has been found that many of the patients, reporting hypertension had hypertensive blood pressures prior to randomization which did not rise while on treatment, which, in my opinion has resolved this review issue.*

7.4.4 Electrocardiograms (ECGs)

In Study LVHG and the open-label extension of Study LVHG (the only studies where ECGs were performed at Baseline and Endpoint), there were no statistically significant mean changes from baseline to endpoint in tadalafil treatment groups in ECG parameters in the Sponsor's opinion. These ECGs were interpreted by both the (b) (4) cardiologist and when indicated by the pre-defined ECG flow chart by a consultant cardiologist. The evaluation criteria and the evaluation results are extensively discussed in the individual reviews of Study LVHG and Study LVHG Open-Label Extension.

Reviewer's Comment: I concur with the Sponsor's opinion concerning ECGs.

7.4.5 Special Safety Studies/Clinical Trials

Post-Void residual volume (PVR)

Post-Void residual volume (PVR) was measured by ultrasound in Studies LVHG, LVHJ, LVHR and LVHS. In Study LVHK, PVR volume was measured by catheterization. In the pivotal BPH analysis set, BPH safety studies LVHK and LVHS, the long-term open-label extension period of Study LVHG or the pivotal BPH/ED analysis set, no clinically adverse or statistically significant changes were observed in mean PVR volume. There were no differences between the tadalafil and placebo groups in the percentages of urinary retention TEAEs in any of the analysis sets and studies. The few urinary retention TEAEs reported were in the pivotal BPH analysis set (tadalafil 5 mg: 0 subjects [0.0%] versus placebo: 2 subjects [0.5%]; p=.159 [Table APP.2.7.4.15]) and in Study LVHS (tadalafil 5 mg: 1 subject [0.6%] versus placebo: 1 subject [0.6%]. One patient experienced urinary retention (0.2%) in the open-label extension period of Study LVHG.

Urodynamics

Uroflowmetry measures were collected as efficacy parameters in the Phase 2b/3 Study LVHG. In subsequent Phase 2 (Study LVHK) and Phase 3 studies (Studies LVHJ, LVHR, and LVHS), uroflowmetry measures were collected as safety parameters. There appear to have been no adverse effects of tadalafil on urodynamic parameters. The uroflowmetry results are discussed in detail in the individual study reviews, but are briefly summarized here.

Study LVHK

The aim of this study was to evaluate the urodynamic effects (as assessed by free-flow and pressure-flow urodynamic parameters) of tadalafil 20 mg once daily for 12 weeks compared to placebo in men with BPH-LUTS. The mean difference of the change from baseline in $p_{detQmax}$ between treatment groups in the primary analysis population was -4.95 cm H_2O, which was not statistically significant (p=.068). The mean difference in PVR_{cath} between treatment groups in the primary analysis population was -10.34 mL for tadalafil 20 mg versus placebo. For a more detailed discussion, the reader is referred to the separate review of this study.

Reviewers Comment: The uroflowmetry results of Studies LVHG, LVHJ, LVHR, and LVHS and urodynamic results in Study LVHK do not indicate that once daily tadalafil is associated with clinically adverse effects on bladder function.

Study LVHS

The aim of this study was to assess the safety of tadalafil 5 mg once daily for 12 weeks in men on selective and non-selective alpha-blocking agents, in the event of off-label combination use. 158 men were exposed to tadalafil and 160 men were exposed to placebo. 78 men >75 years of age participated in the study.

Reviewer's Comment: LVHS did not result in the identification of new safety concerns related to concomitant administration of tadalafil and alpha blocker therapy. No tadalafil patients reported syncope or an SAE attributable to hypotension. A trend toward increased hemodynamic signs and symptoms in men on nonselective alpha blockers, most notably doxazosin, was noted as described in the existing Cialis USPI (2009). In this study, a greater proportion of elderly subjects reported tadalafil-related TEAEs relating to hypotension; however, this might have been due to a significantly lower incidence of hypotension-related adverse events in the elderly placebo subgroup compared to the younger placebo subgroup (5.3% and 10.7%, respectively); which apparently led to a numerically greater difference between taadlafil and placebo-treated elderly tadalafil subjects reporting hypotensive events (12.5% versus 5.3%) compared to younger subjects. For further details the reader is referred to the separate review of this protocol (including Tables 64 and 65) in this NDA review.

7.4.6 Immunogenicity

There were no immunogenicity studies in this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The results of Study LVHG which included 4 different doses of tadalafil are depicted below, as is the incidence of SAEs in the double-blind phase of Study LVHG.

Table 125: Treatment-Emergent Adverse Events Study LVHG by Tadalafil Dose

Subjects with >= 1 TEAE	Placebo	IC 2.5 mg	IC 5 mg	IC 10 mg	IC 20 mg
	(N=212)	(N=209)	(N=212)	(N=216)	(N=209)
	n (%)				
	45 (21.2)	56 (26.8)	65 (30.7)	75 (34.7)	83 (39.7)

IC=tadalafil Source: Table 14.80, LVHG Study Report, page 296

Reviewer's Comment: The incidence of TEAEs appears to be dose dependent. This is compatible with the known safety profile of tadalafil.

Table 126: Serious Adverse Events by Tadalafil Dose Study LVHG

Subjects with >= 1 Serious AE	Placebo	IC 2.5 mg	IC 5 mg	IC 10 mg	IC 20 mg
	(N=212)	(N=209)	(N=212)	(N=216)	(N=209)
	n (%)				
	6 (2.8)	3 (1.4)	1 (0.5)	2 (0.9)	2 (2.4)

IC=tadalafil Source: Table 14.87, LVHG Study Report, page 446

Reviewer's Comment: The incidence of SAEs in the tadalafil 2.5 to 10 mg dose groups does not appear to be dose dependent. However, SAES do increase at the 20 mg dose level.

7.5.2 Time Dependency for Adverse Events

To assess the time dependency of adverse events, the results of Study LVHG were chosen to be analyzed as it had a 1 year safety extension which allows a comparison of the AE occurring in formerly placebo subjects who then started dosing with 5 mg tadalafil once daily as compared to subjects continuing with tadalafil.

Table 127: Treatment-Emergent Adverse Events in Relation to Time of Exposure Study LVHG and LVHG Open-Label Extension

Subjects with >= 1 Serious AE	Formerly Placebo	Previous Tadalafil Dose			
		IC 2.5 mg	IC 5 mg	IC 10 mg	IC 20 mg
	(N=92)	(N=96)	(N=83)	(N=85)	(N=71)
Baseline Visit 7 (Day 0 of OLE period 0)	n (%)				
1 Month After OLE Treatment	17 (18.5)	12 (12.5)	7 (8.4)	4 (4.7)	7 (9.9)
End of OLE Study	44 (47.8)	42 (43.8)	40 (48.2)	37 (43.5)	40 (53.6)
End of Double-Blind Period in Patients Continuing in the OLE Period	20 (21.7)	35 (36.5)	28 (33.7)	31 (36.5)	33 (46.5)

IC=tadalafil Sources: Tables LVHG 11.28, 11.29 and 11.30, LVHG Open-Label Extension Report, pages 867, 879 and 883 respectively.

Reviewer's Comment: By my analysis the table above shows that at the 5 mg once a day dose approximately two thirds of the adverse events associated with tadalafil occur by 3 months. In looking at the formerly placebo subjects taking tadalafil 5 mg once daily, 39% of all AEs occurring in the OLE extension occurred in the first month of tadalafil 5 mg once a day dosing.

7.5.3 Drug-Demographic Interactions

Age

Safety outcomes based on age subgroups (subjects ≤65 and >65 years of age; subjects <75 years and ≥ years of age) were analyzed by the Sponsor. It was their conclusion that across all analysis sets, the TEAE profiles were similar between age groups, in the pivotal and additional BPH and BPH/ED analysis sets. There were no clinically meaningful differences in the frequencies and types of TEAEs across age groups.

In the pivotal and additional analysis sets supporting the BPH and BPH/ED indications (figures based on the June 23, 2011 amendment):

- 1448 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in the BPH and BPH/ED studies, with a total exposure of 624.5 subject years.
- 363 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 296 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

In subjects >65 years of age (contains figures from the June 23, 2011 amendment):

- 586 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission, with a total exposure of 237.9 subject years.
- 130 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 105 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

In subjects 75 years of age (contains figures from the June 23, 2011 amendment):

- 160 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission, with a total exposure of 65.3 subject years.
- 35subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 28 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

Reviewer's Comment: The number of subjects age >65 years and ≥ 75 years is sufficient to assess safety. The duration of exposure in patients > 65 years is sufficient, but the number of patients ≥ 75 with duration of exposure of at least 6 months and of at least 1 year is small. In the 74-Day Letter, Sponsor was asked to submit summaries of safety data in patients ≥75 years of age treated in previous as-needed and daily dosing ED studies in order to better support long-term safety in this age group. This data is included in their Regulatory Response of April 12, 2011, and is included in the discussion below.

Subjects ≤65 and >65 years of age: BPH

Overall in the **pivotal BPH analysis set,** TEAEs for subjects ≤65 and >65 years of age, there appeared to be a significant treatment group difference for subjects >65 years of age, with a greater percentage of subjects reporting at least 1 TEAE overall in the tadalafil 5-mg group compared to the placebo group (30.9% versus 19.1%). When analyzing overall adverse events by each AE term, among subjects >65 years of age, pain in extremity was reported by a significantly greater percentage of subjects in the tadalafil 5-mg group compared with the placebo group (4 subjects [2.7%] versus 0 placebo subjects). In addition, for the Injury, Poisoning, and Procedural complications SOC (4 [2.7%] 5 mg tadalafil versus 1 [0.7%] placebo), the significant hazard odds ratio was likely artifactual in the Sponsor's opinion. There were similar findings for Skin and Subcutaneous disorders SOC. It is the Sponsor's opinion that there was no specific by subgroup interactions for the SOCs mentioned.

In Studies LVHG, LVHJ and LVHR, there were three SAEs in the placebo group (0.9%) and 1 SAE in the tadalafil 5 mg group (0.3%) in the <=65 year old group and in the over 65 group there were 2 placebo SAEs (0.9%) versus 3 SAEs (1.3%) in the tadalafil 5 mg group.

Reviewer's Comment: It is of note in baseline medical history, that a history of cardiovascular disorders is common in both >65 years and >75 years of age subgroups, and there is a slightly larger percentage of patients with baseline cardiovascular disorders in the placebo groups compared to the active treatment groups (24/47 [72.3%] for placebo versus 32/50 [64.0%] for active) in the over 75 years of age group. I do not feel that these findings represent a new safety signal.

In the **additional BPH analysis set of all subjects**, the TEAE profile for subjects ≤65 and >65 years of age was generally similar to that observed in the **pivotal BPH analysis set**, except for a significant treatment-by-subgroup interaction for arthralgia (HOR p=.053), which was reported in a significantly greater percentage of subjects >65 years of age in the tadalafil 5-mg group compared with placebo (1.7% versus 0.0%), though the number of events reported was small.

The Sponsor observes, based on the integrated analysis of Studies LVHG, LVHJ, LVHR, and LVHK co-displayed with data from clinical pharmacology Study LVHN, there appears to be no clear evidence of an age-related decrease in the tolerability of tadalafil among subjects >65 years of age.

Reviewer's Comment: Within the **additional BPH analysis set of all subjects** *72 subjects (30.9%) >65 years of age reported a TEAE versus 94 (27.0%) of subjects <65 years of age reported a TEAE. In my opinion, there does not appear to be evidence of decreased tolerability of tadalafil with age.*

Subjects ≤75 and >75 years of age: BPH

Table 128: TEAEs/SAEs by Age, All Randomized Subjects in BPH Studies LVHG, LVHJ, LVHR, LVHK Double-Blind Period and LVHG Open-Label Period

Subjects With >= 1 TEAE	Age(years)	Placebo	Tadalafil 2.5mg	Tadalafil 5mg
		N n (%)	N n (%)	N n (%)
	<75	599 137 (22.9)	379 99 (26.1)	510 143 (28.0)
	>=75	78 13 (16.7)	28 9 (32.1)	71 23 (32.4)
Subjects With >=1 SAE	<75	599 7 (1.2)	379 4 (1.1)	510 3 (0.6)
	>=75	78 0 (0.0)	28 2 (7.1)	71 1 (1.4)

Source: Table ISS.71, ISS, page 482 and Table ISS.72, ISS, page 566.

For subjects <75 and ≥75 years of age in the **pivotal BPH analysis set**, overall, for subjects reporting at least 1 TEAE, no significant treatment-by-subgroup interactions were observed. However, Table 128 does appear to show an increased incidence of tadalafil-related AEs compared to placebo in the ≥75 years age group compared to the <75, related at least in part to a lower incidence of adverse events being reported in the placebo group in patients >=75. For

individual TEAEs, there appeared to be treatment-by-subgroup interactions for diarrhea and bronchitis. In subjects ≥75 years of age, diarrhea was reported by 4 of 71 subjects (5.6%) in the tadalafil 5-mg group versus 0 of 70 subjects (0.0%) in the placebo group. An exploratory statistical comparison of these incidences (for diarrhea in patients >=75 years) showed no statistically significant difference (p .063) between the tadalafil 5-mg and placebo groups. In subjects <75 years of age, diarrhea was reported by 4 of 510 tadalafil 5 mg subjects (0.8%) versus 6 of 506 subjects (1.2%) placebo subjects. When the older and younger groups were compared statistically for the incidence of diarrhea as an AE, there was a marginally significant result (p .038, not corrected for multiplicity). A significant p-value for bronchitis is, in the Sponsor's opinion, likely an artifact caused by the small number of events reported and opposing treatment group differences within the age subgroups, and therefore does not appear to indicate a true treatment-by-subgroup interaction. Additionally, at the SOC level, no significant treatment-by-subgroup interactions were observed.

> *Reviewer's Comment: Based on small numbers of patients and diarrhea events in the >=75 years category, it is not possible to conclude a tadalafil-related treatment effect on diarrhea in patients >=75 years.*

In the **additional BPH analysis set of all subjects**, the TEAE profile for subjects <75 and ≥75 years of age was generally similar to that observed in the **pivotal BPH analysis set.**

> *Reviewer's comment: The small number of subjects>= 75 years of age in the tadalafil 2.5 mg treatment group make comparisons between groups difficult. Therefore, it appears that the small number of subjects >= 75 years of age in the 2.5 mg tadalafil groups plays some role in difference observed in incidences of SAEs in subjects >= 75 years of age compared with subjects < 75 years of age. It is not possible to draw definite conclusions from this SAE analysis.*

Subjects ≤65 and >65 years of age: BPH/ED

Table 129: TEAEs by Age Pivotal BPH/ED Study LVHR Double-Blind Treatment Period

	Age <=65			Age > 65		
	Placebo	Tad 2.5mg	Tad 5 mg	Placebo	Tad 2.5mg	Tad 5 mg
Subjects With >=1 TEAE	(N=123)	(N=132)	(N=125)	(N=77)	(N=66)	(N=83)
	n (%)					
	27(22.0)	33(25.0)	31(24.8)	12(15.6)	17(25.8)	26(31.3)
Subjects With >=1 TEAE	Age <=75			Age > 75		
	N=177	N=186	N=187	N=23	N=12	N=21
	37(20.9)	46(24.7)	51(27.3)	2(8.7)	4(33.3)	6(28.6)

Source: Table APP 2.7.4.35, Clinical Summary of Safety, page 274 and Table App 2.7.4.38, Clinical Summary of Safety, page 339.

Subjects <75 and >75 years of age: BPH/ED

There appeared to be a modestly increased rate of subjects with at least 1 tadalafil-related adverse event in the older age population (>-75 years) compared to the younger age population (<75 years) in the BPH/ED study. However, some of this appears to be driven by the lower incidence of AEs in the placebo groups in the older age population (2 of 23 subjects [8.7%]) compared to the younger age population (37 of 177 subjects [20.9%]), but some of this apparent difference is related to the small number of subjects and small number of reported adverse events in the >= 75 years subpopulation.

Significant treatment-by-subgroup interactions were observed in 2 SOC categories (Psychiatric disorders and Infections and Infestations) and for several individual TEAEs (nausea, nasopharyngitis, and dizziness). However, these findings, in the Sponsor's opinion may be an artifact caused by the small number of events reported and opposing treatment group differences within the age subgroups. For nasopharyngitis, in subjects >=75 years, 1 of 71 tadalafil subjects (1.4%) versus 1 of 70 placebo subjects (1.4%) reported a nasopharyngitis adverse event. For nausea, in the >=75 years age category, there were no reports of nausea in either the tadalafil or placebo groups. In the Sponsor's opinion, there does not appear to be a true treatment-by-subgroup interaction.

Table 130: Treatment- Emergent Adverse Events by Age (<75, >=75) with Total Incidence >= 4 and Tadalafil Group Exceeding Placebo by > 2 Per Cent Integrated Studies LVHG, LVHJ and LVHR

Preferred Term	Age	Placebo			Tadalafil 5 mg		
		N	n	(%)	N	n	(%)
Subjects with >= 1 TEAE	<75	506	109	(21.5)	510	143	(28.0)
	>=75	70	12	(17.7)	71	23	(32.4)
Headache	<75	506	12	(2.4)	510	21	(4.1)
	>=75	70	1	(1.4)	71	3	(4.2)
Dyspepsia	<75	506	1	(0.2)	510	13	(2.5)
	>=75	70	0	(0.0)	71	1	(1.4)
Diarrhea	<75	506	6	(1.2)	510	4	(0.8)
	>=75	70	0	(0.0)	71	4	(5.6)
Dizziness	<75	506	3	(0.6)	510	3	(0.6)
	>=75	70	0	(0.0)	71	3	(4.2)

Source: Table ISS 32, Integrated Summary of Safety, page 188.

Reviewer's Comment: Overall, no age related safety concern or signal is detected in the review of studies submitted in the NDAs. One of the cases of dizziness in a tadalafil subject >=75 years of age appears to be related to atenolol. In light of the small numbers (2 of 71 subjects (subtracting the atenolol case) versus 0 of 70 subjects for dizziness tadalafil versus placebo in men >=75 years), I do not feel this represents a safety signal or new concern in subjects >=75 years.

With respect to increasing the number of patients ≥ 75 years of age with tadalafil duration of exposure of at least 6 months and of at least 1 year, in their regulatory response of April 12, 2011, describing results from the "Newly Integrated Datasets", the Sponsor provided the following information and comments:

- The Sponsor identified a total of 160 subjects ≥75 years of age receiving tadalafil once daily in doses of 5 mg, 10 mg, or 20 mg in the BPH or BPH/ED studies. Thirty-four subjects ≥75 years were exposed to tadalafil 5 mg, 10 mg or 20 mg for at least 6 months, and 28 subjects ≥ 75 years of age were exposed to tadalafil 5 mg, 10 mg or 20 mg for at least 1 year.

- The Sponsor also assembled subjects ≥ 75 years of age in the double-blind and open-label periods of a "newly integrated" data set from clinical studies for BPH, for daily ED treatment, and for PRN ED treatment. 403 subjects ≥ 75 years of age have been exposed to tadalafil ≤ 5 mg in BPH or daily ED treatment studies, or to tadalafil ≤ 20 mg in PRN ED treatment studies. Of these subjects, 173 had been exposed for at least 6 months, and 102 had been exposed for at least 1 year. The additional studies included in the "newly integrated" data set are shown below:

Table 131: Analysis Sets for "Newly Integrated" BPH and ED Studies

Integrated Data from:	Population	Tadalafil Dose(s)	Study Period Duration
PC, DB, QD IND and non-IND BPH Studies LVHG, LVHJ, LVHR, LVHB, LVHT and LVIA	All randomized subjects	2.5 mg, 5 mg,	12 weeks
PC, DB, QD ED Studies LVCV, LVFP, LVFZ and LVHG	All randomized subjects	2.5 mg, 5 mg,	12 weeks
PC, DB, PRN IND and non-IND ED Studies LVBK, LVBN, LVCE, LVCO, LCCQ, LVCR, LVDI, LVDJ, LVDW, LVDY, LVDZ, LVDI, LVDJ, LVDW, LVDY, LVDZ, LVEF, LVEG, LVEH, LVEI, LVEL, and LVEQ	All randomized subjects	2.5 mg, 5 mg, 10 mg, 20mg	12 weeks
OL extensions tadalafil IND and non-IND BPH Studies LVHG and LVIA.	All enrolled subjects	5 mg	At least 6 months
OL extensions periods of tadalafil QD ED Studies LVCV and LVFP	All enrolled subjects	5 mg	At least 6 months
OL tadalafil PRN ED Studies LVBL, LVCG, LVDR and LVFD	All enrolled subjects	5 mg, 10 mg, 20mg	At least 6 months

BPH=benign prostatic hyperplasia; DB=double-blind; ED=erectile dysfunction; OL=open-label; PRN=as needed; QD=once daily; IND=investigational new drug
Source: Table 4.3, Regulatory Response, April 12, 2011

- The Sponsor analyzed the safety data from this "newly integrated" data set to determine if there was a difference in tadalafil-related adverse events between younger (< 65 years and < 75 years of age) compared to older (≥ 65 years and ≥ 75 years) subjects.

- For subjects < 65 years of age and ≥ 65 years of age, there was no difference in tadalafil-related SAEs.
- For subjects ≥ 75 years of age compared to subjects < 75 years of age, when all data is pooled, including data from open-label studies and 12-week, placebo-controlled studies, there appeared to be a higher incidence of subjects >= 75 years of age, with no clear dose-response relationship.

  Reviewer's Comment: In order to further assess this finding, the reviewer analyzed the SAEs from the 12-week, placebo-controlled studies separately from the uncontrolled data from the open-label extensions. This was believed to provide the best estimate of tadalafil-related SAEs.

- The Sponsor provide several analyses in their regulatory response of April 12, 2011:

  - For the "BPH analysis" (including Studies LVHJ, LVHG and LVHR), for subjects taking once daily tadalafil for BPH, the number of SAEs in subjects < 75 years of age was 3 in 510 subjects (0.6%) taking 5 mg tadalafil, and 5 in 506 placebo subjects (1%). In subjects taking tadalafil once daily for BPH, ≥ 75 years of age, the number of SAEs was 1 event (1.4%) among 71 subjects taking 5 mg tadalafil and 0 (0.0%) among 70 placebo subjects.

  - In a combined analysis of 12-week, placebo-controlled, daily use ED studies (LVCV, LVFP, and LVFZ for ED) as well as LVGH for BPH, for subjects taking daily tadalafil, the number of SAEs in subjects < 75 years of age was 6 in 316 placebo subjects (1.9%), and 6 among 546 tadalafil 5 mg subjects (1.1%). Among subjects ≥ 75 years of age, the SAEs were 0 (0.0%) in 10 placebo subjects and 0 (0.0%) in 22 subjects taking tadalafil 5 mg once daily.

  - In the analysis of SAEs occurring during the double-blind periods, none of the preferred terms was reported by more than 1 tadalafil-treated subject ≥ 75 years of age within an analysis set, although "acute myocardial infarction was reported for 1 subject and myocardial infarction" was reported for another.

  - In the open-label extension periods, a higher percentage of SAEs was reported in subjects ≥ 75 years of age compared to subjects <75 years of age in the newly integrated BPH and daily ED treatment studies. Within the open label extension of LVHG (5 mg tadalafil once daily), 9 subjects (8.8%) out of a total 102 subjects reported SAEs in the > 75 year old age group, compared to 23 subjects (3.2%) out of a total of 720 subjects under 75 years of age. However, the individual SAEs that constituted the higher percentage of SAEs in subjects ≥ 75 years of age are not unexpected given the longer study durations and older study population. None of the SAE preferred terms were reported by more than 1 tadalafil-treated subject ≥ 75 years of age.

Reviewer's Comment: The greater number of SAEs in open-label extensions in patients ≥ 75 years of age compared to younger patients appears to be related to a variety of conditions affecting older individuals.

- In the double-blind periods, the percentages of *discontinuations due to AEs* in subjects <75 years and ≥ 75 years of age in the tadalafil 5 mg and placebo groups in the "newly integrated" data set were consistent with those reported in the additional BPH analysis set of all subjects. With the exception of the tadalafil 20 mg PRN group, there was no apparent dose response relationship for discontinuations due to AEs in subjects ≥ 75 years of age. No trends were apparent to the Sponsor with regard to specific AEs leading to discontinuation in tadalafil subjects ≥ 75 years of age, and the events leading to discontinuations are not unexpected in this older study population.

  In the open-label extension periods, a higher percentage of discontinuations due to AEs was reported for subjects ≥ 75 years of age compared to subjects <75 years of age in the newly integrated BPH and daily ED treatment studies. However, aside from events commonly associated with tadalafil treatment, the individual events contributing to the higher percentage of discontinuations (for example, lung neoplasm, pancreatic carcinoma, and prostatitis) in subjects ≥ 75 years of age would be expected given the older study population and longer study durations.

- In the double-blind periods, the percentages of *overall AEs* in subjects <75 and ≥ 75 years of age in the tadalafil 5 mg and placebo groups in the "newly integrated" data set studies were consistent with those reported in the additional BPH analysis set of all subjects. A similar trend was observed for BPH and daily ED treatment tadalafil subjects, with a higher percentage of subjects ≥ 75 years of age reporting TEAEs than subjects <75 years of age.

  - In the "newly integrated" data set, using the pooled data from placebo-controlled studies LVHG, LVHJ, LVHR along with LVHT, LVIA an LVHB for placebo and 5 mg (n=1629 for < 75 years, and n=227 for >=75 years), there appeared to be no substantial increase in percentage of TEAEs was reported in the tadalafil 5 mg group for subjects ≥ 75 years of age compared to subjects <75 years of age. In those < 75 years of age, the placebo and tadafail 5 mg incidences were 21.3% and 28.3%, respectively. For subjects >=75 years of age, the placebo and tadalafil 5 mg incidences were 24.5% and 32.5%, respectively.

  - In the open-label extension periods, comparable percentages of TEAEs were reported between subjects <75 and ≥ 75 years of age across the "newly integrated" data set, daily ED treatment, and PRN ED treatment studies. Subjects in both age groups reported more TEAEs in the open-label extension periods, as would be expected given the longer study durations, compared with the double-blind study periods.

Reviewer's Comment:

- *In general, the safety profile in subjects ≥ 75 years of age in the double-blind and long-term, open-label periods of the BPH, daily ED treatment, and ED PRN studies is consistent with known safety profile of tadalafil.*

- *Aside from events commonly associated with tadalafil treatment, the types of events reported in subjects ≥75 years of age are generally not unexpected in this elderly patient population with multiple co-morbidities and concomitant medications.*

- *None of the SAE preferred terms were reported by more than 1 tadalafil subject ≥ 75 years of age within an analysis set for either the double-blind or open-label periods. Further, there was no evidence of a decreased tolerance based upon the specific types of events leading to discontinuation for subjects ≥ 75 years of age in the double-blind or open-label periods.*

While there did not appear to be a difference in tadalafil-related SAEs, discontinuations due to AEs, or overall AEs in subjects < 75 years of age compared to subjects >=75 years of age, an analysis was nevertheless conducted to determine whether any difference existed between age groups in adverse events "possibly related to hypotension". The events that were counted in this analysis were pre-defined as those that might reflect hypotension (e.g. headache, dizziness, etc)

Adverse Events Possibly Related to Hypotension and Age

Two separate analyses of TEAEs possibly related to hypotension were performed. The first analysis was "focused" and included the following 7 MedDRA preferred terms: dizziness, dizziness postural, procedural dizziness, hypotension, orthostatic hypotension, syncope, and presyncope. An "expanded" analysis of TEAEs possibly related to hypotension was performed which included the preferred terms headache, asthenia, and fatigue, as well as several other event terms.

Treatment-emergent AEs possibly related to hypotension (based on only the expanded list of terms) were also evaluated by age subgroups (≤ 65 and >65 years of age; <75 and ≥ 75 years of age) and within subgroups of subjects classified by concomitant antihypertensive medication use (defined as no antihypertensive medications, 1 class of antihypertensive medication, or 2 or more classes of antihypertensive medications taken during the double-blind treatment period), including those by age subgroups. Antihypertensive medications were analyzed based on the following classes of drugs typically used to treat hypertension: alpha blockers, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, centrally acting sympatholytics, and other antihypertensive medications.

BPH Analysis Subsets:

Overall, in the **pivotal BPH analysis set,** for subjects (≤ 65 and > 65 years) reporting at

least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions were observed. In the **additional BPH analysis set of all subjects**, the TEAE profile for subjects ≤65 and >65 years of age who reported events possibly related to hypotension was similar to that observed in the **pivotal BPH analysis set.**

In the **pivotal BPH analysis set** for subjects<75 and ≥75 years of age and reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions were observed. In the **additional BPH analysis set of all subjects,** the TEAE profile for subjects <75 and ≥75 years of age who reported TEAEs possibly related to hypotension was generally similar to that observed in the **pivotal BPH analysis set**. Overall, for subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions were observed.

It is notable though, that for subjects ≥75 years of age, although the numbers were small, a greater percentage of subjects in the tadalafil 5-mg group reported at least 1 TEAE possibly related to hypotension compared with placebo (6 subjects [8.5%] versus 1 subject [1.4%]; half of the events reported in this specific analysis for the tadalafil group were headache.

For the adverse event of headache, in the "newly integrated" data set, using the pooled data from placebo-controlled studies LVHG, LVHJ, LVHR along with LVHT, LVIA and LVHB for placebo and 5 mg (n=1629 for < 75 years, and n=227 for >=75 years), the number of reports and incidence of headache for subjects < 75 years of age was 17 (2.1%) and 27 (3.3%) for placebo and tadalafil, respectively. For subjects >= 75 years, the number of reports and incidences of headache were 1 (0.9%) and 3 (2.6%) for placebo and tadalafil, respectively.

> *Reviewer's Comment: Headache is a known adverse event associated with tadalafil and is largely independent of hypotension. In their regulatory response of April 14, 2011, the Sponsor observes, three of the three subjects ≥75 years of age who experienced headache (LVHJ 400-4001, LVHR 206-2600, LVHR 114-2406) did so at times where they did not have hypotension or orthostasis. The data from the newly integrated sets do not support an age-related effect of tadalafil on headache.*

In addition to headache, the adverse events possibly related to hypotension in the tadalafil groups were reported as "dizziness". For subjects ≤65 and >65 years of age in the **pivotal BPH/ED analysis set,** there appeared to be a treatment-by-subgroup interaction for dizziness. However, this finding, in the Sponsor's opinion, may be an artifact caused by the small number of events reported and opposing treatment group differences within the age subgroups and therefore does not appear to indicate a true treatment-by-subgroup interaction. For patients <75 and ≥75 years of age in the **pivotal BPH/ED analysis set,** the results were similar to those reported in subjects ≤65 and >65 years of age.

For the adverse event of dizziness, in the data set including the placebo-controlled studies LVHG, LVHJ, and LVHR for placebo and 5 mg (n=1016 for < 75 years, and n=141 for >=75 years), the number of reports and incidence of dizziness for subjects < 75 years of age was 3

(0.6%) and 3 (0.6%) for placebo and tadalafil, respectively. For subjects >= 75 years, the number of reports and incidences of dizziness were 0 (0.0%) and 3 (4.2%) for placebo and tadalafil, respectively. In the >=75 years of age subgroup, the difference between tadalafil (n=3) and placebo (n=0) was not statistically significant (p 0.065). There also did not appear to be a statistically significant treatment effect by age subcategory in this analysis in this dataset.

Therefore, in the BPH analysis set, no placebo subject ≥75 years of age reported dizziness, but 3 (4.2%) tadalafil subjects did. The subject narratives for these 3 cases are provided below:

Subject LVHJ-107-1711 is a 79-year-old white male randomized to tadalafil 5 mg who reported mild dizziness commencing approximately 7 weeks post-randomization which persisted for 2 days. The subject had preexisting hypertension, coronary artery disease with prior coronary artery bypass graft, peripheral arterial disease, and hypercholesterolemia. His concomitant medications included metoprolol, aspirin, and simvastatin. Further follow up with the site revealed the subject's dizziness had occurred upon awakening. Despite the subject's treatment with metoprolol, his blood pressure recordings remained high throughout the study; however, he met the DBP criterion for a treatment-emergent positive orthostatic test at Visit 7 (supine SBP = 161 mm Hg, standing SBP = 161 mm Hg; supine DBP = 92 mm Hg, standing DBP = 82 mm Hg). He did not report any symptoms during orthostatic testing. The subject completed the study.

Reviewer's Comment: This subject's short period of mild dizziness did not occur in association with the event of orthostasis. The event resolved while the subject continued using tadalafil. During the event of orthostasis, dizziness was not noted. The orthostatic drop was itself small and noted only in diastolic BP.

Subject LVHR-102-1208 is a 78-year-old Asian male randomized to tadalafil 5 mg who reported mild dizziness commencing 17 days post-randomization which persisted for 37 days. The subject had preexisting obesity, Type 2 diabetes mellitus, hypercholesterolemia, edema peripheral, and hypertension. His concomitant medications included metformin, atorvastatin, and atenolol. According to follow-up information received from the site, the subject's dizziness resolved upon discontinuation of atenolol. None of the subject's blood pressure recordings were indicative of hypotension, and he did not meet any of the criteria for a treatment-emergent positive orthostatic test. No additional adverse events possibly related to hypotension were reported. The subject completed the study.

Reviewer's Comment: At no time during the clinical study was hypotension or orthostasis noted. The subject's dizziness resolved upon withdrawal of atenolol and while the patient continued on tadalafil.

Subject LVHR-107-1708 is a 77-year-old white male randomized to tadalafil 5 mg who reported mild dizziness (lightheadedness) commencing 15 days post-randomization which was ongoing at the time of study completion. The subject had preexisting blood

cholesterol increased, hypothyroidism, and vertigo. His concomitant medications included pravastatin and levothyroxine. In addition to the report of ongoing dizziness, the subject also reported dizziness upon standing during orthostatic vital signs assessment at Visits 4, 5, and 6. None of the subject's blood pressure recordings were indicative of hypotension and he did not meet any of the criteria for a treatment-emergent positive orthostatic test. The subject completed the study.

Reviewer's Comment: This subject's dizziness symptoms at Visits 4, 5, and 6 during orthostasis testing was not associated with orthostatic blood pressure readings and the remainder of his blood pressure readings were negative for hypotension. These episodes do not appear to be related to hypotension.

Reviewer's Overall Comment: A detailed review of the cases did not reveal a problem with hypotension. In one of the cases, dizziness appearred to be related to atenolol. As is seen in the narratives, neither dizziness nor headache appearred to be associated with hypotension in men ≥ 75 years of age. The concern regarding dizziness as safety signal for hypotension has been resolved. In addition, there is no clear evidence of a tadalafil-related effect on dizziness in subjects >= 75 years compared to < 75 years of age.

In the "Newly Integrated Data Set" submitted in April, 2011, the Sponsor's analysis showed:

- In the "focused" analysis of TEAEs possibly related to hypotension, the overall incidence of events was low in the double-blind periods of the "newly integrated" data set, daily ED treatment, and ED PRN studies; however, a slightly higher percentage of events was reported in the tadalafil 5 mg group in subjects ≥ 75 years of age compared to subjects <75 years of age in the newly integrated BPH studies. The Sponsor points out that this difference was driven by 3 events of dizziness in subjects ≥ 75 years of age. In Studies LVHG, LVHJ and LVHR combined, the difference between tadalafil and placebo in dizziness in the >=75 years subpopulation was not statistically significant.
- In the "expanded" analysis of TEAEs possibly related to hypotension, the percentages of subjects <75 and ≥ 75 years of age with events in the tadalafil 5 mg and placebo groups in the "newly integrated" data set were slightly lower than those reported in the additional BPH analysis set. In the "newly integrated" data set, a slightly higher percentage of events was reported in the tadalafil 5 mg group in subjects ≥ 75 years of age compared to subjects <75 years of age. This finding was driven by the same 3 events of dizziness in subjects ≥ 75 years of age (as above).
- In the open-label extension periods, in the "focused" analysis of TEAEs possibly related to hypotension, a slightly higher percentage of events was reported in subjects ≥ 75 years of age compared with subjects <75 years of age in the newly integrated ED PRN studies, which was driven by the same 3 events of dizziness in subjects ≥ 75 years of age. In the "expanded" analysis of TEAEs possibly related to hypotension, a slightly higher percentage of events was reported in subjects ≥ 75 years of age compared with subjects <75 years of age in the newly integrated BPH studies.

- In general, the safety profile in subjects ≥ 75 years of age in the double-blind and long-term, open-label periods of the BPH, daily ED treatment, and ED PRN studies is consistent with known safety profile of tadalafil.
- Aside from events commonly associated with tadalafil treatment, the types of events reported in subjects ≥75 years of age are generally not unexpected in this elderly patient population with multiple co-morbidities and concomitant medications.
- There did not appear to be a higher percentage of SAEs, discontinuations due to AEs, patients reporting ≥1TEAE, and TEAEs possibly related to hypotension reported in subjects ≥ 75 years of age compared to subjects <75 years of age in the tadalafil groups.
- None of the SAE preferred terms were reported by more than 1 tadalafil subject ≥ 75 years of age within an analysis set for either the double-blind or open-label periods. Further, there was no evidence of a decreased tolerability based upon the specific types of events leading to discontinuation for subjects ≥ 75 years of age in the double-blind or open-label periods.
- A numerically slightly higher percentage of subjects ≥ 75 years of age compared to subjects <75 years of age in the tadalafil groups reporting TEAEs possibly related to hypotension, and this small difference was driven by 3 dizziness events. The difference between placbo and tadalafil in dizziness events in subjects >= 75 years was not statistically significant.

> *Reviewer's Comment: The "New Integrated Data Set" submitted in April 20011 served to increase the number of men ≥ 75 years of age with duration of exposure of over 6 months. The review of this group has not generated new safety signals or concerns.*

<u>The following section discusses Treatment-Emergent Adverse Events Possibly Related to Hypotension by Concomitant Antihypertensive Medication Use and Age Group.</u>

Overall, for subjects reporting at least 1 TEAE possibly related to hypotension, no significant treatment-by-subgroup interactions were observed between the concomitant antihypertensive therapy subgroups. For individual TEAEs, a significant treatment-by-subgroup interaction was observed only for headache (tadalafil 2.5 mg/placebo HOR p=.081 [Breslow-Day test for homogeneity of odds ratios {a p value ≤ .10 indicates a significant by- subgroup interaction}]).

Table 132: Treatment-Emergent Adverse Events Possibly Related to Hypotension by Concomitant Antihypertensive Therapy Pivotal BPH Studies LVHG and LVHJ

Preferred Term	Number Concomitant Antihypertensives	Placebo			Tadalafil 5 mg		
		N	n	(%)	N	n	(%)
Subjects with >= 1 TEAE	0	227	9	(4.0)	210	11	(5.2)
	1	81	2	(2.5)	94	3	(3.2)
	>=2	68	0	(0.0)	69	4	(5.8)
Headache	0	227	6	(2.6)	210	7	(3.3)
	1	81	1	(1.2)	94	3	(3.2)
	>=2	68	0	(0.0)	69	2	(2.9)
Dizziness	0	227	0	(0.0)	210	3	(1.4)
	1	81	1	(1.2)	94	0	(0.0)
	>=2	68	0	(0.0)	69	1	(1.4)
Asthenia	0	227	2	(0.9)	210	0	(0.0)
	1	81	0	(0.0)	94	0	(0.0)
	>=2	68	0	(0.0)	69	1	(1.4)
Fatigue	0	227	1	(0.4)	210	1	(0.5)
	1	81	0	(0.0)	94	0	(0.0)
	>=2	68	0	(0.0)	69	0	(0.0)
Hypotension	0	227	0	(0.0)	210	1	(0.5)
	1	81	0	(0.0)	94	0	(0.0)
	>=2	68	0	(0.0)	69	0	(0.0)

Source: Table APP 2.7.4.44, Appendix Clinical Summary of Safety, page 410.

In the **additional BPH analysis set of all subjects** (≤65 and >65 Years of Age)**,** no significant treatment-by-subgroup interaction was observed for the age subgroups in the percentage of subjects reporting at least 1 TEAE possibly related to hypotension overall, and no significant treatment group difference was observed for any individual hypotension TEAE.

For subjects <75 and ≥75 years of age in the **additional BPH analysis set of all subjects,** overall TEAEs possibly related to hypotension by concomitant antihypertensive therapy (no, 1, or 2 or more classes of antihypertensive medications) for subjects <75 and ≥75 years of age demonstrated no significant treatment-by-subgroup interaction. For subjects ≥ 75 years of age, no significant treatment group difference was observed for any individual TEAE by antihypertensive subgroup. For subjects <75 years of age, there was a significant treatment-by antihypertensive- therapy subgroup interaction for the TEAE of dizziness (HOR p=.065). The Sponsor stated that this finding is likely due to the small number of events reported and opposing treatment group differences within the subgroups. As percentages of subjects with dizziness did not increase with increasing number of classes of concomitant antihypertensive use, the events were not likely the result of related blood pressure changes, in the Sponsor's opinion.

In the **pivotal BPH/ED analysis set** for Subjects ≤65 and >65 Years of Age, no significant treatment-by subgroup interactions were observed for any individual TEAEs in either age

subgroup. For subjects <75 and ≥75 years of age in the **pivotal BPH/ED analysis set** no significant treatment-by-subgroup interactions were observed. In the tadalafil 5 mg group of patients ≥75 years of age, 1 of 9 patients not taking antihypertensives experienced dizziness compared to 1 of five patients taking 1 antihypertensive medication and 0 of seven patients taking two or more antihypertensive medications. Headache was reported in 2 of 9 subjects not on antihypertensive medication and 0 of 12 patients on one or more antihypertensive mediations (Table AP 2.7.4.53, Appendix Clinical Summary of Safety, page 432). No significant treatment-by-subgroup interactions were observed for any individual TEAEs in either age subgroup.

> *Reviewer's comment: In LVHR, the total 5 mg patients reporting dizziness was 2 (1.0%, N=208) and reporting headache was 12 (5.8%, N=208). The number of subjects ≥75 years of age on antihypertensive therapy is small as is the number of AEs possibly related to hypotension. These numbers at this time do not identify a safety concern. It does not appear that tadalafil presented an increased risk in any age subgroup for hypotension in patients taking concomitant antihypertensive medications*.

Ethnicity

Tadalafil pharmacokinetics in healthy male Japanese and Caucasian subjects were comparable at doses of 5, 10, 20 mg. In Chinese subjects, the pharmacokinetics following doses of 10 and 20 mg were generally similar to those in Japanese and Caucasian subjects. Population-based analyses of tadalafil pharmacokinetics in Caucasian and Japanese ED patients revealed that exposures were similar across both groups requiring no dosing adjustment.

In the non-IND studies conducted in Asian countries (based on integrated data from double-blind periods of Studies LVIA and LVHT, as described in Section 2.7.4.1.1.1), 191 subjects received tadalafil 5 mg for approximately 42.2 subject-years. There were no deaths and no statistically significant differences in the percentages of subjects reporting SAEs, discontinuations due to AEs, TEAEs, or treatment-related AEs. There were no procedure-related AEs. Overall, the percentage of subjects with at least 1 TEAE was not statistically different in the tadalafil 5-mg group (31.4%) compared to the placebo group (29.3%). The most commonly reported TEAEs (in ≥ 2% of the tadalafil 5-mg group and more frequently than in the placebo group) were dyspepsia (2.1%) and myalgia (2.1%), and both were reported in significantly greater percentages of subjects in the tadalafil 5-mg group compared with placebo (p=.044 and p=.045). Six subjects (1.6%) reported 8 SAEs, with 5 subjects (2.6%) in the tadalafil 5-mg group reporting 7 SAEs and 1 subject (0.5%) in the placebo group reporting 1 SAE. A total of 12 subject discontinued due AEs (7 tadalafil subjects and 5 placebo subjects). All AEs leading to discontinuation were reported with a frequency of less than 1 percent.

The Sponsor also included in their submission a non-IND Phase 3 Study LVHB. In this 3-month study, there were 154 placebo subjects, 155 tadalafil 5 mg subjects, 151 tadalafil 2.5 subjects and 152 tamsulosin 0.2 mg subjects.

There were no SAEs or deaths in the tadalafil 5 mg group. The four SAEs in the tadalafil 2.5 mg group were: metastatic colon cancer, hospitalization due to injury not otherwise specified, hospitalization due to hypertension (pre-existing hypertension), and hospitalization for lumbar spinal stenosis. The one SAE in a placebo patient was stage IV lymphoma.

At total of 15 subjects discontinued due to an adverse event. The adverse events in the tadalafil 2.5 mg group were: injury NOS (SAE) myalgia (muscular weakness), orthostatic hypotension, colon cancer and lumbar spinal stenosis. The 7 adverse events leading to discontinuation in the tadalafil 5 mg group were: blood creatine phosphokinase increased, myalgia (3), calculus ureteric, angina pectoris, and liver injury. In the tamsulosin HCl 0.2 mg group there were two discontinuations secondary to adverse events: arrhythmia and hepatitis A.

The TEAEs which incidence ≥ 2% in any treatment group were myalgia (placebo, 0.0%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 3.9%; tamsulosin HCl 0.2 mg, 0.0%), headache (placebo, 0.6%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 1.9%; tamsulosin HCl 0.2 mg, 0.7%), back pain (placebo, 0.6%; tadalafil 2.5 mg, 0.7%; tadalafil 5 mg, 2.6%; tamsulosin HCl 0.2 mg, 0.7%), nasopharyngitis (placebo, 1.9%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 1.3%; tamsulosin HCl 0.2 mg, 0.7%), and dizziness (placebo, 0.0%; tadalafil 2.5 mg, 2.0%; tadalafil 5 mg, 0.0%; tamsulosin HCl 0.2 mg, 1.3%). For myalgia, there was statistically significant difference in the tadalafil 5 mg (p=.030) group compared with placebo.

Three subjects noted fatigue (1 placebo, 1 tadalafil 2.5 mg and 1 tamsulosin). 2 subjects had orthostatic hypotension, 1 subject was in the tadalafil 2.5 mg group, and 1 subject was in the tamsulosin HCl 0.2 mg. A total of 8 subjects had headache during the double-blind treatment period: 1 in the placebo group; 3 in the tadalafil 2.5 mg; 3 in the tadalafil 5 mg; and 1 in the tamsulosin HCl 0.2 mg groups. None of these subjects reported additional events possibly related to hypotension except for 1 subject. Subject 180-1807 had fatigue with headache. Both headache and fatigue had onset 29 days after randomization and both symptoms stopped 33 days after randomization.

A total of 6 subjects experienced at least one TEAE which was possibly related to cardiovascular disorders: palpitations, n=3; chest pain, n=2; and arrhythmia, n=1. Of 6 subjects, 2 subjects were in the tadalafil groups (palpitations, tadalafil 2.5 mg; palpitations, tadalafil 5 mg); 1 subject in the placebo (palpitations); and 3 subjects in the tamsulosin HCl 0.2 mg (chest pain [2], arrhythmia).

In the long-term open-label extension period of Study LVIA (OLE CSR LVIA), 394 subjects received tadalafil 5 mg for approximately 282.9 subject-years. In the open-label extension, 1-year treatment with tadalafil 5 mg once daily was well tolerated, and there were no new safety concerns identified in Japanese men with BPH. The TEAEs reported during the Study LVIA open-label extension period were similar to those reported during the double-blind treatment period. TEAEs were reported for 257 subjects (65.2%) enrolled the in the open-label extension period (Visit 3 as baseline). The percentage of subjects reporting at least 1 TEAE was

numerically higher for subjects who previously received placebo (72.5%) than for either the tadalafil 2.5-mg (60.0%) or 5-mg groups (63.3%). During the open-label extension period, 12 SAEs were reported in 11 subjects (2.8%), including 1 subject who died of subarachnoid hemorrhage. The hemorrhage event was assessed by the investigator as not related to study drug. Of the 394 subjects who entered the study, 36 (9.1%) discontinued due to adverse events.

> *Reviewer's Comment: The tolerability and safety profile of tadalafil in Asians with BPH is similar to that of primarily Caucasian population comprising the study populations of Studies LVHG, LVHR, and LVHJ. No new safety signals are generated and additional labeling, in my opinion, is not indicated.*

Diabetes

In the additional BPH analysis set of all subjects which encompasses all subjects in the three NDA pivotal studies, for subjects reporting at least 1 TEAE, no significant treatment-by-subgroup interaction was observed among subjects based on diabetes status. Where the incidence of an AE in patients with diabetes exceeded that of subjects without diabetes, it was by 1 event or 1.4 %. This difference is too small to be clinically or statistically significant. In addition there are no AEs where the incidence for tadalafil 5 mg diabetic exceeds by > 1 event (or > 1.4%) the incidence in placebo diabetic. Below is a summary of the most frequently reported TEAE in the integrated studies in decreasing order where the difference exceeds 1.4% (>1 event) between tadalafil 5 mg diabetic versus non-diabetic.

Table 133: Treatment-emergent Adverse Events by Baseline by Diabetes Status Where Difference Exceeds 1.4% (>1 event) Between Tadalafil 5 mg Diabetic versus Non-diabetic Studies LVHG, LVHJ and LVHR.

Preferred Term		Placebo			Tadalafil 5 mg		
	Diabetes	N	n	(%)	N	n	(%)
Subjects with >= 1 TEAE	No	502	105	(20.9)	507	150	(29.6)
	Yes	74	16	(21.6)	74	16	(21.6)
Headache	No	502	12	(2.4)	507	22	(4.3)
	Yes	74	1	(1.4)	74	2	(2.7)
Dyspepsia	No	502	1	(0.2)	507	14	(2.8)
	Yes	74	0	(0.0)	74	0	(0.0)

Source: Table ISS 46, Integrated Summary of Safety, page 300.

For the pivotal BPH analysis set, overall, for subjects reporting at least 1 TEAE, no significant treatment-by-diabetes-subgroup interaction was observed. However significant treatment-by-subgroup interactions were observed for dyspepsia, influenza, and insomnia, although all events were reported in subjects without diabetes at baseline.

For the pivotal BPH/ED analysis set, subjects reporting at least 1 TEAE, no significant treatment-by-diabetes-subgroup interaction was observed. For individual TEAEs, significant

treatment-by-subgroup interactions were observed for back pain (tadalafil 2.5 mg/placebo; tadalafil 5 mg/placebo) and myalgia (tadalafil 2.5 mg/placebo); however, in the Sponsor's opinion, these findings are likely an artifact caused by the small number of events reported (most of which were reported in subjects without baseline diabetes) and opposing treatment-group differences within the diabetes subgroups, and therefore do not appear to indicate a true treatment-by-subgroup interaction.

Reviewer's Comment: The data do not show evidence of reduced tolerability of tadalafil 5 mg in subjects with diabetes at baseline.

Renal Impairment

TEAEs by renal status were analyzed in the following renal impairment subgroups at baseline (Visit 3):

- Normal: CrCl> 80 mL/min
- Mild: CrCl> 50 to 80 mL/min
- Moderate: CrCl >30 to 50 mL/min
- Severe: CrCl ≤ 30 mL/min

Subjects with severe renal impairment were excluded from study participation.

The table below encompasses all patients in Studies LVHG, LVHJ, and LVHR who received 5 mg tadalafil for BPH. There were no clinically meaningful differences in TEAEs, in the Sponsor's opinion, in subjects with renal impairment versus patients with normal renal function. The same conclusion was reached with analysis of the pivotal BPH/ED analysis set.

Reviewer's Comment: I agree with the Sponsor's conclusions.

The Sponsor notes that across subjects with renal insufficiency the mean $t_{1/2}$ was prolonged (approximately 50 hours) and hemodialysis contributed negligibly to tadalafil elimination. The Sponsor proposes that the initial once-daily dose in patients with moderate renal impairment be limited to 2.5 mg, increasing to 5 mg based on individual response. The current label approved February 1, 2010, states in Section 2.3, *CIALIS for Once Daily Use, Moderate (creatinine clearance 31 to 50 mL/min): No dose adjustment is required.*

Reviewer's Comment: In light of the starting dose for BPH and BPH/ED of 5 mg once daily, this reviewer agrees with Sponsot's proposal to restrict the dose to 2.5 mg in patients with moderate renal impairment for the treatment of BPH and BPH/ED.

Table 134: Treatment-Emergent Adverse Events by Renal Impairment Status Occurring in > Renally Impaired Patients All BPH 5 mg Tadalafil Patients Studies LVHG, LVHJ and LVHR.

Preferred Term	Renal Status	Tadalafil 5 mg n (%)
Subjects with >= 1 TEAE	Normal (N=440)	134 (30.5)
	Mild (N= 129)	30 (23.3)
	Moderate (N=9)	2 (22.2)
Back Pain	Normal	10 (2.3)
	Mild	4 (3.1)
	Moderate	0 (0.0)
Dyspepsia	Normal	11 (2.5)
	Mild	3 (2.3)
	Moderate	0 (0.0)
Hypertension	Normal	9 (2.0)
	Mild	2 (1.6)
	Moderate	0 (0.0)
Diarrhea	Normal	6 (1.4)
	Mild	1 (0.8)
	Moderate	1 (11.1)
Pain in Extremity	Normal	5 (1.1)
	Mild	3 (2.3)
	Moderate	0 (0.0)
Influenza	Normal	4 (0.9)
	Mild	2 (1.6)
	Moderate	9 (0.0)
Arthralgia	Normal	3 (0.7)
	Mild	2 (1.6)
	Moderate	0 (0.0)
Gastroesophageal Reflux Disease	Normal	3 (0.7)
	Mild	2 (1.6)
	Moderate	0 (0.0)

Source: Table ISS 45, Integrated Summary of Safety, page 252.

Hepatic Impairment

In the efficacy and safety studies evaluating once-daily tadalafil administration to subjects with BPH or BPH/ED, Child-Pugh data were not collected. Patients with clinical evidence of severe hepatic impairment were excluded from participation from all clinical studies (LVHG, LVHJ, LVHR, LVHS and LVHK. Within these studies, no patients met the criteria for both transaminase and bilirubin elevations (ALT or AST ≥3 times the upper limit of normal and total bilirubin≥ 1.5times the upper limit normal. The Sponsor concludes that the clinical experience in subjects with BPH or BPH/ED and chronic hepatic cirrhosis (Child-Pugh Class A and B) remains limited. They therefore conclude that the current dosing recommendations reflected for

the once-daily use regimen for the treatment of ED is scientifically appropriate for the present applications. Specifically, for those with mild or moderate hepatic impairment, as Cialis for once-daily use has not been extensively evaluated, caution is advised.

Reviewer's Comment: These recommendations are reasonable from the clinical perpsective.

7.5.4 Drug-Disease Interactions

The Sponsor analyzed whether patients with BPH alone versus patients with BPH/ED had a different AE frequency and AE profile. The table below compares adverse events in these two patient categories.

Table 135: Overview of Adverse Events Comparison between BPH and BPH/ED Analysis Sets

		Placebo		Tadalafil 5 mg	
	Additional Analysis Set	N	n (%)	N	n (%)
SAEs					
	Without ED	119	3 (2.5)	117	0 (0.0)
	With ED	454	2 (0.4)	464	4 (0.9)
Discontinuation AE					
	Without ED	119	2 (1.7)	117	8 (6.8)
	With ED	454	7 (1.5)	464	13 (2.8)
TEAEs					
	Without ED	119	24 (20.2)	117	41 (35.0)
	With ED	454	96 (21.1)	464	125 (26.9)

Additional BPH analysis set of subjects without ED (LVHG+LVHR)
Additional BPH analysis set of subjects with ED (LVHG+LVHJ+LVHR)
Source: Table 2.7.4.51, Summary Clinical Safety, page 134

The adverse events occurring in at least 2% of subject with BPH/ED associated with tadalafil were headache, back pain, hypertension, and nasopharyngitis. A similar listing of adverse events for BPH alone includes headache, back pain, nasopharyngitis, dyspepsia, influenza, abdominal pain upper, diarrhea and myalgia.

Reviewer's Comment: It appears that patients with ED and BPH have a modestly lower incidence of discontinuation AEs and overall AEs and a slightly higher incidence of SAEs as compared to patients with BPH alone. The AE profile appears similar between the two groups with the exception of certain gastrointestinal AEs. The concern of hypertension and tadalafil use upon review has not been found to be supported by line analysis of blood pressures in patients reporting hypertension.

There were no significant drug-disease interactions identified.

7.5.5 Drug-Drug Interactions

CYP3A4 Inhibitors

Table 137 is a summary of all tadalafil 5 mg subjects who had a >1% incidence of AEs with CYP3A4 exposure versus non- CYP3A4 exposed tadalafil 5 mg subjects in all pivotal studies. There were 28 AEs categories in which there was a total of 4 or more events. There were only 4 AE categories that qualified for inclusion in Table 137 (back pain, pain in extremity, myalgia, and upper respiratory infection). The incidences of these AEs were only modestly increased in CYP3A4 exposed subjects compared to non CYP3A4 exposed subjects. No statistically significant or clinically meaningful differences in TEAEs were observed in subjects reporting concomitant CYP3A4 inhibitor use in the additional BPH analysis set of all subjects in the Sponsor's opinion. The Sponsor reaches similar conclusions for the pivotal BPH/ED analysis set.

Below is a table summarizing studies evaluating CYP3A4 inhibitors and substrates with results provided in the Sponsor's Clinical Summary of Safety:

Table 136: Co-Administration of CYP Substrate Drug and Tadalafil

Study	CYP3 Inhibitor/Substrate	Tadalafil Dose	Result
LVEV	Ketoconazole 400mg QD	Single 20 mg dose	Single dose of tadalafil well tolerated
	Ritonavir 200 or 400 mg BID		
(b) (4)			
LVGZ (CYP inducer)	Bosentan 125 mg BID 10 Days with→	40 mg for 10 Days	100 % AEs (14/14) Mild to Moderate, No SAEs
LVDM	Lovastatin single 40 mg dose	Multiple doses 20 mg	Multiple doses of tadalafil well tolerated
LVAF	Midazolam 15 mg single dose	Multiple doses 10 mg	No clinically significant findings

Source: Summary Sections 2.7.4.3.1.1 and 2.7.4.3.1.2, Clinical Summary of Safety, pages 159-162

Total Frequency >=4 and AE Incidence with CYP3A4 Exposure is 1% > than Non-Exposed Subjects All Tadalafil 5 mg Subjects Studies LVHG, LVHJ and LVHR

Preferred Term	CYP3A4 Inhibitor Use		Tadalafil 5 mg	
			n	(%)
Subjects with >= 1 TEAE	No	N=493	137	(27.8)
	Yes	N=88	29	(33.0)
Back Pain	No	N=493	11	(2.2)
	Yes	N=88	3	(3.4)
Pain in Extremity	No	N=493	6	(1.2)
	Yes	N=88	2	(2.3)
Myalgia	No	N=493	4	(0.8)
	Yes	N=88	3	(3.4)
Upper Respiratory Tract Infection	No	N=493	3	(0.6)
	Yes	N=88	2	(2.3)
Treatment-Emergent Adverse Events Placebo Subjects	No	N=504	99	(19.6)
	Yes	N=71	22	(31.0)

Source: Table ISS 66, Integrated Summary of Safety, page 373.

The Sponsor concludes that there is no evidence of reduced tolerability of tadalafil with CYP3A4 inhibitor therapy. They propose to keep the current labeling, that for patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of 2.5 mg CIALIS is appropriate for patients with BPH and BPH/ED.

> *Reviewer's Comment: For patients on placebo, the incidence of reporting at least 1 TEAE in those using CYP3A4 inhibitors was 31.0% (22 of 71 subjects) versus 19.6% (99 of 504 subjects) in those not on CYP3A4 inhibitors. The incidence of TEAEs in patients using CYP3A4 inhibitors for placebo versus tadalafil 5 mg is 31% versus 33%, respectively. In my opinion, this is not a significant difference. I concur with Sponsor's analysis and labeling recommendations regarding CYP 3A4 inhibitors.*

Antihypertensive Medications

Overall, for subjects reporting at least 1 TEAE possibly related to hypotension, no significant treatment-by-subgroup interactions were observed between the concomitant antihypertensive therapy subgroups. For individual TEAEs, a significant treatment-by-subgroup interaction was observed only for headache (tadalafil 2.5 mg/placebo HOR p=.081 [Breslow-Day test for homogeneity of odds ratios {a p value ≤ .10 indicates a significant by- subgroup interaction}]).

Table 137: Treatment-Emergent Adverse Events Possibly Related to Hypotension by Concomitant Antihypertensive Therapy Pivotal BPH Studies LVHG and LVHJ

Preferred Term	Number Concomitant Antihypertensives	Placebo			Tadalafil 5 mg		
		N	n	(%)	N	n	(%)
Subjects with >= 1 TEAE	0	227	9	(4.0)	210	11	(5.2)
	1	81	2	(2.5)	94	3	(3.2)
	>=2	68	0	(0.0)	69	4	(5.8)
Headache	0	227	6	(2.6)	210	7	(3.3)
	1	81	1	(1.2)	94	3	(3.2)
	>=2	68	0	(0.0)	69	2	(2.9)
Dizziness	0	227	0	(0.0)	210	3	(1.4)
	1	81	1	(1.2)	94	0	(0.0)
	>=2	68	0	(0.0)	69	1	(1.4)
Asthenia	0	227	2	(0.9)	210	0	(0.0)
	1	81	0	(0.0)	94	0	(0.0)
	>=2	68	0	(0.0)	69	1	(1.4)
Fatigue	0	227	1	(0.4)	210	1	(0.5)
	1	81	0	(0.0)	94	0	(0.0)
	>=2	68	0	(0.0)	69	0	(0.0)
Hypotension	0	227	0	(0.0)	210	1	(0.5)
	1	81	0	(0.0)	94	0	(0.0)
	>=2	68	0	(0.0)	69	0	(0.0)

Source: Table APP 2.7.4.44, Appendix Clinical Summary of Safety, page 410.

In the **additional BPH analysis set of all subjects** (≤65 and >65 years of age)**,** no significant treatment-by-subgroup interaction was observed for the age subgroups in the percentage of subjects reporting at least TEAE possibly reflecting hypotension overall, and no significant treatment group difference was observed for any individual TEAE possibly reflecting hypotension.

For subjects <75 and ≥75 years of age in the **additional BPH analysis set of all subjects,** overall TEAEs possibly related to hypotension by concomitant antihypertensive therapy (no, 1, or 2 or more classes of antihypertensive medications) for subjects <75 and ≥75 years of age demonstrated no significant treatment-by-subgroup interaction. For subjects ≥ 75 years of age, no significant treatment group difference was observed for any individual TEAE by antihypertensive subgroup. For subjects <75 years of age, there was a significant treatment-by antihypertensive- therapy subgroup interaction for the TEAE of dizziness (HOR p=.065). The Sponsor stated that this finding is likely due to the small number of events reported and opposing treatment group differences within the subgroups. As percentages of subjects with dizziness did not increase with increasing number of classes of concomitant antihypertensive use, the events were not likely the result of related blood pressure changes, in the Sponsor's opinion.

In the **pivotal BPH/ED analysis set** for Subjects ≤65 and >65 years of age, no significant treatment-by subgroup interactions were observed for any individual TEAEs in either age subgroup. For subjects <75 and ≥75 years of age in the **pivotal BPH/ED analysis set**, no significant treatment-by-subgroup interactions were observed. In the tadalafil 5 mg group of patients ≥75 years of age, 1 of 9 patients not taking antihypertensives experienced dizziness compared to 1 of five patients taking 1 antihypertensive medication and 0 of seven patients taking two or more antihypertensive medications. Headache was reported in 2 of 9 subjects not on antihypertensive medication and 0 of 12 patients on one or more antihypertensive mediations (Table AP 2.7.4.53, Appendix Clinical Summary of Safety, page 432). No significant treatment-by-subgroup interactions were observed for any individual TEAEs in either age subgroup.

> *Reviewer's comment: In LVHR, the total 5 mg patients reporting dizziness was 2 (1.0%, N=208) and reporting headache was 12 (5.8%, N=208). The number of subjects ≥75 years of age on antihypertensive therapy is small as is the number of AEs possibly related to hypotension. These numbers at this time do not identify a safety concern. It does not appear that tadalafil presented an increased risk in any age subgroup for hypotension in patients taking concomitant antihypertensive medications*.

Alpha Blockers

The reader is referred to the separate review of Study LVHS in this NDA review. In Study LVHS, tadalafil 5 mg administered once daily for 12 weeks in men with BPH-LUTS taking concomitant alpha-blocker therapy was generally well tolerated. Overall, SAEs were rare, and none resulted in death. The incidence of TEAEs in the tadalafil group was numerically higher than placebo. Although a higher percentage of subjects in the tadalafil 5-mg group reported at least 1 TEAE compared with the placebo group, this difference was not statistically significant (41.8% versus 33.1%, p=.132). The most commonly reported TEAEs were dizziness, dyspepsia, diarrhoea, back pain, and GERD. In general, the TEAE profile in Study LVHS was similar to that of the pivotal BPH analysis set. A few slight differences were observed, as anticipated, based upon the greater percentage of elderly subjects and concomitant treatment with alpha blockers in this study; specifically, a higher incidence of dizziness was reported in both treatment groups in Study LVHS than was reported in the pivotal BPH analysis set or in the other BPH analysis sets/studies. These data are consistent with the known safety profiles of alpha-blocker therapies, for which dizziness is the most commonly reported TEAE.

Serious adverse events were reported in 6 subjects (tadalafil: 3 subjects; placebo: 3 subjects). None of these SAEs were considered by the investigator to be related to study drug or protocol procedure. No deaths occurred during this study. A total of 13 subjects (tadalafil: 7; placebo: 6) discontinued due to an AE. The only AE leading to discontinuation that occurred in more than 1 subject was headache (2 tadalafil subjects). Only 2 tadalafil subjects discontinued due to a TEAE possibly related to hypotension (both with headache), and neither of the subjects had a treatment-emergent positive orthostatic test. Secondary analyses of TEAEs possibly related to hypotension were conducted using both a focused list and an expanded list of MedDRA preferred terms in order to assess the incidence of clinical AEs related to orthostasis and hypotension. For both the

focused and expanded analyses of TEAEs possibly related to hypotension, similar proportions of subjects in each treatment group reported at least 1 TEAE, with no statistically significant differences between treatment groups. In the orthostatic vital sign assessment, 60 subjects (30 per treatment group, p=1.00) met at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test. Assessment of symptomatic orthostatic hypotension (presence of a clinical symptom simultaneously with a positive orthostatic test) also showed similar results between treatment groups (1 subject per group).

No tadalafil-treated subjects reported syncope. No tadalafil-treated subject reported an SAE attributable to hypotension.

> *Reviewer's Comment: Safety results are comparable with other tadalafil studies. There were no new safety concerns or signals noted in patients concomitantly using alpha blockers and tadalafil. The non selective alpha blockers generated 9 of 14 adverse events possibly related to hypotension (page 126 of LVHS Study Report). As tadalafil is to be used as mono therapy for BPH and BPH/ED, and concomitant use of alpha blockers is to be discouraged in labeling, there are no additional labeling recommendations.*

Adverse Events and IPSS Change Reported During Prior Alpha Blocker Periods

This section is in response to an FDA request for information concerning symptomatic worsening and urinary retention in subjects discontinuing alpha blockers for study participation. The analysis population includes subjects who discontinued therapy within 1 day of the date of the initiation of the screening/washout period (±1 day of the date of Visit 1) for Studies LVHG, LVHK, LVHJ and LVHR. All AEs reported during the washout period (4 weeks between Visit 1 and Visit 2) are summarized. Procedure-related events for Studies LVHJ and LVHR were also evaluated. Changes in total IPSS during the washout period (the 4 week period between Visit 1 and Visit 2) is provided for subjects requiring alpha-blocker washout in Studies LVHJ and LVHR. This analysis is not provided for Studies LVHG and LVHK, as IPSS was not collected at Visit 1 for these earlier studies.

Overall there were 279 patients requiring alpha-blocker washout during the washout periods in Studies LVHG (N=100), LVHK (N=24), LVHJ (N=42) and LVHR (N=113). In Study LVHJ, there were no procedure-related AEs reported during the screening/washout period by any of the 42 subjects requiring washout. In Study LVHG, there were 8 subjects reporting 14 AEs during the screening/washout period. In Study LVHK, 3 of 24 subjects reported 3 AEs during the 4-week washout period. In Study LVHR, a total of 113 subjects who were screened required alpha-blocker washout; 4 of those subjects (3.5%) reported 5 procedure-related AEs, as follows:

- Dysuria and nocturia (1 subject) - Events started Washout Day 1. Events duration 108 days.
- Micturition disorder [worsening nocturia] (1 subject who discontinued) - Event started Washout Day 1. Event duration not stated.

- Residual urine (1 subject, while not discontinuing reported increased symptom of incomplete bladder emptying [PVR not determined]) - Event started Washout Day 7. Event duration 56 days.
- Urinary retention (1 subject who discontinued) - Event started Washout Day 2. Event duration 1 day.

Of the subjects reporting procedure-related AEs following alpha-blocker washout in LVHR, all had discontinued tamsulosin.

In Study LVHK, of 3 events: ecchymosis, skeletal injury, and 1 urinary event of urethral hemorrhage. The event of urethral hemorrhage was most likely related to the invasive urodynamic procedure conducted at Visit 2. In Study LVHG, of the 14 AEs reported by 8 patients, only one (1), dysuria, was referable to the genitourinary system.

Of the 42 patients in Study LVHJ who required washout of alpha blockers, a mean increase of 4.8 points in total IPSS was observed from Visit 1 to Visit 2. At Visit 2, the mean total IPSS of subjects requiring alpha blocker washout was 20.3 versus 18.9 for all other subjects. The Sponsor presents IPSS data for 77 of 113 patients who were screened and required alpha blocker washout. A mean increase of 2.5 in total IPSS was observed from Visit 1 to Visit 2. Symptoms following the screening/washout period were slightly worse for those discontinuing alpha-blocker therapy, as observed by a mean total IPSS for these subjects (n=77) of 22.1, versus 20.1 for all other subjects (n=659).

> *Reviewer's Comment: The adverse events associated with alpha-blocker washout were relatively few and for the most part of modest severity. There was only 1 episode of urinary retention in 279 men who stopped taking alpha-blockers. There is some degree of symptomatic worsening during alpha blocker washout. In my opinion, alpha-blockers can be safely stopped in men with BPH prior to using tadalafil for BPH treatment. Most of the significant adverse events, from a genitourinary standpoint, occurred in Study LVHR and usually occurred in the first 7 days of washout period which was 4 weeks in duration. It would seem reasonable to start tadalafil after a washout period of 1-2 days based on the results of Study LVHS which would further minimize adverse event incidence.*
>
> *Overall, there were no new drug-drug interactions identified.*

Prior Alpha Blocker Therapy

For the pivotal BPH analysis set, there was a significant treatment-by-prior-alpha-blocker-subgroup interaction. There was a significantly greater percentage of TEAEs reported by subjects who did receive prior alpha-blocker in the tadalafil 5 mg group compared with placebo (37.4% versus 21.1%, respectively). For individual TEAEs, a significant treatment-by-subgroup interaction was observed for nasopharyngitis. In the Sponsor's opinion, this appears to be artifact caused by the small number of events reported and opposing treatment group differences. Also among subjects who did receive prior alpha blocker therapy, the percentage of patients

experiencing dyspepsia was significantly greater in the tadalafil 5 mg group (5.6%) compared with placebo (0.0%).

The table below summarizes findings in the additional analysis set of all subjects. This group includes all BPH subjects in the three pivotal studies. A significantly greater percentage of TEAEs was reported by subjects who did receive prior alpha-blocker therapy in the tadalafil 5-mg group compared with placebo (36.8% and 20.0%, respectively). A significantly greater percentage of subjects reporting nasopharyngitis had received prior alpha-blocker therapy in the tadalafil 5 mg group compared with placebo. The Sponsor states that similar differences for gastritis and sinusitis are likely an artifact caused by the small number of events reported and opposing treatment-group differences with the subgroups. Similar findings were noted in the pivotal BPH/ED analysis set.

Table 138: Treatment-Emergent Adverse Events by Prior Alpha Blocker Use with Total Frequency >=4 and AE incidence is 1% > than Non-Alpha Blocker Exposed Subjects All Tadalafil 5 mg Subjects Studies LVHG, LVHJ, and LVHR

Preferred Term	Prior Alpha Blocker Therapy Tadalafil 5 mg		Tadalafil 5 mg	
			n	(%)
Subjects with >= 1 TEAE	No	N=418	106	(25.4)
	Yes	N=163	60	(36.8)
Headache	No		15	(3.6)
	Yes		9	(3.5)
Back Pain	No		8	(1.9)
	Yes		6	(3.7)
Dyspepsia	No		7	(1.7)
	Yes		7	(4.3)
Nasopharyngitis	No		6	(1.4)
	Yes		6	(3.7)
Hypertension	No		6	(1.4)
	Yes		5	(3.1)
Upper Respiratory Tract Infection	No		2	(0.5)
	Yes		3	(1.8)
	No		1	(0.2)
	Yes		2	(1.2)
Placebo				
Treatment-Emergent Adverse Events Placebo Subjects	No	N=415	89	(21.4)
	Yes	N=160	32	(20.0)

Source: Table ISS 44, Integrated Summary of Safety, page 247.

Reviewer's Comment: No clinically important findings relevant to prior alpha blocker use were noted and the TEAEs observed in subjects with prior alpha-blocker use are consistent with the known safety profile of tadalafil.

Prior PDE5 Inhibitor Use

For the pivotal BPH analysis set, the additional BPH analysis set of all subjects and the pivotal BPH/ED analysis set, no significant treatment-by-subgroup interaction was observed for prior PDE5 inhibitor use. However, statistically significant by subgroup interactions were noted for bronchitis, headache, myalgia, abdominal discomfort, and gastritis. For these AEs, the Sponsor observes that these findings are likely an artifact caused by the small number of events reported and opposing treatment-group differences with the subgroups and therefore do not appear to indicate a true treatment-by-subgroup interaction.

Table 139: Treatment-Emergent Events by Prior PDE5 Inhibitor Therapy with Total Frequency >=4 and AE incidence is 1% > than Non-PDE Inhibitor Exposed Subjects All Tadalafil 5 mg Subjects Studies LVHG, LVHJ and LVHR

Preferred Term	Prior PDE5 Inhibitor Therapy Tadalafil 5 mg		Tadalafil 5 mg	
			n	(%)
Subjects with >= 1 TEAE	No	N=429	117	(27.3)
	Yes	N=152	52	(32.2)
Back Pain	No		9	(2.1)
	Yes		5	(3.3)
Placebo				
Treatment-Emergent Adverse Events Placebo Subjects	No	N=430	83	(27.3)
	Yes	N=146	38	(32.2)

Source: Table ISS 44, Integrated Summary of Safety, page 247.

Reviewer's Comment: No clinically important findings relevant to prior PDE5 inhibitor use were noted and the TEAEs observed in subjects with prior alpha-blocker use are consistent with the known safety profile of tadalafil.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no human carcinogenicity studies in this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

There were no reproductive studies or pregnancy data in this sNDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

Growth assessment studies were not performed in this NDA. There were no pediatric studies in this sNDA. The Sponsor requested a full waiver of pediatric studies and based upon the dault indications of BPH and BPH/ED, the reviewer concurs.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As per the product label, for on-demand use of tadalafil, single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. The adverse events at these high doses were similar to that seen in lower doses. In cases of overdose, standard supportive measures are recommended as required. Hemodialysis contributes negligibly to tadalafil elimination.

In light of the much smaller doses used in once-a-day dosing, the experience of on-demand dosing, and the studies supporting the original NDA serve as acceptable information for overdose experience.

7.7 Additional Submissions

Four additional submissions are included in the review of these sNDAs. They are referred to, when appropriate, throughout this review: They are:

- Four-Month Update of Safety Information for Cialis® Benign Prostatic Hyperplasia: Benign Prostatic Hyperplasia and Erectile Dysfunction: March 30, 2011. SDN 244.
- Regulatory Response: Potential Review Issues: April 12, 2011, SDN 245. The five potential review issues were: (b) (4), Adverse events related to hypotension, Exposure data in men ≥ year of age, Myocardial infarction as cause of discontinuation, and Adverse events of hypertension.
- Regulatory Response: Early Discontinuation Due to Subject Decision Open-Label Extension, Study LVHG: May 13, 2011, SDN 247.
- June 23, 2011 Amendment to Information submitted December 6, 2010 and amendments to Clinical Study Report LVHS and LVHR.

8 Postmarket Experience

As of April 15, 2010, approximately 26.3 million patients worldwide had been exposed to tadalafil (excluding use of tadalafil when taken as Adcirca™ for pulmonary arterial hypertension [PAH]). In the 13th PSUR, submitted on December 13, 2010, for the period between 16 April 2010 through 15 October 2010, over [redacted] (b) (4) were reported to have taken tadalafil, excluding tadalafil used for PAH. Tadalafil has been approved for the treatment of ED in 118 countries and is marketed in 108 countries. There is only 1 tadalafil dose form, a film-coated tablet in 4 strengths (2.5, 5, 10, and 20 mg). Tadalafil may be taken on demand (5, 10, and 20 mg) or once daily (2.5 and 5 mg), depending on the regulatory approval in individual countries.

Tadalafil has been approved for the treatment of pulmonary arterial hypertension (PAH) in 33 countries as of 15 April 2010. The recommended dose of tadalafil for PAH in approved countries is 40 mg daily.

Within the 13th PSUR, the Sponsor presented all reported adverse events for that period, as well as detailed reviews for 8 specific safety topics that are being monitored, encompassing adverse event data for the 6-month reporting period as well as in some situations, for the annual reporting period ending October 15, 2010. These 8 topics are discussed briefly below:

1) *Cerebrovascular Accidents*: There were 23 cerebrovascular events reported in 22 cases. Of these, 22 events were serious and 1 was nonserious. Twenty cases were reported spontaneously. Seven were reported by consumers and 15 by health care providers. The Sponsor concluded that the majority of CVA cases presented with confounding factors or contained insufficient information to draw more precise conclusions. No additional changes to the RSI (Reference Safety Core Data Sheet) were deemed warranted.

> *Reviewer's Comment: Review of the narratves for these events demonstrates an overall lack of information (e.g., time of dosing is unknown in most cases) and significant cardiovascular co-morbity in most patients. Based upon insufficient details and significant co-morbidity, it is not possible to attribute these CVA events to tadalafil.*

2) *Hearing Loss/Hearing Impairment*: There were 66 events (in 63 cases) of hearing loss or hearing impairment, including 12 events of "deafness". Of the 66 events, 23 were serious and 43 were nonserious. By Sponsor's analysis, 11 of the 12 reports of "deafness" contained insufficient information for evaluation and assessment, and 4 contained confounding factors. Of 23 cases of "tinnitus", fifteen provided insufficient for evaluation and assessment. The one case of "neurosensory hearing loss" reported insufficient information for evaluation and assessment. Of 27 cases of "hearing loss", 9 had potential confounding factors and 23 provided insufficient information for evaluation. The Sponsor will continue monitoring for hearing abnormalities. The rate of reported events of hearing loss was 0.0931 per 100,000 in 2010, which was lower than the rate in either 2008 or 2009 (0.1318 and 0.2022, respectively). No changes to the RSI are recommended.

Reviewer's Comment: Review of the case narratives for these events confirmed the general lack of detail and presense of confounding factors. Currently, there is insufficient evidence to attribute these hearing loss events to tadalafil.

3) *Ocular Events*: During the reporting period, there were 25 cases (17 spontaneous) of ocular events. There were a total of 15 cases (7 spontaneous and 8 PMS) of possible NAION (non-arteritic ischemic optic neuropathy) during the reporting period. By Sponsor's analysis, the majority of the patients in whom NAION was reported had medical histories or concurrent conditions (i.e. small cup-to-disc ratio, hypertension, diabetes, and hypercholesterolemia) that predispose the patient to NAION. The Sponsor observes that the increase in reporting of possible NAION cases in this period appears to be driven by a retrospective postmarketing study being conducted concurrently by another manufacturer of PDE5 inhibitors. Based on this increase in historic reports, the overall reporting rate of NAION-related events increased from 0.0191 per 100,000 in the 11th PSUR to 0.0519 per 100,000 in the 13th PSUR. The Sponsor concludes that no additional changes to RSI are warranted at this time.

Reviewer's Comment: The additional historic reports of possible NAION, prompted by a retrospective epidemiologic study being conducted by a different Sponsor, lacked detail in many cases, and were confounded in the majority of cases. (b) (4) *Currently, it is not possible to attribute these serious ocular events to tadalafil.*

4) *Events With a Fatal Outcome*: During the 1-year reporting period of 16 October 2009 to 15 October 2010, a total of 22 reports with a fatal outcome were identified. Stated causes of death reported in 2 or more cases included: death (5), cardiac failure (3), myocardial infarction (2) and cerebrovascular accident (2). All other causes of death were reported by 1 case each, and including a variety of serious conditions (e.g. sudden death, lung disease, neoplasm, other cardiovascular conditions). In the 12 cases where a tadalafil dose was reported, the dose ranged from 2.5 mg every other day to 40 mg QD. In 1 case, the dose was reported as 5 mg PRN. The tadalafil dose was unknown in 7 cases. There were an additional 3 cases where the tadalafil dose was reported, but no frequency was given. In most of the cases, confounding factors involving the cardiovascular system, respiratory system and endocrine system were identified. The Sponsor determined that no additional changes to the RSI are warranted at this time.

Reviewer's Comment: Confounding factors were reported in the majority of cases with a fatal outcome. Serious and unrelated conditions were also reported as causes of death. Currently, it is not possible to attribute these events with fatal outcomes to tadalafil.

5) *Safety of the Once Daily Dosing Regimen*: The 13th PSUR provided separate assessments of the PRN and once-daily regimens. For the once-daily regimen, there was a total of 104 cases reporting a total of 164 HCP-reported spontaneous adverse events, exclusive of patients with PAH. There were 9 cases where no events were reported. Of the 164 events, 71 (43.3%) were reported in patients ≥ 65 years of age, and 93 (56.7%) were reported in patients < 65 years of age. Of the 71 events reported in patients ≥ 65 years of age, 10 were serious and 61 were

nonserious. Of the 93 events reported in patients < 65 years of age, 13 were serious and 80 were nonserious.

75.6% of the reported events (124 out of 164) were reported with the 2.5 and 5 mg QD doses. Of these 124 events, 58 were reported in patients ≥ 65 years of age, while 66 occurred in patients < 65 years of age. The system organ classes (SOCs) with the largest number of reports in patients ≥ 65 years of age were Nervous System disorders (14 events) and General disorders (13 events). Of the 14 nervous system events, the majority was nonserious (11 events) and the most frequently reported were headache and dizziness. Of the 13 General disorder events, the majority was nonserious (12 events) and the most frequently reported was "drug ineffective". There were a total of 4 cases with a fatal outcome. Three of these were reported in patients ≥ 65 years of age. These were: two cerebrovascular accidents in 70 and 76 year old males, and a 65 year old male status post bariatric surgery who was found unresponsive at home and pronounced dead in the emergency room. The fourth case was a 27 year old male with a malignant lung neoplasm who sustained a myocardial infarction and cardiac arrest in 2004 and died secondary to lung cancer in 2010. The Sponsor concludes no changes to the RSI are warranted.

Adverse events in patients taking concomitant antihypertensive treatment and daily tadalafil were reported in 20 patients. The most commonly reported events in this patient population were "drug ineffective" (5) and dizziness (3). Headache, hypotension, arrhythmia, and "ECG abnormal" were reported in 2 patients each. Penis disorder, erection increased, back pain, myalgia and cerebrovascular accident were reported in one patient each.

A review of the tadalafil cases involving daily dosing in patients ≥ 65 years of age versus the patients < 65 years of age in this reporting period showed that there were no specific differences between the safety profile of tadalafil between these populations. Therefore, no additional changes to the RSI are warranted.

> *Reviewer's Comment: It appears that the postmarketing safety profile of the tadalafil daily dosing regimen is consistent with the safety profile shown in clinical trials. No new safety signals for the daily dosing regimen were identified in the 13th PSUR. There does not appear to be a worsened AE profile in patients ≥ 65 years of age compared with patients < 65 years of age using the daily dosing regimen in the postmarketing period.*

6) *Patients with PAH*: These results are not described in detail here as they are not directly applicable to this sNDA

7) *Hemorrhagic/Bleeding Events in the PAH Population*: These results not described in detail here as they are not directly applicable to this sNDA

8) *Cardiac Failure in the PAH Population*: These results are not described in detail here as they are not directly applicable to this sNDA.

Reviewer's Comment: Post marketing experience of tadalafil when administered either on demand at doses of 5 mg, 10 mg and 20 mg or as a once a day regimen in the 13th PSUR reveals similar adverse events by type as were noted in the daily use and on demand clinical studies. No new safety concerns were identified in the PSUR and the Sponsor's conclusions are appropriate.

The 14th PSUR covers the reporting period from October 16, 2010 until April 15, 2011. Again, > 4 million patients were reported to have taken tadalafil in this period. The overall safety profile was unchanged during this period, with no new safety signals identified. Analysis of safety issues relating to patients 65 years of age or older did not raise any significant safety concerns and the safety profile in that group is consistent with patients under the age of 65 years of age.

Reviewer's Comment: In both the 13th and 14th PSURs, the information presented did not reveal any new safety signals and no new safety concerns have been identified.

9 Appendices

9.1 Literature Review/References

No specific literature review was conducted as part of this sNDA review.

9.2 Labeling Recommendations

Labeling recommendations from the Clinical perspective were provided at several internal labeling meetings and are documented in the FDA-revised labeling as conveyed to Sponsor on August 26, 2011. Several additional Clinical labeling recommendations will be conveyed to Sponsor as the labeling discussons continue.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for these supplemental applications.

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/s/

A R WIEDERHORN
09/13/2011

MARK S HIRSCH
09/14/2011
I concur.

NDA 21-368 SE1-020 and **NDA 21-368** SE1-021

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Medical Officer's 45-Day Filling Memorandum

Application Letter Date:	NDA 21-368 SE1-020: December 3, 2010 NDA 21-368 SE1-021: December 3, 2010
45-Day Filing Review Date:	January 20, 2011
Mid-Cycle Review Date:	May 9, 2011
Prescription Drug User Fee Act (PDUFA) Goal Date:	October 6, 2011
Related Submissions:	IND #73,502
Product, route and dose:	Tadalafil 5.0 g administered orally once daily for patients with Benign Prostatic Hyperplasia (NDA 21-368/SE1-020); Tadalafil 2.5 and 5.0 g, administered orally once daily for patients with Benign Prostatic Hyperplasia and Erectile Dysfunction (NDA 21-368/SE1021).
Indication:	NDA 21-368/SE1-020: Treatment of signs and Symptoms of benign prostatic hyperplasia (BPH) NDA 21-368/SE1021: Treatment of both ED and Signs and symptoms of BPH (hereafter referred to as BPH/ED)

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I. Summary

Objective:

This review assesses whether NDA 21-368/ (b) (4) and NDA 21-368/ (b) (4) are suitable for filing under CFR 314.50, Content and format of an application, and 21 CFR 314.71, Procedures for submission of a new NDA. This document also serves as the basis for communicating to Sponsor potential clinical review issues identified during the initial review period.

Conclusion:

Following a preliminary review of three phase III pivotal studies (LVHG, LVHJ, LVHR), 1 phase 1 PK study (LVHN), 2 phase 3, special safety studies (LVHS, LVHK), 3 non-IND Asian studies (LVIA, LVHT and LVHB), and 2 open-label safety extensions (LVHG and LVIA), the draft label, and financial disclosures for investigators of the three phase III pivotal studies, NDA 21-368/ (b) (4) and NDA 21-368/ (b) (4) are fileable from a clinical perspective.

The Clinical review issues noted at the time of filing are listed in Section VI of this review. Several of these, as listed in Section VI, should be conveyed to Sponsor in the 74-Day letter.

II. Background

Brief Regulatory History:

Tadalafil is an orally administered selective inhibitory of phosphodiesterase type 5 (PDE5) enzyme. Tadalafil is approved to treat men with erectile dysfunction (ED; dosed either as needed or once daily) and to treat patients with pulmonary arterial hypertension (PAH, dosed once daily). The Sponsor is now seeking approval of this product for the treatment of benign prostatic hyperplasia (BPH) with or without erectile dysfunction (ED). The proposed dose for the BPH indication is 5.0 g once daily. The proposed doses for the BPH/ED indication is 2.5 or 5.0 g daily of tadalafil.

The Sponsor opened IND 73,502 on April 25, 2006. An End-of –Phase 2 meeting was held with the Sponsor on September 25, 2008. During the meeting the following items were discussed:

1. The Division requested relevant (including potential adverse hemodynamic effects) safety data from least 100 men aged 75 years or older be derived from the Phase 3 BPH program.
2. Sponsor was to evaluate both the 2.5 g and 5.0 g once a day tadalafil doses for BPH/ED.
3. Exclusion criteria for Study LVHJ should be modified to exclude patients with a PSA≥4.0 to ≤10.0 ng/mL unless prostate cancer had to be ruled out to the satisfaction of an urologist.
4. In study LVHJ uroflowmetry and measurement of Qmax are to be done at Screening, Baseline, and endpoint.
5. Sponsor is to provide safety data on patients discontinuing alpha blockers and initiating tadalafil as monotherapy.
6. Division agreed that subjects taking alpha blocker and tadalafil in combination could be excluded from Study LVHG.
7. Sponsor agreed to increase the sample size in Study LVHJ to 300 subjects and to include patients using selective and non-selective alpha blockers in assessment of treatment emergent dizziness related to concomitant tadalafil use. Hemodynamic event terms will also be provided. This sub-study within LVHJ (of patients taking concomitant alpha blockers) was eventually performed as Study LVHS as stand alone study with Division agreement that this study would be sufficient to address the Division's concerns (10 March 2009 correspondence).
8. The Division agreed in a follow-up e-mail to the fixed sequence testing procedure proposed in Study LVHJ to control family-wise Type I error in primary and key secondary endpoints and with the proposed multiple testing procedure in Studies LVHJ and LVHR.
9. (b) (4)
10. (b) (4)

11. [redacted] (b) (4)

A Pre-sNDA meeting was held April 13, 2010. During the meeting the following items were discussed:

1. The Division requested datasets from Studies LVHG, LVHJ, LVHR, LVHS, and LVIA in SDTM format.
2. The Agency requested that the application include an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) to accommodate additional presentations of efficacy and safety data.
3. LVIA should be integrated into adverse event data from Asian subjects and the Integrated Summary of Efficacy should include a separate discussion of efficacy in Asians. As a result of limited numbers of Asian subjects in LVHJ, LVHG, LVHR, LVHS, and LVHK, the Division agreed that an integration of efficacy and safety data from Studies LVHT and LVIA would be acceptable in lieu of integrated analyses from study LVIA combined with Asian subjects from Studies LVHJ, LVHG, LVHR, LVHS, and LVHK.
4. In addition to Sponsor's proposed subgroup analysis, the Division requested subgroup analysis by prior alpha blocker therapy (yes/no), by prior PDE5 inhibitor therapy (yes/no), and Asian versus non-Asian.
5. Safety data is to be organized in the ISS in 3 groups: 1) All BPH patients 2) BPH patients without ED 3) Patients with BPH/ED and is to include a discussion of whether safety was different in LVHR.
6. A separate section in the ISE in which safety data from Study LVIA is integrated with data from Studies LVHJ and LVHG.
7. Cardiovascular events should be added to the proposed list of safety topics and the Special Safety Topics Sections should include a brief discussion of myalgias/back pain, seizures and transient global amnesia.
8. A final study report for the completed 1-year Study of LVHG is to be submitted with the application as well as an abbreviated study report for the open-label extension of Study LVIA containing at least 6 months of safety data.
9. [redacted] (b) (4)
10. [redacted] (b) (4)

Additional Agreements Related to Clinical Studies

1. Study LVHN conducted to evaluate the pharmacokinetics and hemodynamics of tadalafil 20 mg administered once daily in young (≤60 years of age) and elderly (70 to 85 years of age) subjects with BPH-LUTS be completed and discussed at EOP2 Meeting. After having reviewed the preliminary results at the EOP2 Meeting, the Division agreed that Study LVHN adequately addressed the pharmacokinetics of tadalafil in elderly subjects and that no

additional pharmacokinetic or clinical pharmacology studies (including drug-drug interaction) were required to support the sNDA for either the BPH or the BPH/ED indication. However, the Division requested clinical safety data from elderly subjects with BPH in the Phase 3 clinical studies (see Regulatory Agreements on Overall Safety).

2. Results from studies LVHS and LVHK would be excluded from the integrated analyses and displayed separately.
3. Uroflowmetry assessment of Qmax would be conducted at Screening, Baseline, and Endpoint for all pivotal Phase 3 studies.

III. Efficacy Data Analysis Sets

Analysis Sets Supporting the BPH Indication

Analyses supporting the BPH indication use data from the placebo and 5-mg tadalafil treatment groups of Studies LVHJ and LVHG. These data define the **pivotal BPH analysis set.**

Additional analyses for the BPH indication used integrated data from subjects without ED and integrated data from Studies LVHG, LVHJ, and LVHR (referred to as the "additional BPH analysis set of all subjects"). Finally, in a separate integration, data from the placebo and tadalafil treatment groups of 3 placebo-controlled studies conducted in Asian countries (Studies LVHT, LVHB and LVIA) were integrated to evaluate the efficacy of tadalafil in Asian countries (non-IND studies conducted in Asian countries analysis set).

Data from the LVHG open-label extension study comprise the primary long-term exposure analysis set as it relates to "persistence of effect". In this open-label extension, subjects previously assigned to placebo, 2.5 mg tadalafil, 5 mg tadalafil, 20 mg tadalafil, or 20 mg tadalafil treatment groups in the double-blind treatment period were administered tadalafil 5 mg.

In a separate integration, data from the placebo and tadalafil 5 mg treatment groups of 2 placebo-controlled studies conducted in Asian countries (Studies LVHT and LVIA were integrated to evaluate the efficacy of tadalafil in subjects in Asian countries **(referred to as "non-IND studies conducted in Asian countries analysis set").**

Data from the LVIA open-label extension study comprise the long-term exposure analysis set as it relates to "persistence of effect" in non-IND studies conducted in Asian countries. In the LVIA open-label extension, subjects were administered tadalafil 5 mg.

Analysis Sets Supporting the BPH/ED Indication

Analyses supporting the BPH/ED indication use the **pivotal BPH/ED analysis set** from placebo, 2.5 mg, and 5 mg tadalafil treatment groups of Study LVHR. Study LVHR enrolled subjects presenting with BPH-LUTS and ED.

Additional analyses for the BPH/ED indication were conducted using integrated data from subjects with ED from the placebo and tadalafil treatment groups of Studies LVHG and LVHR, and integrated data from subjects with ED from the placebo and tadalafil 5 mg treatment groups of Studies LVHG, LVHJ and LVHR (**additional BPH/ED analysis set of all subjects with ED).**

Table 1: Clinical Summary of Efficacy Analysis

Analysis Set	Content	Efficacy Outcomes	
		Primary	Secondary
BPH Indication (Tadalafil 5 mg)			
Pivotal BPH	Pivotal BPH Studies LVHG and LVHJ (Integrated 12-week double-blind treatment period data)	Total IPSS	BII
Long-Term BPH	Long-Term Extension (Data from 52-week, open-label extension of Study LVHG)	Total IPSS	BII
Additional BPH All Subjects	Integrated Pivotal BPH and BPH/ED Studies (LVHG, LVHJ, and LVHR) (Integrated 12-week double-blind treatment period data)	Total IPSS	BII
Additional BPH Subjects Without ED	Subjects Without Erectile Dysfunction Integrated Pivotal BPH Studies LVHG and LVHJ (Integrated 12-week double-blind treatment period data)	Total IPSS	BII
Non-IND studies conducted in Asian countries	Non-IND Studies Conducted in Asian Countries Studies LVIA and LVHT (Integrated 12-week double-blind treatment period data)	Total IPSS	NA
Non-IND Long-Term	Long-Term Extension (Data from 42-week, open-label extension of Study LVIA)	Total IPSS	NA
BPH/ED Indication (Tadalafil 2.5 and 5 mg)			
Pivotal BPH/ED	Pivotal BPH/ED Study LVHR (12-week double-blind treatment period data)	Total IPSS, IIEF EF	BII, SEP Q3
Additional BPH/ED Subjects With ED	Subjects With Erectile Dysfunction Integrated Studies LVHG and LVHR (Tadalafil 2.5 mg versus placebo; integrated 12-week double-blind treatment period data); Integrated Pivotal BPH and BPH/ED Studies LVHG, LVHJ, and LVHR (Tadalafil 5 mg versus placebo; integrated 12-week double-blind treatment period data)	Total IPSS, IIEF EF	BII[b]

Clinical Summary of Efficacy Analysis Sets (Concluded)

Abbreviations: BPH = benign prostatic hyperplasia; BII = BPH impact index; ED = erectile dysfunction; IIEF EF = international index of erectile function - erectile function domain; IND = investigational new drug; IPSS = international prostate symptom score; NA = not applicable; SEP Q3 = Sexual Encounter Profile Question #3.

[a] Designation of primary and secondary measures relate to the presentation in this Clinical Summary of Efficacy and not necessarily that of the individual study or studies.

[b] The Sexual Encounter Profile diary was not collected in Studies LVHG and LVHJ.

Source: Copy of Table 2.7.3.2, Clinical Summary of Efficacy current submission, page 27.

IV. Safety Data Analysis Sets

BPH Indication

For the BPH indication, the primary safety analysis set contains integrated data from the 12-week, double-blind, placebo-controlled Studies LVHG and LVHJ, and is to be

referred to as the **pivotal BPH analysis set**. Long term safety data is presented in the 1 year open-label extension period of Study LVHG. Data from BPH safety studies LVHK and LVHS and from the clinical pharmacology Study LVHN are presented separately.

As requested by the Division, the Pre-NDA Meeting, 24 August 2010, the following additional BPH analysis sets are summarized in this submission:

- **Additional BPH analysis of all subjects**: Contains integrated data from the 12 week, double-blind, placebo-controlled periods of LVHG, LVHJ, and LVHR.
- **Additional BPH analysis set of subjects without ED**: Contains integrated data from the placebo-controlled Studies LVHG and LVHJ for subjects who did not report ED.
- Additional age group analysis set containing integrated data from all doses in Studies LVHG, LVHJ, LVHK, and LVHR. Due to differences in dose, duration, and study design, Studies LVHN and LVHS are displayed separately.
- Additional age group analysis set containing integrated data from the placebo-controlled Studies LVHG, LVHJ and LVHR.
- **Non-IND studies conducted in Asian countries** (LVIA and LVHT): Contains integrated data from placebo-controlled Studies LVIA and LVHT and from the open-label extension period of Study LVIA. The results to Study LVHB were not integrated with the other non-IND Asian studies; as agreed upon with the Division, the LVHB CSR is included with this submission.

BPH/ED Indication

For the BPH/ED indication, the primary safety analysis set contains data from the 12-week, double-blind, placebo-controlled Study LVHR and is referred to as the **pivotal BPH/ED analysis set.**

As requested by the Division at the pre-NDA meeting, 24 August 2010, the **additional BPH/ED analysis set of subjects with ED** contains integrated data from placebo-controlled Studies LVHG, LVHJ, and LVHR for subjects who reported ED and supports the BPH/ED indication.

Table 2: Safety Data Analysis Sets

Analysis Sets	Content	Treatment Group
Analysis Sets Supporting the BPH Indication		
Pivotal BPH analysis set	Integrated data from Studies LVHG and LVHJ	Placebo and tadalafil 5 mg
Pivotal long-term analysis set	Data from 1-year OLE period of Study LVHG	Tadalafil 5 mg
Additional BPH analysis set of all subjects	Integrated data from Studies LVHG, LVHJ, and LVHR (all subjects)	Placebo and tadalafil 5 mg
Additional BPH analysis set of subjects without ED	Integrated data from Studies LVHG and LVHJ (subjects who did not report ED)	Placebo and tadalafil 5 mg
Additional BPH age-group analysis sets	1) Integrated data from Studies LVHG, LVHJ, and LVHR 2) Integrated data from Studies LVHG, LVHJ, LVHR, and LVHK; Study LVHN[a]	1) Placebo and tadalafil 5 mg 2) Placebo and tadalafil 2.5, 5, 10, and 20 mg
Non-IND studies conducted in Asian countries	1) Integrated data from Studies LVIA and LVHT 2) Data from the 42-week OLE period of Study LVIA	1) Placebo and tadalafil 5 mg 2) Tadalafil 5 mg
Analysis Sets Supporting the BPH/ED Indication		
Pivotal BPH/ED analysis set	Study LVHR	Placebo and tadalafil 2.5 and 5 mg
Additional BPH/ED analysis set of subjects with ED	Integrated data from Studies LVHG, LVHJ, and LVHR (subjects who reported ED)	Placebo and tadalafil 2.5 and 5 mg

Abbreviations: BPH = benign prostatic hyperplasia; ED = erectile dysfunction; IND = Investigational New Drug; OLE = open-label extension.

[a] For the age-group analysis, Study LVHN was not integrated with the other studies due to differences in dose, duration, and study design, and results are displayed separately. Study LVHS was not included in this analysis set due to confounding study design (co-administration of alpha-blocker therapy).

Source: Copy Table 2.7.4.2, Clinical Summary of Safety current submission, page 16.

V. NDA Filing Review

Filing Review: The review is based on three criteria proposed in FDA guidance for the filing review, based on the Agency's interpretation of 21 CFR 314.101 (d) (3) and 21 CFR 314.50.

1. Omission of a section of the NDA required under 21 CFR 314.50 or presentation in an incomplete manner.
2. Failure to include evidence of effectiveness compatible with the statue and regulations.
3. Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Submitted Materials: The Sponsor submitted the safety and efficacy data from 10 studies: 1 clinical pharmacology study, 1 phase 2 study, 5 phase 3 studies and 3 non-IND foreign studies (Open-Label extensions are not counted as a separate study) as shown in the table below:

Table 3: Summary of Clinical Studies for Tadalafil and BPH-LUTS

Study Identifier/Type	Objective	Test Product	Subjects Entered/ Number Completed	Treatment Duration
Phase 1 Clinical Pharmacology				
H6D-EW-LVHN/PK	Tadalafil PK evaluation in young/old men with BPH-LUTS: QD administration	Tadalafil 20 mg po QD for 10 Days	27/27 (15 ≤60 years; n=12 ≥70 years)	10 days
Phase 2				
H6D-MC-LVGC (Proof of Concept)	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS	Tadalafil 5 mg QD X 6 weeks Escalated to 20 QD for 6 weeks	281 randomized/ 251 completed	12 weeks
Phase 3				
H6D-MC-LVHG Double-blind Period	Evaluate Efficacy, Dose response and Safety of Tadalafil in men with BPH-LUTS	Tadalafil 2.5, 5, 10, 20 mg and placebo, QD	1058 randomized/ 886 completed	12 weeks
H6D-MC-LVHJ	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS	Tadalafil 5 mg, Placebo, QD	325 randomized/ 300 completed	12 weeks
H6D-MC-LVHR	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS/ED	Tadalafil 2.5, 5 mg, Placebo, QD	606 randomized/ 526 completed	12 weeks
H6D-MC-LVHS (Primarily Safety)	Evaluate Efficacy and Safety of Tadalafil in men with BPH-LUTS on Alpha Blockers	Tadalafil 5 mg, Placebo, QD	318 randomized/ 280 completed	12 weeks

H6D-MC-LVHK Safety	Evaluate Urodynamic effects of Tadalafil QD on Men with BPH-LUTS	Tadalafil 20 mg QD	200 randomized/ 181 completed	12 weeks
H6D-MC-LVHG Open-Label Extension	Evaluate the Safety of Tadalafil 5 mg QD for 1 year in Men with BPH-LUTS	Tadalafil 5 mg QD	428 randomized/ 299 completed	52 weeks
Foreign Non-IND Studies				
H6D-JE-LVIA	Evaluate Efficacy and Safety of Tadalafil 2.5 and 5 mg in Japanese men with BPH	Tadalafil 2.5, 5 mg and Placebo	422 randomized/ 394 completed	12 weeks
H6D-JE-LVIA Open-Label Extension	Evaluate Long-term Efficacy and Safety of Tadalafil 5 mg QD in Japanese men with BPH	Tadalafil 5 mg	394 randomized/ 323 completed	42 weeks
H6D-MC-LVHB	Evaluate Efficacy and Safety of Tadalafil QD in Asian men with BPH-LUTS	Tadalafil 2.5, 5 mg and Placebo	612 randomized/ 561 completed	12 weeks
H6D-MC-LVHT	Evaluate the Efficacy and Safety of Tadalafil and Tamsulosin QD administered in Korean Men with BPH-LUTS	Tadalafil 5 mg Tamsulosin 0.2 mg	151 randomized/ 143 completed	12 weeks

Source: Table 5.1 Tabular Listing of Studies, Module 5.2, pages 5-14.

In the pivotal and additional analysis sets supporting the BPH and BPH/ED indications:

- 1448 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg in the BPH and BPH/ED studies, with a total exposure of 624.5 subject years.
- 352 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 280 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

In subjects >65 years of age:

- 586 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission, with a total exposure of 237.9 subject years.
- 126 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 102 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

In subject's ≥75 years of age:

- 160 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission, with a total exposure of 65.3 subject years.
- 34 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 28 subjects have been exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

Reviewer's Comments*: The Sponsor has submitted extensive safety data for this new indication, including data in geriatric patients >65 years of age (n=586), and patients ≥75 years of age (n=160). 120 subjects and 102 subjects > 65 years of age were exposed for at least 6 months and 1 year, respectively. However, the extent of 6 month and 1 year exposure in patients ≥75 years of age is not as great (34 and 28 subjects for 6 months and 1 year, respectively). This will be a review issue. The Sponsor may wish to submit summaries of safety data in patients ≥75 years of age from the previous ED studies in order to better support long-term safety in this age group.*

Question-Based Filing Review

1. Does this amendment omit a section required under CFR 314.50 or was a particular section presented in such a manner as to render it incomplete for the clinical review?

Response: No.

This NDA contains the critical sections in sufficient detail (see Table 2 and Appendix A).

Table 4: Checklist for Critical Sections

Comprehensive table of contents	Yes
Summary of the Application	Yes
Technical sections (CMC, Pharmacology/Toxicology, Clinical Pharmacology, Clinical)	Yes
Case Report Forms and Tabulations	Yes

2. **Does the NDA(s) clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:**
    a) **Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints.**
    b) **Presentation or what appears to be only a single adequate and well controlled study without adequate explanation.**
    c) **Use of a study design clearly inappropriate.**

Response: No.

Preliminary Efficacy Findings

The following section of the filing review summarizes the preliminary efficacy findings from the randomized, double-blind, placebo-controlled studies LVHG, LVHJ, LVHR, and the Open Label clinical study LVHG. These were all conducted under the US Investigational New Drug (IND) #73,502. These are the three pivotal studies for these sNDAs.

Study LVHG

Study LVHG was a pivotal Phase 2b/3, randomized, double-blind, placebo-controlled, parallel-design, dose-finding study to evaluate the efficacy, dose response, and safety of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks versus placebo in men with BPH-LUTS. The study enrolled subjects ≥45 years old who presented with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Lower urinary tract symptoms as assessed by the IPSS questionnaire consisted of 7 questions regarding urinary storage and voiding symptoms.

Key inclusion criteria were total IPSS≥13 and peak flow rate (Qmax) ≥ and ≤15 mL/sec at the start of the placebo lead-in period. Notable exclusion criteria included prostate-specific antigen (PSA) values >10 ng/mL (men with a PSA of 4 to 10 ng/mL were required to have a prostate biopsy negative for malignancy within the preceding 12 months), clinical evidence of urinary tract infection/inflammation at screening , a post-void residual (PVR) volume ≥300 mL at screening, clinical evidence of prostate cancer, and finasteride or dutasteride treatment within 3 and 12 months before the start of the placebo lead-in period, respectively.

Eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

Randomization was stratified by baseline LUTS severity (total IPSS <20 or ≥20), geographic region (US/Canada, Latin America [Mexico], Europe [France, Germany, Greece, Italy, Spain, and Sweden], and Australia), and history of ED. Randomization was on a 1:1:1:1:1 ratio. 1056 subjects were randomized. 886 subjects completed the study (701 tadalafil and 185 placebos). 540 randomized patients were from the United States.

The 1056 subjects randomized for treatment had similar demographics between the treatment groups. The mean age of subjects was approximately 62 years (range: 45 to 92 years) and were predominantly Caucasian (85.6%). Two hundred ninety-four subjects (27.8%) had used previous therapy for BPH and 348 subjects (33.0%) had used previous therapy for ED. Five hundred forty-one subjects reported experiencing LUTS for >3 years and 354 subjects (33.5%) were classified as having severe LUTS (by International Prostate Symptom Score [IPSS]). At baseline, 67.8% of subjects reported a history of ED and 26.9% of subjects reported having used previous therapy for ED. Of those subjects with a history of ED at baseline, 84.8% reported ED duration of ≥1 year. The majority of subjects reported moderate ED severity (54.5%). There were 80.6% of subjects reporting that they were sexually active with a female partner and 55.0% reported that they were sexually active and had ED.

The majority of randomized patients (83.7%) completed the 12-week treatment comparison period. The most common reasons for discontinuation among all tadalafil-treated patients were AEs (n=41; 4.85%) and subject decision (n=36; 4.26%). In placebo-treated subjects, 9 subjects (4.25%) discontinued due to subject decision and 5 subjects (2.36%) discontinued due to both AE's and lost to followup.

The primary objective of Study LVHG was to evaluate the efficacy of tadalafil 5 mg once daily for 12 weeks compared to placebo in improving total IPSS in men with BPH-LUTS.

The secondary efficacy objectives included:

- Examining whether a dose-response relationship exists for placebo and tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks in the treatment of BPH-LUTS.
- Evaluating the efficacy of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks compared to placebo in the treatment of BPH-LUTS as assessed by the following measures:
    - Total IPSS (for tadalafil 2.5-, 10-, and 20-mg doses);
    - IPSS storage and voiding subscores and nocturia question;
    - The BPH Impact Index (BII);
    - LUTS-General Assessment Questions (GAQ);
    - Uroflowmetry parameters, including Qmax, mean flow rate (Qmean), and voided volume (Vcomp); and

- IIEF EF Domain score in sexually active men with ED.

In Study LVHG, across the treatment groups, 90.0% to 95.0% of subjects were ≥70.0% compliant with study drug treatment.

The primary efficacy outcome was the change in IPSS total from baseline to Visit 6 (Week 12) for subjects taking tadalafil 5 mg once-daily versus placebo. These results are a shown in the table below:

Table 5: Primary Efficacy Outcome - IPSS (International Prostate Symptom Score) Test Results (Tadalafil 5-mg versus Placebo) - All Randomized Subjects in the Primary Efficacy Analysis Population (Study LVHG)

Parameter at Time Point	Placebo (N=210)	Tadalafil 5 mg (N=212)
Change from Baseline		
n	205	205
Mean (SD)	-2.25(6.17)	-4.92(5.67)
Treatment p-value	<0.01	
Endpoint		
n	205	205
Mean(SD)	14.83(7.69)	12.38(7.23)
Baseline		
n	205	205
Mean(SD)	17.08(6.36)	17.30(5.97)

Source: Table LVHG.11.10, H6D-MC-LVHG Study Report, page 92.

The results of the secondary efficacy endpoints are shown in Table 6 below:

Table 6: Secondary Efficacy Outcomes - All Randomized Subjects in the Primary Analysis Population Study LVHG

	Placebo N=210	Tadalafil 2.5mg N=208		Tadalafil 5mg N=212		Tadalafil 10mg N=216		Tadalafil 20mg N=208	
Outcome	n LS Mean	Treatment Difference LS Mean	p-value	Treatment Difference LS Mean	p-value	Treatment Difference LS Mean	p-value	Treatment Difference LS Mean	p-value
Total IPSS	205 -2.23	-1.58	.005	-2.60	<.001	-2.90	<.001	-2.94	<.001
BII	205 -0.83	-0.13	.583	-0.57	.013	-0.55	.016	-0.62	.007
IPSS Storage	205 -0.98	0.57	.025	-0.90	<.001	-0.96	<.001	-1.07	<.001
IPSS Voiding	205 -1.31	-0.97	.008	-1.69	<.001	-1.89	<.001	-1.87	<.001
IPSS Nocturia	205 -0.30	-0.07	.503	-0.13	.206	-0.08	.452	-0.26	.012
IPSS QoL	205 -0.52	-0.26	.029	-0.37	.002	-0.43	<.001	-0.40	<.001
IEFF EF Domain	113 2.04	3.36	<.001	4.75	<.001	7.87	<.001	6.15	<.001

Source: Table 2.7.3.3, Summary of Clinical Efficacy, Current Submission, page 38

Reviewer's Comment: Tadalafil 5 mg once daily appears to favorably alter in a significant manner the primary efficacy endpoint. A dose response effect is noted up to 10 mg a day dosing, but the increase in IPSS in the 10 mg versus 5 mg once daily dosing is quite small. The same is true for the IPSS storage, and voiding domains. The change-from-baseline BII was small, and was marginally statistically significant versus placebo for doses of 5mg and higher. The nocturia domain was not significantly statistically improved. The IIEF EF domain was favorably changed in a statistically significant manner showing dose effect across all doses.

There were small improvements in the median changes from baseline in flow rate for tadalafil 2.5 mg (1.10 mL/second), 5 mg (1.15 mL/second), 10 mg (1.30 mL/second, and 20 mg (l.65 mL/second) when compared to placebo but the differences observed were not statistically significant.

Study LVHJ

Study LVHJ was a pivotal Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of tadalafil 5 mg once daily for 12 weeks versus placebo in men with BPH-LUTS.

The enrollment criteria for Study LVHJ were generally similar to those for Study LVHG with minor modifications that aligned with FDA feedback (End-of-Phase 2 Meeting,

Minutes 23 October 2008; revised exclusion criteria for subjects with PSA ≥4.0 to ≤10.0 ng/ml at screening to rule out prostate cancer to the satisfaction of an urologist instead of documentation of a histologic biopsy of the prostate negative for cancer within 12 months and added exclusion criteria for subjects with clinically significant microscopic hematuria. In addition, subjects who had received dutasteride treatment within 6 months, rather than the 12 months as required in Study LVHG, before the start of the placebo lead-in period were excluded).

After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period. Randomization was stratified by baseline LUTS severity (IPSS <20 or ≥20), geographic region (US, Latin America [Argentina and Mexico], or Europe [Germany and Italy]), and history of ED. The subjects were randomized in a 1:1 ratio. 325 subjects were randomized. 300 subjects completed the study (148 tadalafil and 152 placebo).

Subjects had a mean age of 64.9 years with a range of 44.8 to 87.0 years. Overall, 20.0% of randomized subjects (placebo, 21.3%; tadalafil, 18.6%) were at least 75 years of age or older. Most subjects (91.1%) were white. The tadalafil and placebo treatment groups were well-balanced with respect to age, ethnicity, and region. 31.4% (102) of the subjects in Study LVHJ were from the United States.

At randomization, approximately one-third of subjects (35.4%) were categorized as having severe LUTS (IPSS >20) with the remainder (64.6%) having a total IPSS <20. At randomization, approximately one-half of subjects (47.5%) had a peak urine flow rate (Q_{max}) of 10 to 15 mL/second; 38.0% had a Q_{max} <10 mL/second. Overall, mean PVR volume at randomization was 54.2 mL (placebo, 63.3 mL; tadalafil, 44.9 mL). At screening, mean PSA was 2.1 ng/mL, overall. Overall, 30.5% of subjects reported taking previous alpha blocker therapy, 8.6% reported taking previous LUTS therapy other than an alpha blocker, and 1.2% reported previous use of OAB therapy. Overall, the majority of subjects (68.9%) reported a history of ED at screening. Of those with a history of ED, 86.2% reported ED duration of ≥1 year, 53.6% reported ED of moderate severity, 33.0% reported ED of mild severity, and 49.1% reported ED of mixed etiology (psychogenic and organic). Of all randomized subjects, 79.1% reported being sexually active with a female partner with >99% of these subjects expecting to remain sexually active. Both treatment groups were well-balanced with respect to baseline characteristics associated with BPH-LUTS, previous alpha-blocker or other BPH-LUTS therapy, and ED and sexual activity related characteristics.

The majority of randomized subjects in both treatment groups (tadalafil, n=148 [91.9%]; placebo, n=152 [92.7%]) met the definition of the per protocol population, that is, they completed (as indicated by the investigator) the 12-week double-blind treatment period and were ≥70% compliant. The most common reason for study discontinuation among tadalafil treated subjects was entry criteria not met (n=4, 2.5%). 1.9% of the tadalafil treated patients discontinued for an adverse event. There was 1 death and this will be

discussed under safety evaluations. The most common reason for study discontinuation among placebo-treated subjects was subject decision (n=4, 2.4%).

The primary objective for Study LVHJ was to evaluate the efficacy of tadalafil 5 mg once daily for 12 weeks compared to placebo in improving total IPSS in men with BPH-LUTS. The key secondary analyses comparing the changes from baseline between tadalafil 5 mg and placebo were performed in the following pre-specified order:

- IIEF EF Domain score after 12 weeks (in sexually active subjects with ED);
- Total IPSS after 4 weeks of treatment;
- BII after 12 weeks of treatment;
- Total modified IPSS (mIPSS) after 1 week of treatment; and
- BII after 4 week of treatment.

In Study LVHJ, 99.7% of subjects were ≥70% compliant with study drug treatment.

Table 7: Primary and Secondary Efficacy Outcomes - All Randomized Subjects in the Primary Analysis Population Study LVHJ

	Placebo N=164	**Tadalafil 5 mg N=161**		
	n	**n**	**Treatment Difference**	
	LS Mean	**LS Mean**	**LS Mean±(SE)**	**p-value**
Primary	164	160		
Total IPSS	-3.6	-5.6	-1.9 (0.7)	.004
Key Secondary				
IEFF EF	84	88		
Domain	2.0	6.7	4.7 (1.1)	<.001
IPSS	162	158		
(at 4 weeks)	-3.5	-5.3	-1.8 (0.6)	.003
	163	160		
BII (12 week)	-1.3	-1.8	-0.6 (0.3)	.057
mIPSS	150	147		
(at 1 week)	-2.7	-3.4	-0.7 (0.5)	.029
BII	163	160		
(at 4 weeks)	-1.2	-1.8	-0.6 (0.3)	.029
Other Secondary				
IPSS Storage	164	160		
	-1.3	-2.3	0.9 (0.3)	.002
IPSS Voiding	164	160		
	-2.3	-3.3	-1.0 (0.4)	.020
IPSS Nocturia	164	160		
	-0.4	-0.5	-0.1 (0.1)	.233
IPSS QoL	164	160		
	-0.7	-1.0	-0.4 (0.2)	.013

Source: Table 2.7.3.4. Summary of Clinical Efficacy, current submission, page 41.

Reviewer's Comment: The result of the primary efficacy analysis in Study LVHJ appear to demonstrate favorable effect of tadalafil 5mg daily. It appears that based on the prescribed gatekeeping procedure, tadalafil 5 mg resulted in a statistically significant improvement in the IPSS and in the IIEF Domain score change from baseline to endpoint compared to placebo. Tadalafil 5 mg also resulted in a statistically significant improvement in total IPSS change from baseline after 4 weeks of treatment. After 12 weeks of treatment there was not a statistically significant numerical decrease in the BII.

LVHG Open-Label Extension

The long-term safety and "persistence of efficacy" of tadalafil 5-mg once-daily dosing was assessed in a 52-week, open-label extension period of Study LVHG. Subjects from the US and Canada who completed the double-blind treatment period of Study LVHG were given the option to continue into the open-label extension. Subjects with PSA at entry to the open-label extension ≥2 times higher than PSA at randomization of the double-blind treatment period were not eligible for the open-label extension. The double-blind period together with the open-label extension provided 64 weeks of assessments.

Subjects who entered the open-label extension had a mean age of approximately 63 years at Visit 1, similar to previous treatment groups (range of approximately 62 to 64 years). A majority of subjects were <65 years of age (60%); 7.7% were ≥75 years of age. Most Subjects were Caucasian (91.6%).

Of the 428 subjects who entered the open-label extension, 427 subjects received at least one dose of study drug. There were 128 subjects (29.9%) who discontinued the open-label extension early. The most common reasons for early discontinuation were due to subject decision (59 subjects, 13.8%), AEs (22 subjects, 5.1%), subject lost to follow-up (16 subjects, 3.7%), and perceived lack of efficacy (15 subjects, 3.5%).

Study LVHR

Study LVHR was a pivotal Phase 3, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of tadalafil 2.5 mg and 5 mg once daily for 12 weeks versus placebo for the treatment of ED and the treatment of signs and symptoms of BPH in men with ED and BPH symptoms

Study LVHR enrolled subjects ≥45 years of age who presented with BPH-LUTS (as diagnosed by a urologist and evidenced by IPSS ≥ 13 points, and Qmax of ≥ 4 to ≤ 15 mL/sec) for >6 months and a history of ED for ≥3 months. Subjects in Study LVHR were also required to be sexually active with an adult female partner, expected to remain sexually active with the same adult female partner for the duration of the study, and expected to make at least 4 sexual intercourse attempts during the 4-week placebo lead-in period. In general, inclusion and exclusion criteria used in Study LVHR were similar to the inclusion and exclusion criteria used for the BPH Studies LVHG and LVHJ and in once-daily ED studies.

After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

Randomization was stratified by baseline LUTS severity (IPSS <20 or ≥20), baseline ED severity (mild, moderate, or severe as defined by the IIEF EF Domain score), and geographic region (North America [Canada and US], Mexico, and Europe [France, Germany, Greece, Italy, Portugal, and Russian Federation]). 46.4% (281) patients were from North America. Subjects were randomized in a 1:1:1 ratio. 606 subjects were randomized and 526 subjects completed the study (184 tadalafil 5 mg, 172 tadalafil 2.5 mg and 170 placebo).

The most common reasons for discontinuation among subjects in the placebo group were lack of efficacy (8; 4.0%) and subject decision (8; 4.0%). The most common reasons for discontinuation among subjects in the tadalafil 5-mg group were adverse event (6; 2.9%) and entry criteria not met (6; 2.9%). The most common reason for discontinuation among subjects in the tadalafil 2.5-mg group was entry criteria not met (8; 4.0%). The majority of randomized subjects (526; 86.8%) completed the 12-week double-blind treatment period, with a similar number of completed subjects in each treatment group (placebo, 170 [85.0%]; tadalafil 5 mg, 184 [88.5%]; tadalafil 2.5 mg, 172 [86.9%]).

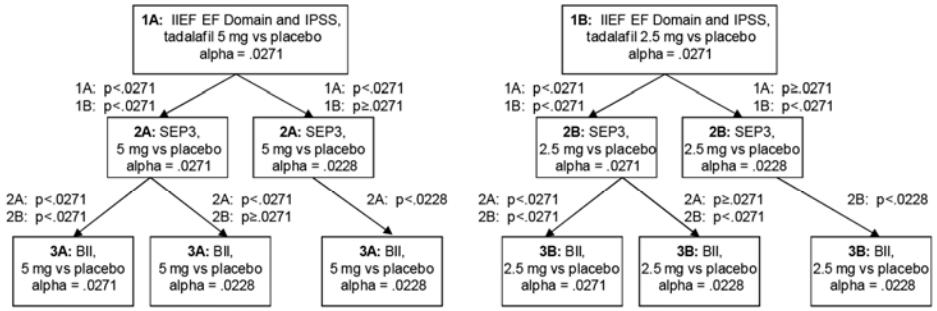
9.2% of subjects were 75 years of age or older (placebo, 11.5%; tadalafil 5 mg, 10.1%; tadalafil 2.5 mg, 6.1%). Most subjects were white (93.2%) and non-Hispanic (84.5%). The majority of subjects were either from North America (46.4%) or Europe (41.1%). Demographics and baseline characteristics were well balanced across all treatment groups. At randomization, 39.0% of subjects were categorized as having severe LUTS (IPSS ≥20), while 61.0% were categorized as having mild to moderate LUTS (IPSS <20). At randomization, approximately one-half (50.6%) of subjects had a Qmax of <10 mL/sec, 39.9% had a Qmax of 10 to 15 mL/sec, and 9.5% had a Qmax of >15 mL/sec. Mean PVR volume at randomization was 53.2 mL. Mean PSA at screening was 1.9 ng/mL. All treatment groups were well-balanced with respect to these BPH-associated characteristics.

23.4% of subjects reported previous alpha blocker therapy, 8.6% reported previous BPH-LUTS therapy other than alpha blockers, and 2.0% reported previous OAB therapy. All treatment groups were well-balanced for previous use of these therapies.

The majority of subjects (91.6%) reported ED of ≥1 year duration. At randomization, 48.8% had mild ED (IIEF EF Domain score 17 through 30), 24.6% had moderate ED (IIEF EF Domain score 11 through 16), and 26.6% had severe ED (IIEF EF Domain score 1 through 10). The most commonly reported ED etiologies were organic (36.3%) and mixed (36.6%). Overall, 28.5% of subjects reported previous ED therapy; the most commonly reported previous ED therapies were tadalafil (13.4%) and sildenafil (12.0%). All treatment groups were well balanced for ED profile parameters and previous use of ED therapies.

The co-primary objectives of Study LVHR were to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared with placebo in improving both total IPSS and IIEF EF Domain score in men with both ED and BPH-LUTS. Key secondary efficacy objectives were to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared with placebo in improving the Patient SEP Q3 and BII. To control the Type I error rate associated with these primary and key secondary endpoints for comparison of 2 doses of tadalafil with placebo, a 3-step gatekeeping procedure was applied (see CSR LVHR Section 9.7.1.4). See figure below:

Figure 1: LVHR Testing Strategy for Primary and Key Secondary Efficacy Hypotheses



Abbreviations: BII = Benign Prostatic Hyperplasia (BPH) Impact Index, EF = erectile function, IIEF = International Index of Erectile Function, IPSS = International Prostate Symptom Scale, SEP3 = Sexual Encounter Profile Question 3.

Source: Scanned Copy, Figure LVHR.9.2, H6D-MC-LVHR Clinical Study Report, page 54.

In Study LVHR, 98.5% of subjects were ≥70% compliant with study drug treatment.

The table below summarizes the efficacy outcomes for the co-primary efficacy endpoints and the key secondary efficacy endpoints in Study LVHR:

Table 8: Co-Primary and Key Secondary Efficacy Outcomes - All Randomized Subjects in the Primary Analysis Population Study LVHR

Outcome	Placebo	Tadalafil 2.5 mg (N=198)			Tadalafil 5 mg (N=208)		
	N=200	n	Treatment Difference		n	Treatment Difference	
	n LS Mean	LS Mean	LS Mean (±SE)	p-value	LS Mean	LS Mean (±SE)	p-value
Co-primary							
Total IPSS	194 -3.8	191 -4.6	-0.8 (0.59)	.181	206 -6.1	-2.3 (0.58)	<.001
IIEF EF Domain	190 1.8	190 5.2	3.4 (0.67)	<.001	203 6.5	4.7 (0.66)	<.001
Key Secondary							
SEP Q3 (% "yes")	187 12.0	148 -2.8	12.5 (2.85)	<.001	199 31.7	19.7 (2.80)	<.001
BII	190 -1.2	190 -1.6	-0.4 (0.26)	.156	203 -2.1	-0.9 (0.26)	<.001

Source: Table 2.7.3.5, Summary of Clinical Efficacy, current submission, page 44.

Treatment with tadalafil 5 mg appeared to favorably effect the total IPSS change from baseline to endpoint compared with placebo as well as the IEFF EF Domain Score change from baseline to endpoint compared to placebo. It appears that the co-primary objectives were met after 12 weeks of tadalafil 5 mg once-daily dosing. However, treatment with tadalafil 2.5 mg daily was not as favorable. It appears that the co-primary objectives were not met after 12-weeks of tadalafil 2.5 mg once-daily dosing due to a failure to achieve a statistically significant improvement in the total IPSS.

As the co-primary objectives were not met after 12 weeks of treatment with tadalafil 2.5 mg once-daily dosing, further tests for the 2.5 mg dose would not results in claims for that dose.

> *Reviewer's Comment: Treatment with tadalafil 5 mg dosed once daily appears to have demonstrated statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo in subjects with BPH-LUTS in Studies LVHG and LVHJ. The 5 mg once-daily dose of tadalafil appears to have demonstrated statistically significant improvement in total IPSS as well as in the EF Domain of the IIEF in patients with both ED and BPH-LUTS. It appears that the 2.5 mg dose of tadalafil failed to show statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo in subjects with BPH-LUTS and ED. It, therefore, appears that for both indications (BPH-LUTS and BPH-LUTS/ED) there is one effective tadalafil dose, 5 mg.*

This section summarizes the non-IND studies conducted in Asian Countries.

In comparison to baseline characteristics and demographics in the **pivotal BPH analysis set,** the Asian subjects in the **non-IND studies conducted in the Asian countries analysis set** had a smaller mean BMI, less history of cardiac disease and more often had been previously treated with alpha-blocker therapy. The baseline LUTS (IPSS) was lower (milder) in subjects in the **non-IND studies conducted in the Asian countries analysis set** than in the **pivotal BPH analysis set.** The other baseline characteristics and demographics (mean total IPSS, Qmax, PSA, and history of diabetes mellitus) appeared similar between the 2 analysis sets.

Study LVIA

Study LVIA was a Phase 2, randomized, double-blind, placebo-controlled, 12-week, dose-ranging study. The double-blind period was designed to examine the efficacy and safety of tadalafil 2.5 mg and 5 mg administered once daily for 12 weeks versus placebo in Japanese men with BPH-LUTS.

Study LVIA enrolled Japanese subjects ≥45 years old with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Notable inclusion criteria also included total IPSS ≥13 and Qmax ≥4 and ≤15 mL/sec at the start of the placebo lead-in period and prostate volume ≥20 mL estimated by transabdominal or transrectal ultrasound at screening. After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

Randomization was stratified by baseline (after placebo lead-in period) LUTS severity (IPSS <20 or ≥20) and prior alpha-blocker therapy (within 12 months of screening [yes/no]). The primary objective was to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared to placebo in improving the total IPSS in men with BPH-LUTS. Key secondary efficacy objectives were to evaluate the efficacy of tadalafil 2.5 mg and 5 mg once daily for 12 weeks compared with placebo in improving the Patient SEP Q3 and BII.

422 patients were randomized (1:1:1) and 394 patients completed the study (135 tadalafil 2.5 mg, 128 tadalafil 5 mg, and 131 placebo).

In the primary efficacy analysis, tadalafil 5 mg treatment group showed no statistically significant change in IPSS total score from baseline to endpoint compared with placebo (-1.1 [95% CI = -2.2 to 0.1; p=0.062] ANCOVA). The tadalafil 2.5 treatment group also showed no statistically significant change compared with placebo (-0.7 [95% CI = -1.8 to 0.4; p=0.201]).

Each efficacy valuable was evaluated using subgroups of baseline BPH severity, previous α-blocker therapy, previous BPH therapy other than α-blocker, baseline age and baseline prostate volume. For both the tadalafil 2.5 and 5 mg treatment groups, subjects with severe BPH at baseline show numerically greater changes from baseline to endpoint in IPSS total score than those with mild to moderate BPH (moderate BPH symptoms at

baseline: -4.0 [tadalafil 2.5 mg] and -3.8 [tadalafil 5 mg]; severe BPH symptoms at baseline: -5.9 [tadalafil 2.5 mg] and -7.9 [tadalafil 5 mg]).

A review of the pharmacokinetic results, collected through sparse sampling of Study LVIA revealed that the measured tadalafil concentrations were higher than observed in previous studies of 2.5 mg and 5 mg once-daily dosing and according to the Sponsor, demonstrated uncharacteristically marked intra-subject variability. The overall compliance rate for the double-blind treatment period of LVIA was 96.9%.

Study LVHT

Study LVHT was a Phase 2, randomized, placebo-controlled pilot study. The purpose of Study LVHT was to estimate total IPSS change from baseline and the variability of that change in Asian men in order to guide design of future studies examining tadalafil effect in the treatment of BPH-LUTS in Asian men in comparison to tamsulosin.

Study LVHT enrolled Korean subjects ≥45 years old with BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening. Subjects had total IPSS ≥ 13and Qmax ≥4 and ≤15 mL/sec at the start of the placebo lead-in period. After screening, all eligible subjects entered a 4-week, single-blind, once-daily placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period.

151 subjects were randomized, and 143 subjects completed the study (48 tadalafil, 48 tamsulosin, and 51 placebo).

The primary objective was to evaluate the change from baseline of tadalafil 5 mg once daily compared to placebo in total IPSS score after 12 weeks.

While numerically superior, once-a-day dosing of tadalafil 5 mg did not result in a statistically significant improvement of total IPSS score as compared to placebo (tadalafil , -5.8; placebo, -4.2; p=.073). Notably, once-a-day dosing of tamsulosin 0.2 mg also did not result in a statistically significant improvement in total IPSS as compared to placebo (tamsulosin -5.4; placebo -4.2; p=.186).

Study LVIA Open-Label Extension

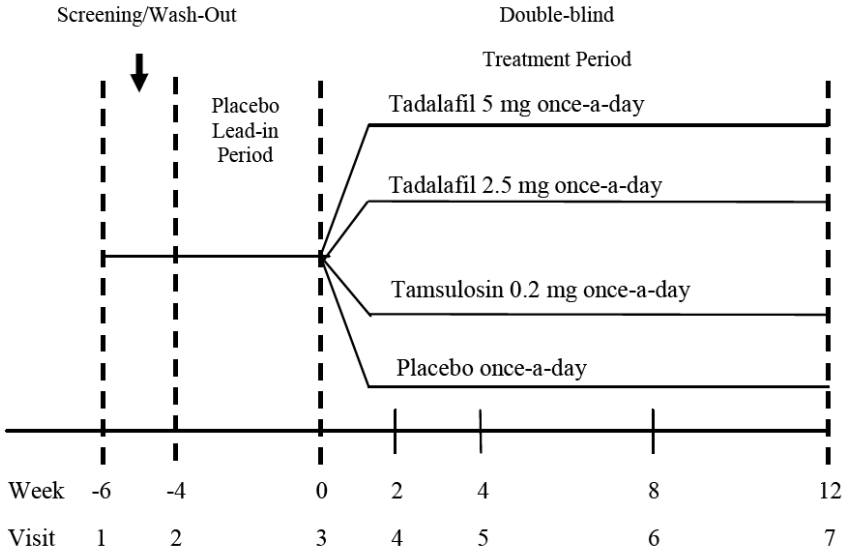
The long-term safety and “persistence of efficacy” of tadalafil 5-mg once-daily dosing was assessed with a 42-week, open-label extension period of Study LVIA. Subjects who completed the double-blind treatment period were given the option to continue in the open-label extension receiving tadalafil 5 mg once daily. The double-blind period together with the open-label extension provided 54 weeks of assessments.

Study LVHB

Study LVHB was a Phase 3, randomized, placebo-controlled, four group (including one active-control arm-tamsulosin 0.2 mg daily) comparison study in Asian men in Japan, Republic of Korea, and Taiwan. The primary objective of Study LVHB was to compare the IPSS total score change of tadalafil 5 mg from baseline at Week 12 versus placebo in Asian men with signs and symptoms of BPH.

Study LVHB enrolled Asian subjects ≥45 years old with BPH (as diagnosed by a qualified physician) for >6 months at screening. Subjects had an IPSS total score of ≥13 and Qmax ≥4 and ≤15 mL/sec at the start of the placebo lead in period. After screening, all eligible subjects entered a 4-week, single-blind, once-daily lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period. At the beginning of the treatment period, eligible subjects were randomly assigned on a 1:1:1:1 ratio to one of four treatment groups: placebo, tadalafil 2.5 mg, tadalafil 5 mg, and tamsulosin 0.2 mg once daily for 12 weeks. Approximately 560 subjects (140 per treatment group) were to be randomized.

Figure 2: LVHB Study Design



Source: Figure LVHB.9.1, H6D-MC-LVHB Clinical Study Report, page 32

The primary objective was to compare the IPSS total score change from baseline for tadalafil 5 mg QD versus placebo in Asian men with signs and symptoms of BPH.

98.7% of all randomized of all randomized subjects were at least 70% compliant. All efficacy analyses were performed on an ITT basis.

Table 9: Total IPSS Change from Baseline to Endpoint - Full Analysis Set in Study LVHB

Treatment Group	Time Point	n	Mean (SD)	p-value
Placebo				
(N=154)	Baseline	154	16.8 (6.1)	
	Endpoint	154	13.6 (7.0)	
	Change	154	-3.1 (5.6)	
Tadalafil 2.5 mg	Baseline	151	16.6 (6.5)	0.003
N=151	Endpoint	151	11.7 (6.6)	
	Change	151	-4.9 (5.0)	
Tadalafil 5 mg	Baseline	154	17.2 (6.0)	0.004
N=155	Endpoint	154	12.2 (7.1)	
	Change	154	-5.0 (5.9)	
Tamsulosin	Baseline	152	16.6 (6.4)	<.001
0.2 mg	Endpoint	152	11.0 (6.2)	
N=152	Change	152	-5.6 (5.8)	

Source: Table LVHB.11.6, H6D-MC-LVHB Clinical Study Report, page 80.

> *Reviewer's Comment: The primary efficacy endpoint changes appear to demonstrate a favorable effect of tadalafil on reducing BPH symptoms compared to placebo in this study in the Asian population. The use of an active comparator also affirms that the metrics utilized are appropriate. The p-value for analysis by country was 0.335, suggesting no effect related to specific country . In addition the Sponsor conducted an additional analysis to identify the site effect by exchanging country with site in the statistical model. The results were consistent with the primary analysis (Table LVHB, 14.11). It is possible that the previous Asian studies LVIA and LVHT were underpowered to detect significant change, especially since an effect was not demonstrated with the active comparator tamsulosin in LVHT.*

For secondary measures, once daily dosing of tadalafil 5 mg, but not 2.5 mg appeared to demonstrate a statistically significant improvement in the IPSS irritative (storage) subscore after 12 weeks of treatment compared with placebo. In repeated measures analysis of total IPSS change from baseline, statistically significant least squared mean differences in the changes from baseline were observed beginning at Week 2 and continued through week 12 in the tadalafil 5mg group while statistically significant differences were observed beginning at Week 8 and continued through Week 12 in the tadalafil 2.5 mg group. Once daily dosing of tadalafil 2.5 mg and 5 mg did not appear to result in a statistically significant change in the BII score after 12 weeks of treatment compared to placebo.

Preliminary Efficacy Conclusions

After a preliminary review, the treatment of BPH and BPH/ED with tadalafil 5 mg once daily appears to result in a statistically significant improvement in the IPSS in the two study populations of men with BPH and men with BPH/ED. The 2.5 mg dose of tadalafil once daily did not appear to result in a significant improvement in the IPSS in men with BPH/ED. The key secondary endpoints were supportive of the findings of the primary endpoint.

Safety Encompassing All the Data Sets

Exposure and Disposition

Patient demographics and disposition are discussed in the summaries of each pivotal BPH and BPH ED Study.

Table 10: Number of Subjects Exposed and Subject-year Exposure to Tadalafil All Randomized Subjects - Placebo Controlled Studies LVHG, LVHK, LVHR, and LVHG Open Label Extension

			Tadalafil				
Indication	Study Type	Protocol	2.5 mg n subj yrs	5 mg n subj yrs	10 mg n subj yrs	20 mg n subj yrs	>=5mg n subj yrs
BPH	Long-term Open-label	LVHG		427 347.6			427 347.6
BPH	Pivotal Placebo-controlled	LVHG	208 47.6	212 47.6	216 47.1	209 45.1	637 139.2
BPH		LVHJ		161 36.6			161 36.6
BPH/ED		LVHR	197 43.3	208 45.3			208 45.3
BPH	Special Safety - Placebo-Controlled	LVHK				96 22.3	96 22.3
BPH		LVHS		158 34.3			158 34.3
Total Subject-Years			405 90.9	1083 510.4	216 47.1	305 67.4	1448 624.5

Source: Table 2.7.4.4, Summary of Clinical Safety, page 28

Table 11: Duration of Exposure to Tadalafil by Dosage All Randomized Subjects – Placebo-Controlled Studies LVHG, LVHJ, LVHK, LVHR and LVHS and Open-label Extension of LVHG

Duration	Tad 2.5 mg	Tad 5 mg	Tad 10 mg	Tad 20 mg	Tad=>5 mg
	n	n	n	n	n
>= 3 mos	355	1025	174	251	1450
>= 6 mos		351			352
>= 12 mos		280			280

Source: Table 2.7.4.5, Summary of Clinical Safety, page 29.

Reviewer's Comment: The numbers of patients exposed to tadalafil and the exposure durations are adequate for filing and consideration in these NDAs. There is also a vast amount of safety data from the tadalafil for ED NDAs, both for the prn and daily dosing regimens.

Adverse Events

Table 12: Overview of Adverse Events, All Randomized Subjects - Pivotal BPH Studies LVHG and LVHJ Double-Blind Period

Adverse Events	Placebo (N=376) n (%)	Tadalafil 5 mg (N=373) n (%)
Deaths	0 (0.0)	1 (0.3)
SAEs	4 (1.1)	3 (0.8)
AE Discontinuation	6 (1.6)	15 (4.0)
TEAE	82 (21.8)	109 (29.2)

Source: Table 2.7.4.10, Clinical Summary of Safety, page 41.

Table 13: Overview of Adverse Events, All Subjects Enrolled in the Open-label Extension Period LVHG

Adverse Events	Plac N=92	IC 2.5 mg N=96	IC 5 mg N=83	IC 10 mg N=85	IC 20 mg N=71
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	5 (5.4)	3 (3.1)	6 (7.2)	4 (4.7)	2 (2.8)
AE Discontinuation	6 (6.5)	4 (4.2)	4 (4.8)	5 (5.9)	3 (4.2)
TEAE	44 (47.8)	42 (43.8)	40 (48.8)	37 (43.5)	40 (56.3)

Source: Table 2.7.4.11., Clinical Summary of Safety, page 42.

Table 14: Overview Adverse Events, All Randomized Subjects - Pivotal BPH/ED Study LVHR Double-Blind Period

	Placebo	Tad 2.5 mg	Tad 5 mg
Adverse	N=200	N=198	N=208
Events	n (%)	n (%)	n (%)
Deaths	0 (0.0)	1 (0.5)	0 (0.0)
SAEs	1 (0.0)	2 (1.0)	1 (0.5)
AE Discontinuation	3 (1.5)	3 (1.5)	6 (2.9)
TEAE	39 (19.5)	50 (25.3)	57 (27.4)

Source: Table 2.7.4.12., Clinical Summary of Safety, page 44.

Deaths:

Below are narratives from the 3 deaths in this application:

LVHJ-303-3316: The LVHJ subject was an 81-year old white male in the tadalafil 5-mg group who had preexisting conditions of hyperlipidemia and hypertension (BP 140/90 mm Hg while on lisinopril and study drug). Concomitant medications included lisinopril and simvastatin. The patient also had degenerative arthritis and polyneuropathy. Approximately 2.5 months after receiving the first dose of study drug (tadalafil 5 mg), the subject was hospitalized with chest pain and diagnosed with an acute posterior myocardial infarction (MI) and third degree atrioventricular block; study drug was discontinued. Cardiac catheterization was performed and demonstrated 75%, 90%, and 90% occlusion of the LAD, circumflex and right coronary ariteries, respectively. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequent intra-aortic balloon pump. The subject's condition worsened and he died 3 days later.

LVHK-117-2705: The LVHK subject was a 59-year old male in the placebo group who had preexisting conditions of ED, type 2 diabetes mellitus, and GERD. Concomitant medications included metformin, esomeprazole magnesium, acetylsalicylic acid, vitamin D, B12, and multivitamins. Approximately 2 months after initially receiving study drug (placebo), the subject died of an MI.

LVHR-208-2806: This LVHR subject was a 67-year old white male randomized to tadalafil 2.5 mg, died 2 months post-randomization. The subject's wife found him dead in his home 4 days after his last dose of study drug. The subject may have been dead for 2 or 3 days when found. No autopsy was performed. Myocardial infarction was listed on the death certificate as the presumed cause of death. The subject's medical history included sinusitis (1980) and back pain (1984); other medical conditions included impaired glucose tolerance, sleep apnea, mild mitral valve prolapse, and episodic atrial fibrillation. He was concomitantly receiving tiaprofenic acid, a multivitamin, ascorbic acid, vitamin B, and ergocalciferol. His systolic blood pressure (SBP) was slightly elevated at screening, as well as at several other study visits. Five days prior to his death, a TEAE of "allergy to arthropod sting" was reported.

There have been no deaths reported in any of 68 clinical pharmacology studies.

Serious Adverse Events:

Table 15: Serious Adverse Events by Decreasing Frequency in the Tadalafil 5-mg Group, All Randomized Subjects - Pivotal BPH Studies LVHG and LVHJ Double-Blind Treatment Group

Preferred Term	Placebo N=376	Tad 5 mg N=373
	n (%)	n (%)
Subjects with >=1 SAE	4(1.1)	3(0.8)
Acute MI	0(0.0)	1(0.3)
Cholecystitis	0(0.0)	1(0.3)
Endocarditis	0(0.0)	1(0.3)
Pancreatitis	0(0.0)	1(0.3)
Cartilage Injury	1(0.3)	0(0.0)
Cerebrovascular Accident	1(0.3)	0(0.0)
Coronary Artery Stenosis	1(0.3)	0(0.0)
Indwelling Catheter	1(0.3)	0(0.0)
Renal Colic	1(0.3)	0(0.0)
Rheumatoid Arthritis	1(0.3)	0(0.0)
Ureteral Catheterization	1(0.3)	0(0.0)
Urinary Retention	1(0.3)	0(0.0)

Source: Table 2.7.4.25. Summary of Clinical Safety, page 80

Table 16: Serious Adverse Events by Decreasing Frequency in the Total Tadalafil Group, All Subjects Enrolled in the Open-label Extension Period LVHG

Preferred Term	Previous Therapy				
	Placebo	IC 2.5mg	IC 5mg	IC 10mg	IC 20mg
Patients with >=1 SAE	N=92	N=96	N=83	N=85	N=71
Arthritis	0 (0.0)	0 (0.0)	1 (1.2)	1(1.2)	0(0.0)
Knee arthroplasty	1 (1.1)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Non-cardiac chest Pain	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Basedow's disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Bladder neoplasm	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac congestive failure	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Coronary artery stenosis	1 (1.1)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)
Fibula fracture	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GERD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Global Amnesia	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Hip arthroplasty	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Meniscus lesion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Osteoarthritis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Sinus polyp	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

IC=tadalafil
Source: Table 2.7.4.26., Clinical Summary of Safety, page 81.

Table 16: Serious Adverse Events, All Randomized Subjects - Pivotal BPH/ED Study LVHR Double-Blind Treatment Period

Preferred Term	Placebo	Tadalafil 2.5mg	Tadalafil 5mg
	N=200	N=198	N=208
Subjects with >=1 SAE	1(0.5)	2(1.0)	1(0.5)
Pancreatitis Hemorrhagic	0(0.0)	0(0.0)	1(0.5)
Intravertebral Disc Protrusion	0(0.0)	1(0.5)	0(0.0)
Myocardial Infarction	0(0.0)	1(0.5)	0(0.0)
Non-Hodgkin's Lymphoma	1(0.5)	0(0.0)	0(0.0)

Source: Table 2.7.4.27, Summary of Clinical Safety, Current Submission, page 83.

Reviewer's Comment: The SAEs at this preliminary level of review do not indicate any trends or raise any safety concerns.

Below are selected narratives (in brief) of SAEs from the entire application:

Subject LVHG 1243419: The subject is a 67 year-old male on multiple concomitant medications who during the placebo lead-in phase of study period II experienced a syncopal episode and was hospitalized for 23 hour observation. CAT and NMRI scans of the head were within normal limits.

Subject LVHG 3172752: The subject is a 59 year-old male with no concomitant medications. On 17 March 2007, the patient first received the study drug. On 17 March 2007, 9 days after starting the study drug while in the 4 week placebo run in period, the patient experienced acute bacterial prostatitis and was hospitalized. The narrative does not discuss baseline demographic data concerning severity of BPH disease. The subject was permanently discontinued from the study.

Subject LVHG6001084: The subject is a 70 year-old male with a history of a mini-stroke 16 months prior to report and is on multiple medications. The patient had been randomized to placebo and after 1 month was hospitalized due to a stroke. The event did not result in permanent discontinuation of the study drug.

Subject LVHG 2041420: The subject is a 67 year-old male with essentially a negative medical history aside from smoking 1 cigarette a day. He was randomized to tadalafil 10 mg a day. Approximately 12 weeks after receiving the first dose of study drug, he was hospitalized with unstable angina. He underwent an angioplasty. The findings at angioplasty were proximal "roughening" of 20% of the right coronary artery, the left anterior descending(LAD) artery was 80% narrowed proximally and there was 60-75 narrowing at the origin of the first diagonal and 60-75% narrowing of the proximal septal vessel. "Roughening" was noted in the distal LAD in the circumflex. Angioplasty without stent was performed on the LAD. The patient went on to complete the study.

Subject LVHG 4006007: The subject is a 56 year-old male who also had ED. His tadalafil 20 mg daily treatment started 10 April 2007. On 11 May 2007, an NMRI was performed due to headache and right arm weakness which revealed an "insult to the pons" estimated to have occurred 4 weeks prior. The patient was permanently discontinued.

Subject LVHG 4096925: The subject is a 68 year-old male with known 1 vessel coronary artery disease (CAD). He was randomized to tadalafil 20 mg once daily. Three months after receiving the first dose of study drug (exposure day 62), he was hospitalized for the placement of a coronary stent for a 75% stenosis of the "proximal ramus circumflexis (RCX)." There was also 30% stenosis in the right medial coronary artery (RCA). The drug was permanently discontinued.

Subject LVHJ 3333316: The subject is an 82 year-old male. The subject was randomized to tadalafil 5 mg once daily. Two and a half months after receiving the first dose of study drug (exposure day 62), he was hospitalized with chest pain and diagnosed with an acute STE-infarction of the posterior myocardium and atrioventricular block III, and coronary

artery disease (LAD 75%, CxT 90%, RCA 90% occluded). A stent was placed in the CxT artery. The patient eventually expired. This is case discussed under deaths.

Subject LVHK 1172705: The subject is a 59 year-old male randomized to placebo. Two months after receiving the study drug, the patient died of a massive myocardial infarction.

Subject LVHR 4004003: The subject is a 56 year-old randomized to placebo and on no concomitant medications. The patient was diagnosed with non-Hodgkin's lymphoma after 13 days of exposure to the study drug. The study drug was discontinued.

Subject LVHR 2082806: This LVHR subject was a 67-year old white male randomized to tadalafil 2.5 mg, died 2 months post-randomization. The subject's wife found him dead in his home 4 days after his last dose of study drug. The subject may have been dead for 2 or 3 days when found. No autopsy was performed. Myocardial infarction was listed on the death certificate as the presumed cause of death as MI. The subject's medical history included sinusitis (1980) and back pain (1984); other medical conditions included impaired glucose tolerance, sleep apnea, mild mitral valve prolapse, and episodic atrial fibrillation. He was concomitantly receiving tiaprofenic acid, a multivitamin, ascorbic acid, vitamin B, and ergocalciferol. His systolic blood pressure (SBP) was slightly elevated at screening, as well as at several other study visits. Five days prior to his death, a TEAE of "allergy to arthropod sting" was reported.

Subject LVHR 4014104: The subject is a 69 year-old male randomized to tadalafil 5 mg once daily. On exposure day 25, the patient was admitted to hospital for necrotic hemorrhagic pancreatitis and therapy discontinued. A cholecystectomy was performed approximately one month after hospitalization. Approximately 1 month post surgery, endoscopic retrograde cholangio-pancreatography was performed (results not in report). The patient recovered.

Subject LVHS 1192812: The subject is a 78 year-old male randomized to placebo who on exposure day 87 did not see a cinderblock in his yard and tripped over it, fracturing his hip. The fall was not considered secondary to orthostasis. The patient continued on therapy.

Subject LVHS 1283701: The subject is a 50 year-old male randomized to tadalafil 5 mg daily. On exposure day 64, he fell off a curb at work suffering a complete tear of the quadriceps tendon. Drug therapy was discontinued. He underwent surgical repair. The fall resulted from a misstep and was not associated with orthostasis.

Subject LVHG 1354508 Open-Label: The subject is a 55 year old male former smoker (25 years) on tadalafil 5 mg once daily. On exposure day 345, he developed hematuria and was found to have grade 3 papillary transitional cell carcinomas of the bladder which were resected and not found to be muscle invasive. He was subsequently treated with BCG bladder instillations.

Subject LVHG 1233324 Open-Label: The subject is a 63 year-old male originally randomized to tadalafil 2.5 mg once daily. He had a history of coronary artery disease, ED, and sinus bradycardia. On day 169 of exposure to tadalafil 5 mg once daily, the patient was admitted to the hospital. The patient stated he was diagnosed as having a cardiac arrest. "Corrective treatment was not given and the event was listed as improved." The study drug was discontinued. Five months later, the patient was still having occasional chest pain.

Subject LVHG 2058001 Open-Label: The subject is of unknown age and has a medical history of coronary artery disease. He was initially randomized to tadalafil 10 mg once daily. On exposure day 205 in the Open-Label period, a worsening of his coronary artery disease and was hospitalized. He was treated medically for acute coronary syndrome and recovered. The study drug was discontinued.

> *Reviewer's Comment: These selected SAE events do not suggest significant orthostasis or increase of coronary events in tadalafil patients. The falls that occurred appear to be due to inattention or poor sensory function and not syncope. At this point in the review, I do not discern a safety issue.*

Discontinuations Due to Adverse Events

Rather than duplicate description of events considered under SAEs, this section will concentrate on events of lesser severity to see if any discernible trend leading to discontinuation can be identified. The percentage of subjects discontinuing due to an AE was greater in the tadalafil 5 mg group compared to the placebo group (4.0% versus 1.6%). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5 mg group. In the tadalafil 5 mg group, there were 15 AEs leading to discontinuation: headache (4 subjects), myalgia, pain in extremity, pain, dyspepsia, upper abdominal pain (3subjects), pancreatitis, retinal tear, rotator cuff syndrome, and acute MI. In the placebo group, there were 6 AEs leading to discontinuation. In the open-label extension of Study LVHG, 22 subjects discontinued due to AEs. Dyspepsia (2 subjects) and stomach discomfort (2 subjects) were the only AEs leading to discontinuation that occurred in more than 1 subject in that study. See tables below:

Table 17: Adverse Event Reported as Reason for Study Discontinuation, All Randomized Subjects - Pivotal Studies LVHG and LVHJ Double-Blind Treatment Period

Preferred Term	Placebo	Tadalafil 5 mg
	N=376	N=373
	n (%)	
Subject Discontinued	6(1.6)	15(4.0)
Headache	0(0.0)	4(1.1)
Abdominal Pain Upper	2(0.5)	3(0.8)
Acute Myocardial Infarction	0(0.0)	1(0.3)
Dyspepsia	0(0.0)	1(0.3)
Myalgia	0(0.0)	1(0.3)
Pain	0(0.0)	1(0.3)
Pain in Extremity	0(0.0)	1(0.3)
Pancreatitis	0(0.0)	1(0.3)
Retinal Tear	0(0.0)	1(0.3)
Rotator cuff Syndrome	0(0.0)	1(0.3)
Back Pain	1(0.3)	0(0.0)
Coronary Artery Stenosis	1(0.3)	0(0.0)
Dizziness	1(0.3)	0(0.0)
Eye Pain	1(0.3)	0(0.0)

Source: Table 2.7.4.29, Summary of Clinical Safety, page 87.

Table 18: Adverse Events Reported as Reason for Study Discontinuation, All Subjects Enrolled in the Total Tadalafil Group in All Subjects Enrolled in the Open-label Extension

Preferred Term	Total (N=427)
	n (%)
Subjects with >=1 AE leading to Discontinuation	
Dyspepsia	2(0.5)
Stomach Discomfort	2(0.5)
Acute Coronary Syndrome	1(0.2)
Arrhythmia	1(0.2)
Bladder Neoplasm	1(0.2)
Carpal Tunnel Syndrome	1(0.2)
Coronary Artery Disease	1(0.2)
Deafness Unilateral	1(0.2)
Gastroesophageal Reflux Disease	1(0.2)
Hepatic Enzyme increased	1(0.2)
Hepatic Function Abnormal	1(0.2)
Hot Flush	1(0.2)
Muscle Tightness	1(0.2)
Esophagitis	1(0.2)
Pollakiuria	1(0.2)
Prostate Cancer	1(0.2)
Prostatic Intraepithelial Neoplasm	1(0.2)
Residual Urine	1(0.2)
Seasonal Allergy	1(0.2)
Visual Disturbance	1(0.2)

Source: Table 2.7.4.30, Summary of Clinical Safety, page 88

Reviewer's Comment: Aside from headache and upper abdominal pain, both of which are labeled AEs for tadalafil, there were no other AEs leading to study discontinuation that occurred more than once in the double-blind pivotal BPH studies. For the open-label extension of Study LVHG, only "dyspepsia" and "stomach discomfort" were reported as AEs leading to study discontinuation in more than 1 subject.

Table 19: Adverse Events Reported as Reason for Study Discontinuation in the Tadalafil 5 mg Group, All Randomized Subjects with ED - Studies LVHG, LVHJ, LVHR Double-Blind Treatment Period

Preferred Term	Placebo	Tadalafil 2.5 mg	Placebo	Tadalafil 5 mg
	N=342	N=333	N=454	N=464
	n (%)			
Subject Discontinued due to AE	6(1.8)	6(1.8)	7(1.5)	13(2.8)
Headache	0(0.0)	0(0.0)	0(0.0)	3(0.6)
Acute Myocardial Infarction	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Back Pain	0(0.0)	0(0.0)	1(0.2)	1(0.2)
Muscle Spasms	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Myalgia	0(0.0)	1(0.3)	0(0.0)	1(0.2)
Pain	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Pain in Extremity	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Pancreatitis	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Pancreatitis Hemorrhagic	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Rotator Cuff Syndrome	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Syncope	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Abdominal Discomfort	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Abdominal Pain Upper	1(0.3)	0(0.0)	1(0.2)	0(0.0)
Blood CPK increased	1(0.3)	0(0.0)	1(0.2)	0(0.0)
Dizziness	1(0.3)	1(0.3)	1(0.2)	0(0.0)
Eye Pain	1(0.3)	0(0.0)	1(0.2)	0(0.0)
Non-Hodgkin's Lymphoma	1(0.3)	0(0.0)	1(0.2)	0(0.0)
Myocardial Infarction	0(0.0)	2(0.6)	0(0.0)	0(0.0)
Nocturia	0(0.0)	1(0.3)	0(0.0)	0(0.0)
Ureteric Rupture	0(0.0)	1(0.3)	0(0.0)	0(0.0)

Source: Table ISS.14, Integrated Summary of Safety, page 68

Two subjects in the tadalafil 2.5 mg group (myocardial infarction) and one subject in the tadalafil 5 mg group (acute myocardial infarction) discontinued secondary to myocardial infarction versus none for placebo.

- In one of these subjects (Subject LVHR-208-2806, tadalafil 2.5 mg), the patient was found dead in his house by his wife 4 days after his last dose of study drug. No autopsy was perfomed. Myocardial infarction was presumed to be his cause of death.

- In another of these subjects (Subjects LVHG-101-1166, tadalafil 2.5mg), the patient was a 93 year old man who took study drug for two weeks, then suffered a myocardial infarction when performing "heavy manual labor, including digging out tree roots".

- In the last of these patients (Subject LVHJ-303-3316, tadalafil 5mg), the patient was an 80 year male with hypertension (140/90 mmHg while on lisinopril and study drug), hyperlipidemia, degenerative arthritis, and polyneuropathy who suffered a myocardial infarction approximately 10 weeks after initiating study medication. His cardiac cath revealed 75% , 90%, and 90% occlusion of the LAD, circumflex and right coronary arteries. He underwent percutaneous angioplasty of the circumflex artery with stenting and subsequently an intra-ortic ballon pump. He died 4 days after his MI.

Reviewer's Comment: There were three myocardial infarctions that led to study discontinuation in the 2.5 and 5.0 mg dose groups of tadalafil (N=797) versus 0 myocardial infarctions that led to study discontinuations in the placebo groups (N=786) among all randomized subjects in the double-blind periods of the pivotal studies (LVHG, LVHJ, LVHR). This will be a review issue.

Common Treatment Emergent Adverse Events

Table 20: Common Treatment-Emergent Adverse Events ,All Randomized Subjects in Pivotal BPH Studies LVHG and LVHJ Double-Blind Period

Preferred Term (TEAEs >2% in tadalafil 5 mg group)	**Placebo** N=376	**Tadalafil 5 mg** N=375
	n (%)	
Subjects with >=1 TEAE	82(21.8)	109(29.2)
Headache	7(1.9)	12(3.2)
Dyspepsia	1(0.3)	11(2.9)
Back Pain	5(1.3)	8(2.1)
Hypertension	4(1.1)	8(2.1)

Source: Table 2.7.4.13, Summary of Clinical Safety, page 48

Table 21: Common Treatment-Emergent Adverse Events in the Total Population Compared to Visit 7 (Baseline), All Subjects Enrolled in the Open-label Extension Period Study LVHG

Preferred Term	**Total N=427**
Patients with>=1 TEAE	**203(47.5)**
	n (%)
Sinusitis	11(2.6)
Back Pain	10(2.3)
Dyspepsia	9(2.1)
Common TEAE is defined as TEAEs >=2% in the Total Group	

Source: Table 2.7.4.14, Clinical Summary of Safety, page 49.

Table 22: Common Treatment Emergent Events, All Randomized Subjects with ED Studies LVHG, LVHJ, and LVHR Double-Blind Treatment Period

Preferred Term	Placebo	Tadalafil	Placebo	Tadalafil
		2.5 mg		5 mg
	N=342	N=333	N=454	N=464
	n (%)			
Subjects with >=1 TEAE	70(20.5)	89(26.7)	96(21.1)	125(26.9)
Headache	10(2.9)	10(3.0)	11(2.4)	18(3.9)
Back pain	4(1.2)	3 (0.9)	6(1.3)	11(2.4)
Hypertension	2(0.6)	0(0.0)	3(0.7)	11(2.4)
Dyspepsia	0(0.0)	2(0.6)	1(0.2)	9(1.9)
Nasopharyngitis	5(1.5)	10(3.0)	7(1.5)	9(1.9)
Pain in Extremity	0(0.0)	1(0.3)	0(0.0)	7(1.5)
Dizziness	3(0.9)	2(0.6)	3(0.7)	6(1.3)

Common TEAEs are defined as >1% in the 5 mg tadalafil group.
Source: Table ISS.12, Integrated Summary of Safety, page 55.

Hypertension was reported as an adverse event in 0.6% and 0.7% of the placebo groups in these studies, versus 0.9% for the 2.5 mg group, and 2.4% of the 5 mg group. Of the 11 subjects in the tadalafil 5-mg group with a TEAE of hypertension (**Pivotal BPH analysis set of subjects)**, 3 had preexisting hypertension and 4 had preexisting risk factors for hypertension (4 with hypercholesterolemia and 1 with diabetes), including 1 subject who had both preexisting hypertension and risk factors for hypertension (diabetes and hypercholesterolemia). Of the 14 subjects in the **additional BPH/ED analysis set of subjects with ED** reported to have a TEAE of hypertension, 9 had systolic blood pressures prior to randomization that were equal to or higher than those recorded after randomization (7 tadalafil, 2 placebo); 5 had systolic blood pressures after randomization exceeding those recorded prior to randomization (4 tadalafil, 1 placebo). Of the 5 subjects with a TEAE of hypertension and increases in systolic blood pressure reported after randomization, 3 had a preexisting diagnosis of hypertension (2 tadalafil, 1 placebo). One subject (tadalafil 5 mg) had preexisting risk factors of diabetes and high cholesterol in addition to preexisting hypertension.

Reviewer's Comments:

1. *There appears to be no discernible difference in common AEs between the ED, BPH, and BPH/ED populations summarized in Table 21.*
2. *The increased incidence of "hypertension" reported as an adverse event in tadalafil 5 mg treatment group (2.4%) compared to the 2.5 mg treatment group (0%) and the placebo groups (0.6 –0.7%) in the double-blind periods of the pivotal studies LVHG, LVHJ, and LVHR will be a review issue. Sponsor should submit detailed narratives for each of these "hypertension" AE cases, as well as a rationale/explanation for this finding. Sponsor should also provide a detailed narrative for each and every adverse event report of "hypertension" in this application.*

3. *The Sponsor points out that hypertension was reported as an adverse event in a larger proportion of tadalafil-treated patients compared to placebo-treated patients in one, 6-month, placebo-controlled, Phase 3 study of tadalafil for daily use (placebo 0%, tadalafil 2.5 mg 1% and tadalfil 5 mg 3%). However, hypertension as an adverse event was not reported more frequently than placebo in the eight, pooled, 12-week, double-blind, placebo-controlled, Phase 3 studies of the use of tadalafil as needed for ED, nor after 12 weeks treatment duration in the three pooled, double-blind, placebo-controlled studies of tadalafil for once daily use for ED. The Clinical review of the daily dosing ED supplement stated that many of the reported "hypertension" cases were neither hypertension nor increased blood pressure at all, and most had hypertension at baseline. There did not appear to be an effect of tadalafil on increasing blood pressure in the daily dosing ED studies.*

Special Safety Studies LVHK, LVHS, and LVHN

Study LVHK: Study LVHK was a Phase 2, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the potential urodynamic effects of tadalafil once daily for 12 weeks in men with BPH-LUTS with or without bladder outlet obstruction. The primary objective was to compare the effect of tadalafil 20 mg once daily for 12 weeks on detrusor pressure at peak urinary flow rate (pdetQmax) versus placebo in men with signs and symptoms of BPH-LUTS. Secondary objectives included an examination of the urodynamic effects of tadalafil 20 mg once daily for 12 weeks (compared with placebo) in the treatment of men with BPH-LUTS on pressure flow and free flow urodynamic parameters including peak urinary flow rate (Qmax), mean urinary flow rate (Qmean), voided volume (Vcomp), maximum detrusor pressure (max pdet) during voiding, post-void residual (PVR) volume measurement by catheterization (PVRcath), total bladder capacity, bladder contractility index (BCI), bladder outlet obstruction index (BOOI), bladder voiding efficiency (BVE), presence of involuntary detrusor contractions during bladder filling, and bladder volume at first involuntary detrusor contraction. The key issue was to discern any potential negative effect on bladder emptying. Secondary measures also included AEs, vital signs, and clinical laboratory tests. Subjects were randomly assigned to placebo or tadalafil 20 mg once daily for 12 weeks. Of the 200 randomized subjects, 101 were assigned to placebo and 99 to tadalafil 20 mg.

The primary analysis appears to show neither statistically significant nor clinically adverse effects of tadalafil 20 mg on detrusor pressure at peak urinary flow rate (the mean difference of change from baseline between treatment groups was -4.95 cm H_2O; p=.068) in the primary analysis population. While this result represents a decrease in detrusor pressure in the actively treated tadafail group versus the placebo group, it was not considered clinically adverse. Furthermore, the negative change was the result of a slight increase in pressure for the placebo treatment group with a slight decrease in pressure for the tadalafil treatment group. Upon review of the individual patient data by external consultants, 3 subjects (2 placebo, 1 tadalafil) were noted to have nonphysiologic

changes from baseline to endpoint due to detrusor overactivity at the initiation of the voiding event. When data from these 3 subjects were removed from the analyses, the mean difference of the change from baseline in $P_{det}Q_{max}$ between active and placebo groups was smaller -2.18 cm H_2O.

The external consultants also recommended that subjects who had free-flow parameters measured via mechanical fill after pressure-flow studies were inappropriate for inclusion and should be removed from all free-flow studies. This was done in post hoc analysis. Secondary analyses on free-flow and pressure-flow urodynamic parameters (both prespecified including all subjects in the primary analysis population and post hoc excluding subjects with invalid tracings and/or mechanical fill) also showed neither statistically significant nor clinically adverse effects of tadalafil 20 mg. These parameters included peak urinary flow rate (Q_{max}), mean urinary flow rate (Q_{ave}), voided volume (V_{comp}), maximum detrusor pressure during voiding (max p_{det}), postvoid residual volume (PVR), total bladder capacity, bladder voiding efficiency (BVE), bladder contractility index (BCI), and bladder outlet obstruction index (BOOI).

In analyses of BOOI shift (obstructed, equivocal, and unobstructed) from baseline to end of therapy, there appeared to be a numerical trend toward less bladder outlet obstruction at endpoint in the tadalafil treatment group compared with placebo. A post hoc categorical shift analysis appears to show approximately two-fold greater proportion of subjects in the placebo treatment group with increased (worsened) BOOI category at endpoint than in the tadalafil treatment group (p=.025).

Mean change from baseline to endpoint in total International Prostate Symptom Score (IPSS) appeared clinically meaningful and significantly different (p<.001) for the tadalafil 20 mg treatment group (-9.13) compared with placebo (-5.04). Tadalafil 20 mg dosed once daily also appeared to result in statistically significant improvement in the IPSS Storage (Irritative) subscore, the IPSS Obstructive (Voiding) subscore, and the IPSS Quality of Life (QoL) index compared with placebo (p=.006). However, appeared to be no statistically significant difference between tadalafil and placebo on IPSS Question 7 (Nocturia) subscore.

In this study, tadalafil 20 mg once daily for 12 weeks in men with BPH-LUTS appeared to be generally well tolerated. The incidence of discontinuations due to adverse events was low (tadalafil: 2.0%; placebo: 1.0%). Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity.

The incidence of TEAEs in the tadalafil treatment group (55 subjects, 55.6%) was numerically higher than placebo (28 subjects, 27.7%). The most commonly reported TEAEs (incidence >2% in the tadalafil treatment group) were dyspepsia, headache, back pain, and gastroesophageal reflux disease (GERD). There was a higher percentage of subjects with adverse events assessed by the investigator to be possibly related to study drug in the tadalafil 20 mg treatment group than placebo (tadalafil: 26.3%, placebo: 3.0%). The majority of these adverse events included headache, back pain, flushing, dyspepsia, and GERD. These adverse events were consistent with the known safety

profile of tadalafil and thus, were not unexpected considering the high tadalafil daily dose of 20 mg.

In this study, serious adverse events were reported in 3 subjects (placebo: 2 subjects; tadalafil 20 mg: 1 subject). One death was reported in this study (placebo). No clinically adverse changes were observed in laboratory values or vital signs with tadalafil treatment. There were no adverse event reports of urinary retention in tadalafil-treated subjects.

Reviewer's comment: Overall, the urodynamic data do not appear to show any evidence of a negative effect on bladder function. Outliers will be evaluated in the final NDA review.

Study LVHS: Study LVHS was a Phase 3, randomized, double-blind, placebo controlled, parallel-design study to assess the safety of tadalafil once daily for 12 weeks in men with BPH-LUTS on concomitant alpha-blocker therapy. The Division requested that Sponsor conduct this study, not to support concomitant use of tadalafil and alpha blockers for BPH, but rather to get a better understanding of the type of adverse events that could occur if the two drug classes were used in combination, contrary to the labeled precautions. The primary objective was to evaluate the proportion of men with BPH-LUTS experiencing treatment-emergent dizziness when adding tadalafil 5 mg once daily to concomitant alpha-blocker therapy compared to adding placebo to concomitant alpha-blocker therapy. Secondary measures included AEs (including those possibly related to hypotension), orthostatic vital signs, PVR volume, uroflowmetry, and clinical laboratory tests. Subjects continued concomitant alpha-blocker therapy throughout the study and were randomly assigned to placebo or tadalafil 5 mg once daily for 12 weeks. Of the 318 subjects randomized, 160 were assigned to placebo and 158 were assigned to tadalafil 5 mg.

The primary analysis appears to show no difference between treatment groups in the proportion of subjects experiencing treatment emergent dizziness. The distribution of elderly and nonselective alpha blocker subjects in each treatment group was balanced. There appeared to be similar proportions of subjects in each treatment group reporting a TEAE possibly related to hypotension. Repeat measurements of orthostatic vital signs appeared to show no greater impact of tadalafil on hemodynamic signs than placebo in men on concomitant alpha blocker therapy. Assessment of symptomatic orthostatic hypotension (defined as the presence of a symptom simultaneously with a positive orthostatic test) also showed similar results between treatment groups (1 subject per group).

In the subgroup analysis of TEAEs possibly related to hypotension by age (≥75 years, <75 years), there appeared to be no difference in hypotension-related adverse events between tadalafil and placebo within the younger subgroup. There also was no major differences in the incidences of hypotension-related AEs between between different age subgroups among tadalafil-treated patients. However, there was a lower incidence of hypotension-related adverse events in the elderly placebo subgroup compared to the

younger placebo subgroup (5.3% and 10.7%, respectively); which apparently led to a numerically greater proportion of elderly tadalafil subjects reporting events compared to the elderly placebo subjects (12.5% versus 5.3%).

Treatment-emergent AEs possibly related to hypotension were also analyzed by alpha blocker type subgroups (nonselective, selective). In this analysis, a larger proportion of subjects on nonselective alpha blockers reported these TEAEs compared to those taking selective alpha blockers, regardless of treatment group (nonselective alpha blocker: tadalafil 19.2%, placebo 15.1%; selective alpha blocker: tadalafil 5.7%, placebo 6.5%); results between treatment group within each of these subgroups were similar.

Subgroup analyses of orthostatic vital signs by age (≥75 years, <75 years) appeared to show similar proportions of subjects on tadalafil and placebo meeting at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test, regardless of age subgroup, however, a larger proportion of elderly subjects compared to placebo subjects met at least 1 of the criteria, regardless of treatment group.

In the subgroup analysis of orthostatic vital signs by alpha blocker type (nonselective, selective), the combination of tadalafil and nonselective alpha blocker showed a higher proportion of subjects meeting at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test compared with placebo or compared with either treatment group taking concomitant selective alpha blocker.

The incidence of discontinuations due to adverse events was low and similar between treatment groups (tadalafil: 4.4%, placebo: 3.8%). Most TEAEs were mild or moderate in severity.

Generally, the AE profile of tadalafil subjects in this study was similar to that observed in past studies of tadalafil in men with BPH; the most commonly reported TEAEs in the tadalafil group were dizziness, dyspepsia, diarrhoea, back pain, and GERD. Slight differences in TEAEs were observed, as anticipated, based upon a greater proportion of elderly subjects and concomitant treatment with alpha blockers; specifically, a slightly higher incidence of dizziness was reported in both treatment groups than is typical in past studies of tadalafil in men with BPH.

Serious adverse events (SAEs) were reported in 6 subjects (tadalafil: 3 subject; placebo: 3 subjects). No deaths occurred in this study. Safety parameters of uroflowmetry, postvoid residual, and clinical laboratory values showed no clinically adverse changes with tadalafil treatment.

A numerically greater improvement in IPSS was observed in the tadalafil group compared to placebo, but the results were not clinically significant. It is to be noted that all subjects were on concomitant BPH therapy and there was a lack of LUTS severity eligibility requirement resulting in a lower mean baseline IPSS score.

Reviewer's Comment: LVHS did not result in the identification of new safety concerns related to concomitant administration of tadalafil and alpha blocker therapy. No tadalafil patients reported syncope or an SAE attributable to hypotension. A trend toward increased hemodynamic signs and symptoms in men on nonselective alpha blockers, most notably doxazosin, was noted as described in the existing Cialis USPI (2009). A greater proportion of elderly subjects reported tadalafil-related TEAEs relating to hypotension; however, this appears to have been due to a lower incidence of hypotension-related adverse events in the elderly placebo subgroup compared to the younger placebo subgroup (5.3% and 10.7%, respectively); which apparently led to a numerically greater proportion of elderly tadalafil subjects reporting events compared to the elderly placebo subjects (12.5% versus 5.3%). This will be reviewed in detail. A review for outliers will be conducted as part of the final NDA review.

Study LVHN: Study LVHN was an open-label clinical pharmacology study conducted to evaluate the pharmacokinetics and hemodynamics of tadalafil 20 mg administered once daily in elderly (70 to 85 years of age [n=12]) and young (below and including 60 years of age [n=15]) subjects with BPH-LUTS.

There appears to have been no significant difference in the systemic exposure (based on AUC (0-24)) to tadalafil between elderly and young subjects with BPH following single- and multiple-dose administration of 20-mg tadalafil qd for 10 days. Mean tadalafil AUC and C_{max} values were reduced by approximately 13% following single- and multiple-dose administration of 20-mg tadalafil in elderly subjects compared to young BPH subjects; however, these slight differences were not statistically different. Despite the moderate reduced renal function in elderly subjects in this study (37% reduction in mean Cockcroft-Gault creatinine clearance values in elderly compared to young subjects with BPH), tadalafil exposures did not exceed those estimated in young subjects, and any difference in tadalafil pharmacokinetics between the cohorts was not deemed to be clinically meaningful by the Sponsor. The lack of an age effect would be expected as tadalafil is cleared predominantly via hepatic metabolism by CYP3A, and the activity of CYP3A is proposed to be stable throughout normal aging, with intestinal and hepatic CYP3A induction being independent of age.

Estimates of tadalafil accumulation (approximately 1.8-fold for both AUC and C_{max}) for elderly and young subjects with BPH appeared to be comparable to that expected based upon once-daily dosing with a $t_{1/2}$ of 25 hours and similar to that in healthy subjects (1.6-fold).

The hemodynamic profile appeared broadly comparable for elderly and young subjects with BPH. Although there appeared to be a larger decrease from baseline (Day 1, predose) in supine and standing systolic and diastolic blood pressure for elderly subjects compared to young subjects with BPH over the first 4 hours postdose on Days 1 and 10, it is the Sponsor's opinion that this was attributable to a higher baseline blood pressure (Day 1, predose) in the elderly subjects and probable impaired baroreceptor function in this age group. None of the elderly subjects experienced adverse events associated with

orthostatic changes in blood pressure, whereas 2 young subjects experienced orthostatic hypotension.

In the multiple dose period, there were no serious or severe adverse events reported, and no subjects were withdrawn due to adverse events. The incidence of adverse events was highest over the first 2 days of dosing. The most frequently-reported drug-related adverse events were myalgia, headache, dyspepsia, pain in extremity, back pain, diarrhoea, and nausea. This adverse event profile was similar to that seen in previous studies with tadalafil. The incidence of myalgia, headache, and dyspepsia was similar for both age groups. Diarrhoea was reported only by elderly subjects, whereas pain in extremity and nausea were reported by the young subjects only. Most incidences of back pain were reported by the elderly subjects. Although 2 young subjects reported a total of 4 episodes of orthostatic hypotension, these episodes were mild in severity and of no clinical concern. There were no safety concerns in terms of clinical laboratory evaluations, vital signs, ECGs, or physical examinations following administration of multiple doses of 20-mg tadalafil for 10 days.

Reviewer's Comment: Tadalafil was safe and reasonably tolerated when administered as single and multiple 20 mg daily doses for 10 days to elderly and young subjects with BPH in Study LVHN. There appeared to be no differences in tolerability profile between the age groups in Study LVHM.

Adverse Events Related to Special Safety Topics

The Sponsor was asked to provide summaries for several safety topics of interest and they complied with this request. The following section provides brief discussions of this information:

Bleeding Events: In the **additional BPH analysis set of all BPH** patients, 6 subjects (1.0%) reported a total of 6 bleeding TEAEs compared to none for placebo. None of these events were SAEs or led to study discontinuation.

In the **BPH/ED analysis set**, two subjects (1.0%) in the tadalafil 5 mg group reported 2 bleeding episodes compared to none in the placebo group. One subject (LVHR-401-4104) reported an SAE of hemorrhagic pancreatitis that led to discontinuation.

Cardiovascular Events: For the **pivotal BPH analysis set**, the Sponsor reported that there were no significant differences between treatment groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs. Twenty-two subjects (2.9%) reported a total of 24 cardiovascular disorder TEAEs. In the placebo group there were 9 (2.4%) cardiovascular TEAEs. In the tadalafil 5 mg group there were 13 (3.5%) cardiovascular TEAEs. Three events were SAEs: 1 SAE (Subject LVHJ- 303-3316, tadalafil 5 mg) of acute MI in an 80 year old man with documented triple vessel

occlusive disease that resulted in discontinuation/death, 1 SAE (Subject LVHG-309-1952, placebo) of coronary artery stenosis that led to study discontinuation, and 1 SAE (Subject LVHG-600-1084, placebo) of cerebrovascular accident. No other cardiovascular TEAEs led to study discontinuation.

Twenty-five subjects in the **long-term, open-label extension of LVHG** (5.9%) reported a total of 39 cardiovascular disorder TEAEs. Six of these events were SAEs: coronary artery stenosis (Subject LVHG-118-2804), coronary artery disease (Subject LVHG-123-3315), cardiac arrest (Subject LVHG-123-3324), atrial flutter (Subject LVHG-138-4801), congestive cardiac failure (Subject LVHG-138-4809), and acute coronary syndrome (Subject LVHG-205-8001). The SAEs of coronary artery disease, arrhythmia, and acute coronary syndrome resulted in study discontinuation. No other cardiovascular TEAEs resulted in study discontinuation. When the Sponsor adjusted the incidence of these TEAEs based on time of exposure, their conclusion the rates of incidence were lower than in the **pivotal BPH analysis set**.

In the **additional BPH analysis set of all subjects**, there were no significant differences between treatment groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs. Twenty-nine subjects (2.5%) reported a total of 31 cardiovascular disorder TEAEs.

There were no significant differences between the tadalafil 5- and 2.5-mg groups in the percentages of subjects reporting cardiovascular disorders overall, nor in any of the cardiovascular categories or subcategories, nor in any individual cardiovascular TEAEs, when compared with placebo except for study discontinuation in the **pivotal BPH/ED analysis set**. Two subjects in the tadalafil 2.5 mg group (myocardial infarction) and one subject in the tadalafil 5 mg group (acute myocardial infarction) discontinued secondary to these adverse events versus none for placebo (Table ISS.14 page 68 ISS). Ten subjects (1.7%) reported a total of 10 cardiovascular disorder TEAEs. One subject (LVHR-208-2806, tadalafil 2.5 mg) was found ead in his house by his wife 4 days after his last dose of study drug with a presumed cause of death related to an MI, and this case was reported as an SAE of myocardial infarction that resulted in discontinuation/death.

> *Reviewer's Comment: In the* **pivotal BPH/ED analysis set,** there were 3 *myocardial infarctions leading to discontinuation in the tadalafil group and none in the placebo group. This will be a review issue.*

Ear Disorders: In the **long-term open-label LVHG extension period**, a total of 5 subjects (1.2%) reported a total of 8 ear disorder TEAEs. None of these events were SAEs, and 1 event of unilateral deafness (Subject LVHG-106-1604) led to study discontinuation.

In the **additional BPH analysis set** of all subjects, 5 subjects reported a total of 6 ear disorder TEAEs. Two of the ear disorder TEAEs occurred in the **pivotal BPH analysis**

set (vertigo, tinnitus [neither led to discontinuation]). The additional 4 ear disorder TEAEs occurred in the **pivotal BPH/ED analysis set.**

In the **pivotal BPH/ED analysis set,** few ear disorder TEAEs were reported, and no significant differences were observed across treatment groups.

Eye Disorders: In the **pivotal BPH analysis set,** few eye disorder TEAEs were reported, and no significant differences were observed between treatment groups. Three subjects (0.4%) reported a total of 5 eye disorder TEAEs: 2 subjects (0.5%) in the tadalafil 5-mg group reported 4 events, and 1 subject (0.3%) in the placebo group reported 1 event. None of these events were SAEs. One event of retinal tear (Subject LHVG-106-1605, tadalafil 5 mg) led to study discontinuation. NAION was not reported.

In the **long-term open-label extension period** of Study LVHG, six subjects (1.4%) reported a total of 6 eye disorder TEAEs. One subject (LVHG-102-1201) reported an SAE of Basedow's disease (exophthalmic goiter).

In the **additional BPH analysis set of all subjects**, seven eye disorder TEAEs (in five patients were reported, and no significant differences were observed between treatment groups. Five subjects (0.4%) reported a total of 7 eye disorder TEAEs.

For the **pivotal BPH/ED analysis set,** few eye disorder TEAEs were reported, and no significant differences were observed across treatment groups. Four subjects (0.7%) reported a total of 6 eye disorder TEAEs: 2 subjects (1.0%) in the tadalafil 5-mg group reported 2 events, and 2 subjects (1.0%) in the tadalafil 2.5-mg group reported 4 events. None of these events were SAEs or led to study discontinuation.

Treatment-Emergent Event Possibly Related to Hypotension, Including Headache, Asthenia, and Fatigue: Two separate analyses of TEAEs possibly related to hypotension were performed. The first analysis focused on the following 7 MedDRA preferred terms: dizziness, dizziness postural, procedural dizziness, hypotension, orthostatic hypotension syncope, and presyncope. An expanded analysis of TEAEs possibly related to hypotension was performed which included the preferred terms of headache, asthenia, and fatigue, as well as several other event terms. The Sponsor presents a complete list of MedDRA (version 13.0) preferred terms used in this expanded analysis.

For the **pivotal BPH analysis set,** with respect to TEAEs possibly related to hypotension, including headache, asthenia, and fatigue, no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension. Twenty-nine subjects (3.9%) reported a total of 30 events possibly related to hypotension. Of these, 19 were reports of headache (2.5%), which was the most frequently reported event in both treatment groups (tadalafil 5 mg: 3.2%; placebo: 1.9%). No events possibly related to

hypotension were SAEs, and 4 events of headache (Subjects LVHG-101-1169, LVHG-522-3278, LVHG-600-1086, and LVHJ-107-1712; all tadalafil 5 mg) led to study discontinuation. Three AEs of headache (1 tadalafil 5-mg subject and 2 placebo subjects) were reported on the same day as randomization and therefore were not included in the statistical output of TEAEs possibly related to hypotension based on the definition of a TEAE. Inclusion of these events would not have altered the interpretation of the analysis of TEAEs possibly related to hypotension.

In the **long-term open-label extension period** of LVHG, TEAEs possibly related to hypotension, including headache, asthenia, and fatigue occurred in thirteen subjects (3.0%) who reported a total of 16 TEAEs. Of these, 7 were reports of headache (1.6%), occurring primarily (6 of 7 reports) in subjects who had been previously assigned to receive tadalafil 10 or 20 mg during the double-blind period of Study LVHG. No TEAEs possibly related to hypotension were SAEs or led to study discontinuation.

In the **additional BPH analysis set of all subjects**, no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension using both the expanded and focused list of preferred terms. Fifty-two subjects (4.5%) reported a total of 54 TEAEs possibly related to hypotension using the expanded list of terms. Of these, 30 events occurred in the **pivotal BPH analysis set.** The additional 24 events occurred in the tadalafil 5-mg and placebo groups in the **pivotal BPH/ED analysis set** along with the 8 TEAEs possibly related to hypotension occurring in the tadalafil 2.5 mg group.

With respect to the **pivotal BPH/ED analysis set.** No significant differences were observed for either tadalafil group in the percentage of subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, when compared to placebo. Thirty subjects (5.0%) reported a total of 32 events possibly related to hypotension. Of these, 23 were reports of headache (3.8%), which was the most frequently reported event in all treatment groups (tadalafil 5 mg: 5.8%; tadalafil 2.5 mg: 2.5%; placebo: 3.0%). No TEAEs possibly related to hypotension were SAEs. Three TEAEs possibly related to hypotension led to study discontinuation: 1 event of headache (Subject LVHR-112-2216, tadalafil 5 mg), 1 event of syncope (LVHR-207-2710, tadalafil 5 mg), and 1 event of dizziness (LVHR-104-1404, tadalafil 2.5 mg). One AE of dizziness (tadalafil 2.5 mg) and 1 AE of headache (tadalafil 5 mg) were reported on the same date as randomization and therefore were not included in the statistical output of TEAEs possibly related to hypotension based on the definition of a TEAE. Inclusion of these events would not have altered the interpretation of the analysis of TEAEs possibly related to hypotension.

Myalgias and Back Pain: Thirty-one subjects (4.1%) reported a total of 35 myalgia/back pain TEAEs in the **pivotal BPH analysis set**. The percentage of subjects reporting at least 1 myalgia/back pain TEAE was significantly greater in the tadalafil 5-mg group compared with the placebo group (6.2% versus 2.1%, p=.006). The most commonly reported myalgia/back pain TEAE in the tadalafil 5-mg group was back pain (2.1%), which was not significantly different between the tadalafil 5-mg group and placebo.

Among the TEAEs that were reported in less than 2% of subjects, pain in extremity (p=.008), myalgia (p=.025), and arthralgia (p=.044) were reported by a significantly greater percentage of subjects in the tadalafil 5-mg group compared to the placebo group. No myalgia/back pain TEAEs were SAEs and 4 events led to study discontinuation: myalgia (Subject LVHG-102-1200, tadalafil 5 mg), pain in extremity (Subject LVHG-102-1206, tadalafil 5 mg), and pain (Subject LVHG 110-120-2008, tadalafil 5 mg), and back pain (Subject LVHJ-401-4101, placebo). One AE of back pain (tadalafil 5 mg) and 1 AE of myalgia (placebo) were reported on the same date as randomization and therefore were not included in the statistical output of myalgia/back pain TEAEs based on the definition of a TEAE. Inclusion of these events would not have altered the interpretation of the analysis of myalgia/back pain TEAEs.

Twenty-eight subjects (6.6%) in the **long-term open-label extension** of Study LVHG reported a total of 30 myalgia/back pain TEAEs. Overall, the percentages of subjects reporting at least 1 myalgia/back pain TEAE were similar (3.1% to 6.0%) between subjects previously treated with tadalafil 2.5, 5, 10, and 20 mg, compared with a numerically greater percentage of subjects previously treated with placebo reporting at least 1 myalgia/back pain TEAE (13.0%), which was driven by a numerically greater percentage of previously treated placebo subjects reporting back pain, myalgia, and arthralgia compared to the other previous tadalafil dose groups. No myalgia/back pain TEAE were SAEs and 1 event of muscle tightness (Subject LVHG-139-4907) led to study discontinuation.

In the **additional BPH analysis set of all subjects** (tadalafil 5 mg or placebo), the percentage of subjects reporting at least 1 myalgia/back pain TEAE was significantly greater in the tadalafil 5-mg group compared with the placebo group (5.9% versus 2.4%, p=.004). Forty-eight subjects (4.1%) reported a total of 54 myalgia/back pain TEAEs. Of these, 35 events occurred in the **pivotal BPH analysis set.** The additional 12 events occurred in the tadalafil 5-mg and placebo groups in the **pivotal BPH/ED analysis set** along with the 7 myalgia/back pain events occurring in the tadalafil 2.5 group.

In the **pivotal BPH/ED analysis set,** no significant differences were observed in the percentage of subjects reporting at least 1 myalgia/back pain TEAE, or any individual myalgia/back pain TEAEs, in the tadalafil 5-mg or 2.5-mg groups when compared to placebo. Twenty four subjects (4.0%) reported a total of 26 myalgia/back pain TEAEs. The most commonly reported myalgia/back pain TEAE in the tadalafil 5-mg group was back pain (2.9%). No other myalgia/back pain TEAE was reported with a frequency of greater than 1 percent. No myalgia/back pain events were SAEs. Three myalgia/back pain TEAEs led to study discontinuation: 1 event of myalgia (Subject LVHR-209-2913, tadalafil 5 mg), 1 event of back pain (Subject LVHR-702-7215, tadalafil 5 mg), and 1 event of muscle spasms (Subject LVHR-704-7401, tadalafil 5 mg). One AE of muscle spasms (tadalafil 5 mg) was reported on the same date as randomization and therefore was not included in the statistical output of myalgia/back pain TEAEs based on the definition of a TEAE. Inclusion of this event would not have altered the interpretation of the analysis of myalgia/back pain TEAEs.

Seizures: No seizure TEAEs were reported in the **pivotal BPH analysis set,** in the **long-term open-label extension** of Study LVHG, in the **additional BPH analysis set of all subjects,** in the **pivotal BPH/ED analysis set,** or in the combined clinical pharmacology studies.

Transient Global Amnesia: No transient global amnesia TEAEs were reported in the **pivotal BPH analysis set**, or in the **additional BPH analysis set of all subjects**.

For the **long-term open-label extension period** of Study LVHG, two subjects (0.5%) reported a total of 2 transient global amnesia TEAEs. One event was an SAE (transient global amnesia, Subject LVHG-204-1431). Neither of the transient global amnesia TEAEs led to study discontinuation. In Subject LVHG-204-143, the transient global amnesia occurred 4 days after the 12 month study period had ended and after weight lifting. In the second case, LVHG-110-2011 (a non-serious case), the event occurred after 3 months of drug exposure and the patient completed the LVHG study period.

No transient global amnesia TEAE's were reported in the **pivotal BPH/ED analysis set.**

Other Safety-Related Assessments: orthostatic vital signs, PVR volume, Q_{max}, clinical chemistry, hematology, and urine laboratory analytes, and ECGs

All Phase 3 studies assessed orthostatic vital signs, PVR volume, Q_{max}, clinical chemistry, hematology, and urine laboratory analytes. In addition, Study LVHG assessed electrocardiograms (ECGs).

Overall, there was no evidence of an adverse impact of tadalafil therapy on orthostatic vital signs, including when evaluated by age category (≤65 and >65 years; <75 and ≥75 years.

There were no clinically adverse or statistically significant changes observed in mean PVR volume in the **pivotal BPH analysis set** or the **pivotal BPH/ED analysis set**. There were no reports of urinary retention in the tadalafil 5-mg group in the **pivotal BPH analysis set** or the **pivotal BPH/ED analysis set**. The few urinary retention TEAEs reported were in the **pivotal BPH analysis set** (tadalafil 5 mg: 0 subjects [0.0%] versus placebo: 2 subjects [0.5%]; p=.159) and in Study LVHS (tadalafil 5 mg: 1 subject [0.6%] versus placebo: 1 subject [0.6%]). One urinary retention TEAE (0.2%) was reported in the open-label extension period of Study LVHG at day 99 (Subject 119-2105). He initiated treatment with alfuzosin and was discontinued. Two months later, laser surgery was performed. Subject 126-3633 received tadalafil 5 mg in the double-blind period. At Visit 9 he had the AE of residual urine (PVR 319mL [baseline PVR 164mL]). 11 days after Visit 9 the PVR was 183 mL.

In Study LVHG, Qmax was assessed as an efficacy measure; however, the mean change from baseline to endpoint was not statistically significantly different from placebo after 12 weeks. In Studies LVHJ, LVHR, and LVHS, Qmax was therefore assessed as a safety parameter to ensure no detrimental effect of tadalafil on urinary flow rate. Overall, the results from all of these studies showed small numerical increases (Studies LVHJ and LVHR) or equal changes (Study LVHS) from baseline to endpoint compared to placebo. These results indicate that treatment with tadalafil 5 mg does not adversely impact bladder function and confirm the finding from a separate Phase 2 study (LVHK) which evaluated the urodynamic effects of tadalafil using free-flow and pressure-flow urodynamic parameters.

The analysis of clinical chemistry, hematology, and urine laboratory analytes provides no evidence of clinically adverse impact of tadalafil 5-mg treatment on any laboratory parameter.

A review of ECG results in Study LVHG provides no evidence of clinically adverse effects on ECG changes associated with tadalafil in the 12-week double-blind period or the 1-year open label extension.

Table 23: Summary of Treatment-Emergent ECG Abnormalities by Specific Abnormality Myocardial Infarction Abnormalities - Study LVHG Double-Blind Period

Myocardial Infarction Abnormalities	Placebo N=210			Tadalafil All Doses N=844		
	n	N*	(%)	n	N*	(%)
No Infarct Present	178	181	(98.34)	663	672	(98.66)
Cannot R/O Infarction	0	181	(0.00)	3	672	(0.44)
Age Undetermined MI	1	181	(0.55)	1	672	(0.14)
Inferior Infarct	0	181	(0.00)	1	672	(0.14)
Unable to Evaluate	2	182	(1.10)	5	672	(0.77)

N*=number of subjects with a normal baseline for the category
Source: Table LVHG 14.126, H6D-MC-LVHG Study Report, page 1121.

> *Reviewer's Comment: These results do not indicate a safety signal in my opinion. There was also no increase in these AEs with increasing dose. With respect to the Open-Label Extension Period of LVHG (Table LVHG 11.50), there was no indication of a safety signal in my opinion.*

Subgroup Analyses including Extrinsic and Intrinsic factors.

Age: Safety outcomes based on age subgroups (subjects ≤65 and >65 years of age; subjects <75 years and ≥ years of age) were analyzed by the Sponsor. It was their conclusion that across all analysis sets, the TEAE profiles were similar between age groups, in the pivotal and additional BPH and BPH/ED analysis sets. There were no clinically meaningful differences in the frequencies and types of TEAEs across age groups.

In the pivotal and additional analysis sets supporting the BPH and BPH/ED indications:

- 1448 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in the BPH and BPH/ED studies, with a total exposure of 624.5 subject years.
- 352 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 280 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

In subjects >65 years of age:

- 586 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission, with a total exposure of 237.9 subject years.
- 126 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 102 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

In subject's ≥75 years of age:

- 160 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg in all BPH and BPH/ED studies supporting this submission, with a total exposure of 65.3 subject years.
- 34 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 6 months in placebo-controlled and open-label extension periods combined.
- 28 subjects were exposed to tadalafil 5 mg, 10 mg, or 20 mg for at least 1 year in placebo-controlled and open-label extension periods combined.

Reviewer's Comment: The number of subjects age >65 years and ≥ 75 years is sufficient to assess safety. The duration of exposure in patients > 65 years is sufficient, but the duration of exposure in patients ≥ 75 years is a review issue.

Subjects ≤65 and >65 years of age: BPH

Overall in the **pivotal BPH analysis set,** TEAEs for subjects ≤65 and >65 years of age, there appeared to be a significant treatment group difference for subjects >65 years of age, with a greater percentage of subjects reporting at least 1 TEAE overall in the tadalafil 5-mg group compared to the placebo group (30.9% versus 19.1%, CMH p=.003). Among subjects >65 years of age, pain in extremity was reported by a significantly greater percentage of subjects in the tadalafil 5-mg group compared with the placebo group (4 subjects [2.7%] versus 0 subjects CMH p=.043).

In Studies LVHG, LVHJ and LVHR, there were three SAEs in the placebo group(0.9%) and 1 SAE in the tadalafil 5 mg group(0.3%) in the <=65 year old group and in the over 65 group there were 2 placebo SAEs(0.9%) versus 3 SAEs (1.3%) in the tadalafil 5 mg group.

Reviewer's Comment: It is of note in baseline medical history, that a history of cardiovascular disorders is common in both >65 years and >75 years of age subgroups, and there is a slightly larger percentage of patients with baseline cardiovascular disorders in the placebo groups compared to the active treatment groups (77/153 [63.6%] for placebo versus 93/150[62%] for active in the over 65 years of age group; and 24/47 [72.3%] for placebo versus 32/50 [64.0%] for active in the over 75 years of age group.

In the **additional BPH analysis set of all subjects**, the TEAE profile for subjects ≤65 and >65 years of age was generally similar to that observed in the **pivotal BPH analysis set**, except for a significant treatment-by-subgroup interaction for arthralgia (HOR p=.053), which was reported in a significantly greater percentage of subjects >65 years of age in the tadalafil 5-mg group compared with placebo (1.7% versus 0.0%, CMH p=.045), though the number of events reported was small.

Based on the integrated analysis of Studies LVHG, LVHJ, LVHR, and LVHK co-displayed with data from clinical pharmacology Study LVHN, there appears to be no clear evidence of an age-related decrease in the tolerability of tadalafil among subjects >65 years of age.

Subjects ≤75 and >75 years of age: BPH

Table 24: TEAEs/SAEs by Age, All Randomized Subjects in BPH Studies LVHG, LVHJ, LVHR, LVHK Double-Blind Period and LVHG Open-label Period

Subjects With >= 1 TEAE	Age(years)	Placebo			Tadalafil 2.5mg			Tadalafil 5mg		
		N	n	(%)	N	n	(%)	N	n	(%)
	<75	599	137	(22.9)	379	99	(26.1)	510	143	(28.0)
	>=75	78	13	(16.7)	28	28	(32.1)	71	23	(32.4)
Subjects With >=1 SAE	<75	599	7	(1.2)	379	4	(1.1)	510	3	(0.6)
	>=75	78	0	(0.0)	28	2	(7.1)	71	1	(1.4)

Source: Table ISS.71, ISS, page 482 and Table ISS.72, ISS, page 566.

For subjects <75 and ≥75 years of age in the **pivotal BPH analysis set**, overall, for subjects reporting at least 1 TEAE, no significant treatment-by-subgroup interactions were observed. However, Table 24 does appear to show an increased incidence of tadalafil-related AEs compared to placebo in the ≥75 years age group compared to the <75. For individual TEAEs, there appeared to be significant treatment-by-subgroup interactions for diarrhea and bronchitis. A significant p-value for diarrhea was driven by a numerically greater percentage of subjects ≥75 years of age in the tadalafil 5-mg group versus placebo (6.0% versus 0.0%) reporting diarrhea and no apparent treatment group difference between the tadalafil 5-mg and placebo groups in subjects <75 years of age (1.2% versus 1.5%). A significant p-value for bronchitis is, in the Sponsor's opinion, likely an artifact caused by the small number of events reported and opposing treatment

group differences within the age subgroups, and therefore does not appear to indicate a true treatment-by-subgroup interaction. Additionally, at the SOC level, no significant treatment-by-subgroup interactions were observed.

In the **additional BPH analysis set of all subjects**, the TEAE profile for subjects <75 and ≥75 years of age was generally similar to that observed in the **pivotal BPH analysis set.**

Subjects ≤65 and >65 years of age: BPH/ED

Table 25: TEAEs by Age Pivotal BPH/ED Study LVHR Double-Blind Treatment Period

	Age <=65			Age > 65		
	Placebo	Tad 2.5mg	Tad 5 mg	Placebo	Tad 2.5mg	Tad 5 mg
Subjects With >=1 TEAE	(N=123)	(N=132)	(N=125)	(N=77)	(N=66)	(N=83)
	n (%)					
	27(22)	33(25.0)	31(24.8)	12(15.6)	17(25.8)	26(31.3)
Subjects With >=1 TEAE	Age <=75			Age > 75		
	N=177	N=186	N=187	N=23	N=12	N=21
	37(20.9)	46(24.7)	51(27.3)	2(8.7)	4(33.3)	6(28.6)

Source: Table APP 2.7.4.35, Clinical Summary of Safety, page 274 and Table App 2.7.4.38, Clinical Summary of Safety, page 339.

Subjects <75 and ≥75 years of age: BPH/ED

There appeared to be an increased rate of subjects with at least 1 tadalafil-related adverse events in the older age populations compared to the younger age populations in the BPH/ED study. Some of this appears driven by the lower incidence AE sufferers in the placebo groups in the older age population compared to the younger age population, but some is related to increased incidence in the actively treated groups.

Significant treatment-by-subgroup interactions were observed in 2 SOC categories (Psychiatric disorders and Infections and infestations) and for several individual TEAEs (nausea, nasopharyngitis, and dizziness). However, these findings may be an artifact caused by the small number of events reported and opposing treatment group differences within the age subgroups. In the Sponsor's opinion, there does not appear to be a true treatment-by-subgroup interaction.

Treatment-Emergent Adverse Events Possibly Related to Hypotension.

Two separate analyses of TEAEs possibly related to hypotension were performed. The first analysis focused on the following 7 MedDRA preferred terms: dizziness, dizziness postural, procedural dizziness, hypotension, orthostatic hypotension, syncope, and

presyncope. An expanded analysis of TEAEs possibly related to hypotension was performed which included the preferred terms of headache, asthenia, and fatigue, as well as several other event terms.

Treatment-emergent AEs possibly related to hypotension (based on only the expanded list of terms) were also evaluated by age subgroups (≤65 and >65 years of age; <75 and ≥75 years of age) and within subgroups of subjects classified by concomitant antihypertensive medication use (defined as no antihypertensive medications, 1 class of antihypertensive medication, or 2 or more classes of antihypertensive medications taken during the double-blind treatment period), including those by age subgroups. Antihypertensive medications were analyzed based on the following classes of drugs typically used to treat hypertension: alpha blockers, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, centrally acting sympatholytics, and other antihypertensive medications.

BPH Analysis Subsets:

Overall, in the **pivotal BPH analysis set,** for subjects (≤ 65 and > 65 years) reporting at Least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions were observed. In the **additional BPH analysis set of all subjects**, the TEAE profile for subjects ≤65 and >65 years of age who reported events possibly related to hypotension was similar to that observed in the **pivotal BPH analysis set.**

In the **pivotal BPH analysis set** for subjects<75 and ≥75 years of age and reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions were observed. In the **additional BPH analysis set of all subjects,** the TEAE profile for subjects <75 and ≥75 years of age who reported TEAEs possibly related to hypotension was generally similar to that observed in the **pivotal BPH analysis set**. Overall, for subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions were observed. For subjects ≥75 years of age, although the numbers were small, a significantly greater percentage of subjects in the tadalafil 5-mg group reported at least 1 TEAE possibly related to hypotension compared with placebo (6 subjects [8.5%] versus 1 subject [1.4%], CMH p=.035); half of the events reported in the tadalafil group were headache.

For subjects ≤65 and >65 years of age in the **pivotal BPH/ED analysis set,** no significant treatment-by-subgroup interactions were observed. Although there appeared to be a significant treatment-by-subgroup interaction for dizziness, this finding, in the Sponsor's opinion, may be an artifact caused by the small number of events reported and opposing treatment group differences within the age subgroups and therefore does not appear to indicate a true treatment-by-subgroup interaction. For patients <75 and ≥75 years of age in the **pivotal BPH/ED analysis set,** the results were similar to those reported in subjects ≤65 and >65 years of age.

Reviewer's Comment: Overall, for subjects ≥75 years of age there was a significantly greater percentage of subjects in the tadalafil 5-mg group versus placebo reporting at least 1 TEAE possibly related to hypotension (6 subjects [8.5%] versus 1 subject [1.4%], CMH p=.035); this finding was driven by the events of headache (3 [4.2%] versus 1 [1.4%]) and dizziness (3 [4.2%] versus 0). Headache is the most commonly reported TEAE known to be associated with tadalafil treatment.

The following section discusses Treatment-Emergent Adverse Events Possibly Related to Hypotension by Concomitant Antihypertensive Medication Use and Age Group.

Overall, for subjects reporting at least 1 TEAE possibly related to hypotension, no significant treatment-by-subgroup interactions were observed between the concomitant antihypertensive therapy subgroups. For individual TEAEs, a significant treatment-by-subgroup interaction was observed only for headache (tadalafil 2.5 mg/placebo HOR p=.081).

In the **additional BPH analysis set of all subjects** (≤65 and >65 Years of Age)**,** no significant treatment-by-subgroup interaction was observed for the age subgroups in the percentage of subjects reporting at least 1 hypotension TEAE overall, and no significant treatment group difference was observed for any individual hypotension TEAE.

For subjects <75 and ≥75 years of age in the **additional BPH analysis set of all subjects,** overall TEAEs possibly related to hypotension by concomitant antihypertensive therapy (no, 1, or 2 or more classes of antihypertensive medications) for subjects <75 and ≥75 years of age demonstrated no significant treatment-by-subgroup interaction. For subjects ≥ 75 years of age, no significant treatment group difference was observed for any individual TEAE by antihypertensive subgroup. For subjects <75 years of age, there was a significant treatment-by antihypertensive- therapy subgroup interaction for the TEAE of dizziness (HOR p=.065). The Sponsor stated that this finding is likely due to the small number of events reported and opposing treatment group differences within the subgroups. As percentages of subjects with dizziness did not increase with increasing number of classes of concomitant antihypertensive use, the events were not likely the result of related blood pressure changes, in the Sponsor's opinion.

In the **pivotal BPH/ED analysis set** for Subjects ≤65 and >65 Years of Age, No significant treatment-by subgroup interactions were observed for any individual TEAEs in either age subgroup. For subjects <75 and ≥75 years of age in the **pivotal BPH/ED analysis set** no significant treatment-by-subgroup interactions were observed. No significant treatment-by-subgroup interactions were observed for any individual TEAEs in either age subgroup.

Co-Administration and Prior Use of Alpha Blocker Therapy

With respect to coadministration of tadalafil and alpha blockers there was a higher percentage of subjects in the tadalafil 5 mg group reporting at least 1 TEAE compared to the placebo group in Study LVHS. This difference was small and may not be clinically significant (41.8% versus 33.1%, p =.132). The most commonly reported TEAEs were dizziness, dyspepsia, diarrhea, back pain and GERD. In LVHS the only AE leading to discontinuation in more than 1 subject was headache which is possibly related to hypotension. For both the focused and expanded analyses of TEAEs possibly related to hypotension, similar proportions of subjects in each treatment group reported at least 1 TEAE, with no statistically significant differences between treatment groups. In the orthostatic vital sign assessment, 60 subjects (30 per treatment group, p=1.00) met at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test. Assessment of symptomatic orthostatic hypotension (presence of a clinical symptom simultaneously with a positive orthostatic test) also showed similar results between treatment groups (1 subject per group). In the Sponsor's opinion, these safety results were comparable with other tadalafil studies and no new safety concerns were identified related to concomitant administration of tadalafil with alpha-blocker therapy. No tadalafil-treated subjects reported syncope, nor did any tadalafil subjects report an SAE attributable to hypotension.

In the **additional BPH analysis set of all subjects,** when comparing individual TEAEs between prior alpha-blocker therapy subgroups, significant treatment-by-subgroup interactions were observed for nasopharyngitis (HOR p=.012), sinusitis (p=.084) and gastritis (HOR p=.044). Nasopharyngitis is known to be associated with tadalafil treatment, and also has been reported during alpha-blocker therapy. In addition, there was a difference in the reported TEAE of hypertension.

Table 26: Adverse Events of Hypertension by Prior Alpha-Blocker Therapy, All Randomized Subjects Studies LVHG, LVHJ, and LVHR Double-Blind Treatment Period

Hypertension	Prior Alpha Blocker	Placebo			Tadalafil 5 mg	
		N	n	(%)	N	n (%)
	No	415	3	(0.7)	418	6 (1.4)
	Yes	160	2	(1.3)	163	5 (3.1)

Source: Table ISS.44, Integrated Summary of Safety, page 247.

> *Reviewer's Comment: In prior alpha blocker users in Studies LVHG, LVHJ and LVHR, the rates of "hypertension" reported as an AE are twice that reported for those not previously using alpha blockers. The doubling of incidence is seen both in the placebo group and in the tadalafil 5 mg group. The independent role of tadalafil is unclear.*

For the **pivotal BPH/ED analysis set,** in the tadalafil 2.5 mg group compared with placebo a significant group interaction was observed. This interaction was driven by the significantly greater percentage of subjects reporting at least 1 TEAE in the tadalafil 2.5-mg group compared with placebo who did receive prior alpha-blocker therapy (45.0% versus 17.4%, CMH p=.009 Table APP.2.7.4.132). For individual TEAEs, a significant treatment-by-prior-alpha-blocker-subgroup interaction was observed for nasopharyngitis in both tadalafil groups (tadalafil 5 mg and placebo HOR p=.074; tadalafil 2.5 mg and

placebo HOR p=.023). This interaction appears to be driven by a significantly greater of percentage of subjects who did receive prior alpha-blocker therapy in the tadalafil 2.5-mg group compared with placebo (10.0% versus 0.0%, respectively; CMH p=.043), while the significant HOR p-value for the tadalafil 5-mg and placebo groups appears to be an artifact caused by the small number of events reported and opposing treatment-group differences, in the Sponsor's opinion.

The Sponsor also evaluated adverse events and change in IPSS during the alpha-blocker washout periods of Studies LVHG, LVHJ, LVHK and LVHR. This was done at the request of the Division to determine the likely effect of discontinuing alpha blockers in order to initiate therapy with tadalafil. Analysis of IPSS score changes was not provided for Studies LVHG and LVHK as the IPSS was not collected at Visit 1 for these studies.

In Study LVHK, of the 24 screened subjects requiring alpha-blocker washout during the screening/washout period, 3 subjects (12.5%) reported a total of 3 events: ecchymosis, skeletal injury, and 1 urinary event of urethral hemorrhage (post urodynamics). The event of urethral hemorrhage was most likely related to the invasive urodynamic procedure conducted at Visit 2. In Study LVHG, of the 100 screened subjects requiring alpha-blocker washout during the screening/washout period, 8 subjects (8.0%) reported 14 events, including 1 urinary event of dysuria. The other events were cough, depression, endodontic procedure, influenza, muscle spasms, nightmare, decreased neutrophils, osteoarthritis, procedural pain, sinus operation, toothache and vomiting. In Study LVHJ, no procedure-related AEs were reported during the screening/washout period by any of the 42 subjects requiring alpha-blocker washout.

In Study LVHR, a total of 113 subjects who were screened required alpha-blocker washout; 4 of those subjects (3.5%) reported 5 procedure-related AEs: dysuria and nocturia (1 subject), micturition disorder (1 subject), residual urine (1 subject), and urinary retention (1 subject). Of the subjects reporting procedure-related AEs following alpha-blocker washout, all had discontinued tamsulosin.

In Study LVHJ, in subjects who required alpha-blocker washout, from Visit 1 to Visit 2, a mean increase in IPSS of 4.8 points was observed. In Study LVHJ, of the 42 subjects who participated in the placebo lead-in period by alpha-blocker washout at Visit 2, their mean IPSS was 20.3 points, versus 18.9 for all other subjects who did not require alpha-blocker wash-out (n=303).

In Study LVHR, in subjects who required alpha-blocker washout (n=77), from Visit 1 to Visit 2, a mean increase in IPSS of 2.5 points was observed. In Study LVHR, of the 77 subjects who participated in the placebo lead-in period by alpha-blocker washout at Visit 2, their mean IPSS was 22.1 points versus 20.1 points for all other subjects who did not require alpha blocker washout (n=659).

> *Reviewer's Comment: There was some degree of symptomatic worsening during alpha-blocker washout. Nonetheless, there were few urinary system related AEs during the washout period of these studies.*

AEs by Prior PDE5 Inhibitor Therapy

For the **pivotal BPH analysis set, additional BPH analysis set of all subjects, and pivotal BPH/ED analysis set** although several significant treatment-by-subgroup interactions were observed, the Sponsor considers these findings are likely an artifact caused by the small number of events reported and opposing treatment-group differences within the subgroups and therefore do not appear to indicate a true treatment-by subgroup interaction.

> *Reviewer's Comment: Prior PDE5 Inhibitor therapy does not appear to confer additional morbidity to BPH patients subsequently treated with tadalafil.*

Safety in Special Groups and Situations

Ethnicity: According to the Sponsor, and pending final Clinical Pharmacology review of the submission, through the tadalafil clinical development program, tadalafil pharmacokinetics in healthy male Japanese and Caucasian subjects were comparable at doses of 5, 10, and 20 mg, with a slightly lower exposure in Japanese subjects at 40 mg. Similarly, tadalafil pharmacokinetics following doses of 10 and 20 mg in Chinese subjects were generally similar to those in Japanese and Caucasian subjects. Furthermore, population-based analyses of tadalafil pharmacokinetics in Caucasian and Japanese ED patients revealed that exposures were similar across both groups and no dosage adjustment was warranted.

Preliminary Safety Conclusions

Upon preliminary review, the safety profile of tadalafil 5 mg once daily for men with BPH is quite similar to men with ED alone (Table 44). The most common TEAEs (≥2% and greater than placebo) with tadalafil 5 mg once daily were headache, dyspepsia, back pain, and hypertension. Dyspepsia was the only TEAE that was statistically greater than placebo. The incidence of AEs leading to discontinuation was low in Studies LVHG and LVHJ. Few SAEs were reported. The TEAE profile of tadalafil 5 mg in the **pivotal BPH analysis set** is generally similar across subpopulations of age and prior PDE5-inhibitor use. The safety assessments of TEAEs in subjects with prior alpha-blocker or PDE5 –inhibitor use were consistent with the known safety profile of tadalafil.

AEs possibly related to hypotension and AEs related to hypotension in men taking concomitant antihypertensive medications were few and generally similar for tadalafil 5 mg and placebo regardless of age.

In Studies LVHG and LVHJ, the mean Qmax from baseline to endpoint for tadalafil 5 mg was 1.6 mL/sec in both studies and was not statistically significant compared to placebo (Study LVHG: 1.2 mL/sec; Study LVHJ: 1.1 mL/sec). In a urodynamic study (Study LVHK), no adverse effects on bladder function were observed in subjects taking tadalafil 20 mg once daily for 12 weeks.

The types and frequency of individual TEAEs in the open-label extension period were similar to those in the placebo-controlled period of Study LVHG, the **pivotal BPH analysis set**, and to the known safety profile of tadalafil.

In a clinical pharmacology trial conducted in elderly and young subjects with BPH, the pharmacokinetics, hemodynamics, and safety of tadalafil 20 mg were similar in elderly and young subjects (Study LVHN); additionally, the results were generally comparable to those of healthy subjects.

In Study LVHS by preliminary review, when subjects with BPH-LUTS on stable alpha-blocker therapy for BPH added tadalafil 5 mg, the percentage of TEAEs possibly related to hypotension (such as dizziness, orthostatic hypotension and syncope) from coadministration of tadalafil and alpha blocker was similar to coadministration of placebo with alpha blocker. There was no statistically significant difference in the percentage of subjects with at least 1 treatment-emergent positive orthostatic test. Assessments of symptomatic orthostatic hypotension (presence of a clinical symptom simultaneously with a positive orthostatic test) showed similar results between the tadalafil 5-mg and placebo treatment groups.

Preliminary review of adverse changes in any laboratory parameter, vital signs measurement, of ECGs in the studies conducted with men with BPH-LUTS has not detected any significant adverse changes associated with tadalafil treatment.

No new safety issues have been identified.

No clinically adverse changes attributable to tadalafil treatment were observed in any laboratory parameters or vital sign measurements in Study LVHR.

In both men with BPH and men with BPH/ED, no new safety issues were identified and the safety profiles were similar.

VI. Summary of Preliminary Clinical Review

In regard to Efficacy:

1. A preliminary review of the efficacy data appears to support efficacy of tadalafil 5 mg once daily in the treatment of the signs and symptoms of BPH, and treatment of both ED and the signs and symptoms of BPH (BPH/ED).

2. [redacted] (b) (4) The Study Endpoints and Labeling Development Team (SEALD) in the Office of New Drugs has previously conducted a review of the BII and found it to be "not well defined and reliable," (not validated). The Division agrees. [redacted] (b) (4) A separate regulatory letter will be conveyed to Sponsor containing detailed regulatory review comments for the BII.
3. Two, small, non-IND studies in Asian subjects (out of three non-IND Asian studies) failed to demonstrate statistical significance versus placebo. Efficacy in Asian subjects will be a review issue.

In regard to Safety:

4. After a preliminary evaluation, the safety profile appears to be similar to other patient groups using tadalafil (e.g., tadalafil as needed for ED, and tadalafil once daily for ED) and on its face, appears acceptable.
5. Tadalafil-related adverse events related to hypotentsion may be more common in the elderly (≥ 75 years of age):
   a. An increased incidence of hypotension-related adverse events was observed in tadalafil-treated elderly patients (≥ 75 years of age) compared to placebo-treated elderly patients in Study LVHS. The independent effect of tadalafil on hypotension-related adverse events appeared greater in the elderly (≥75 years of age) compared to the young (< 65 years of age) in that study, both in patients taking alpha blockers and those not taking alpha blockers.. This will be a review issue.
   b. In addition, in the pivotal BPH/ED analysis set, for subjects ≥75 years of age there was a significantly greater percentage of subjects in the tadalafil 5-mg group versus placebo reporting at least 1 adverse event possibly related to hypotension (6 subjects [8.5%] versus 1 subject [1.4%]. This finding appears to be driven by adverse event reports of headache (3 [4.2%] versus 1 [1.4%]) and dizziness (3 [4.2%] versus 0). This will be a review issue.
6. In the pooled double-blind periods from the "pivotal" studies (LVHG, LVHJ, and LVHR), there were reports of three myocardial infarction resulting in study discontinuation in the tadalafil 2.5 and 5.0 mg dose groups (N=797) versus 0 myocardial infarctions in the placebo groups (N=786) resulting in study discontinuation. This will be a review issue. Case narratives will be reviewed in more detail. In addition, all cardiovascular adverse events reported in the application will be reviewed in great detail.
7. No additional formal risk management program (RMP) activities are anticipated at this time.

Other Issues:

8. Review of the submitted financial disclosure did not reveal conflict of interest.
9. The format of the proposed label complies with the Physician Labeling Rule (PLR) and there are no clearly apparent deficiencies in the label.

10. The Sponsor has complied with previous agreements to provide certain data efficacy and safety analysis sets. They have also provided both an ISS and ISE.
11. As per previous agreements, appropriate numbers of men with BPH > 65 and >75 years of age have been included in the pivotal studies.
12. Sponsor has evaluated the data relative to special potential safety concerns including: age, ethnicity, hypotension, cardiovascular TEAEs, previous and concomitant alpha blocker use, previous PDE5 inhibitor use, diabetes, urodynamic effects of tadalafil use, and the possibility of worse tolerability in BPH patients versus ED patients.
13. In the Clinical reviewer's opinion, there are no previous commitments outstanding.

Conclusion/Recommended Regulatory Action: From a clinical perspective, the NDA is fileable. The following Clinical review issues noted at filing should be conveyed to Sponsor in the 74-Day letter:

1. The Study Endpoints and Labeling Development Team (SEALD) in the Office of New Drugs has completed its review of the BPH Impact Index (BII), a questionnaire used in the Phase 3 studies, (b) (4) SEALD finds the BII to be not well defined nor reliable (not "validated"). The Division agrees. (b) (4) A separate regulatory letter will be conveyed to you containing detailed regulatory review comments for the BII.

2. Tadalafil-related adverse events related to hypotension may be more common in geriatric patients ≥ 75 years of age compared to < 65 years:

    a. An increased incidence of hypotension-related adverse events was observed in tadalafil-treated elderly patients (≥ 75 years of age) compared to placebo-treated elderly patients in Study LVHS. The independent effect of tadalafil on hypotension-related adverse events appeared greater in the elderly (≥75 years of age) compared to the young (< 65 years of age) in that study, both in patients taking alpha blockers and those not taking alpha blockers. This will be a review issue.

    b. In the pivotal BPH/ED analysis set, encompassing all patients with ED from Studies LVHG, LVHJ and LVHR, for subjects ≥75 years of age there was a significantly greater percentage of subjects in the tadalafil 5 mg group versus placebo reporting at least 1 adverse event possibly related to hypotension (6 subjects [8.5%] versus 1 subject [1.4%]). This finding appears to be driven by adverse event reports of headache (3 [4.2%] versus 1 [1.4%]) and dizziness (3 [4.2%] versus 0). This will be a review issue.

3. Safety data has been provided in geriatric patients >65 years of age with BPH (n=586), and in geriatric patients ≥75 years of age (n=160). A total of 120 subjects and 102 subjects > 65 years of age were exposed for at least 6 months and 1 year, respectively. However, the extent of 6 month and 1 year exposure in geriatric patients ≥75 years of age is not as great (34 and 28 subjects ≥ 75 years of age, for 6 months and 1 year, respectively). This will be a review issue. Sponsor may wish to submit summaries of safety data in patients ≥75 years of age treated in previous as-needed and daily-dosing ED studies in order to better support long-term safety in this age group.

4. In the pooled double-blind periods from the Studies LVHG, LVHJ, and LVHR, there were reports of three patients who experienced myocardial infarctions resulting in study discontinuation in the tadalafil 2.5 and 5.0 mg dose groups (N=797) versus 0 myocardial infarctions (N=786) resulting in study discontinuation in the placebo group. This will be a review issue. Case narratives for these three adverse events will be reviewed in great detail. In addition, there are other cardiovascular adverse events reported in this application, some resulting in serious outcome or discontinuation, and others of clinical significance, and these too will be reviewed in detail, for each study and for the entire application.

5. In the pivotal BPH/ED analysis set, encompassing all patients with ED from Studies LVHG, LVHJ and LVHR, an increased incidence of "hypertension" reported as an adverse event was observed in the tadalafil 5 mg group (2.4%, 11/464) compared to the tadalafil 2.5 mg group (0%, 0/333) and the placebo groups (2.5 mg placebo 0.6%, 2/342, 5 mg placebo 0.7%, 3/454). This will be a review issue. Detailed narratives for each of these "hypertension" AE cases should be submitted. A rationale/explanation for the differences between groups should be provided. In addition, detailed narratives should be provided for each and every adverse event report of "hypertension" in this supplemental efficacy application.

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/s/

A R WIEDERHORN
02/14/2011

MARK S HIRSCH
02/14/2011
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
Jeffrey B. Medwid, PhD	ONDQA Div II, Branch VI and ODEIII/DRUP	**21-368/ S-020** and **S-021**
3. NAME AND ADDRESS OF APPLICANT		**4. Supplement Numbers**
ELI LILLY AND CO LILLY CORPORATE CENTER INDIANAPOLIS, IN 46285		S-020 , S-021
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
Cialis	TADALAFIL	PAS Efficacy Received 06-December-2010 PDUFA Date 06-October-2011

8. COMMUNICATION PROVIDES FOR:

These two Prior Approval Supplements (PAS) to NDA No. 21-368 S-020 and NDA 21-368 S021 are efficacy supplements for the following indications:

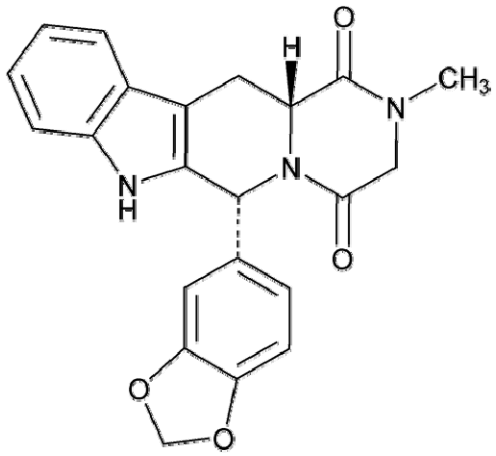
- The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
- The treatment of ED and the signs and symptoms of BPH (ED/BPH)

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Sexual Dysfunction (Male)	Rx	15-Sept-2011, Original Review 28-Sept-2011 Addendum
12. DOSAGE FORM	**13. POTENCY**	
Tablets	Multiple	

14. CHEMICAL NAME AND STRUCTURE

Tadalafil
(6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl] pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione; (3) (6*R-trans*)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione

$C_{22}H_{19}N_3O_4$. 389.40



15. COMMENTS

These two Prior Approval Supplements (PAS) to NDA No. 21-368 S-020 and NDA 21-368 S-

021 are efficacy supplements for the following indications:
• The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
• The treatment of ED and the signs and symptoms of BPH (ED/BPH)

Since these supplements are efficacy supplements, the emphasis of these two supplements will focus on the clinical aspect. As a result, the CMC review of this supplement will be minimal except for labeling.

At the time of the first CMC review on Sept 15, 2011 several minor labeling issue had yet to be resolved (minor PI edit and container/carton).

In this addendum to the first review, CMC finds all of the labeling to be acceptable. Based on the e-mail provided by Mark Hirsch from the applicant on September 19, 2011, the PI label is acceptable from a CMC point of view. The applicant has made all of the recommended CMC changes. See approved PI label in attachment 1 of this review.

*The Categorical Exclusion submitted by the applicant applies to both supplements including NDA **21-368 S-020** and S-0**21.** The final calculation predicted concentration of tadalafil that may be discharged into the aquatic environment would be less that 0.11 ppb, which is below the 1 ppb limit allowed in 21 CFR 25.31 (b).*

The DMEPA review (dated 14-SEP-11) by Yelena Maslov, Pharm.D., found the container/carton labeling acceptable. DMEPA states that the revised container/carton labels address all their original concerns. They find the "blister cards" to be "not ideal", but they are acceptable to DMEPA nonetheless.

All facilities are currently approved for this NDA. As per IQP 5102, no inspection request was required.

From a CMC perspective this supplement is recommended for approval from a CMC point of view based on acceptable review of the PI, container/carton labeling and categorical exclusion.

16. CONCLUSION AND RECOMMENDATION		
The supplement is recommended for approval from a CMC standpoint		
17. NAME	**18. REVIEWERS SIGNATURE**	**19. DATE COMPLETED**
Jeffrey B. Medwid, PhD	See appended electronic signature sheet	28-Sept-2011

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/s/

JEFFREY B MEDWID
09/28/2011

THOMAS F OLIVER
09/28/2011

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
Jeffrey B. Medwid, PhD	ONDQA Div II, Branch VI and ODEIII/DRUP	**21-368 S-020** and S-0**21**
3. NAME AND ADDRESS OF APPLICANT		**4. Supplement Numbers**
ELI LILLY AND CO LILLY CORPORATE CENTER INDIANAPOLIS, IN 46285		S-020 , S-021
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
Cialis	TADALAFIL	PAS Efficacy Received 06-December-2010 PDUFA Date 06-October-2011

8. COMMUNICATION PROVIDES FOR:

These two Prior Approval Supplements (PAS) to NDA No. 21-368 S-020 and NDA 21-368 S021 are efficacy supplements for the following indications:

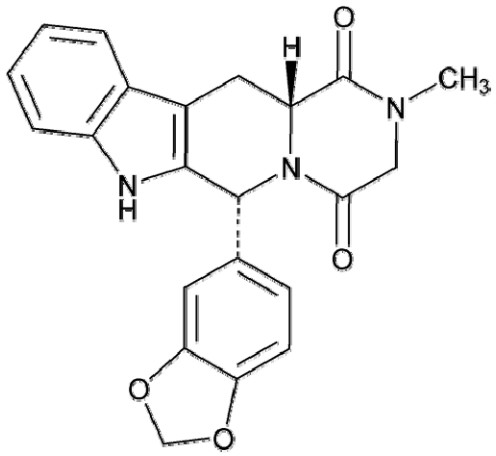
- The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
- The treatment of ED and the signs and symptoms of BPH (ED/BPH)

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Sexual Dysfunction (Male)	Rx	Only if referred to in the review
12. DOSAGE FORM	**13. POTENCY**	
Tablets	Multiple	

14. CHEMICAL NAME AND STRUCTURE

Tadalafil
(6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl] pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione; (3) (6*R-trans*)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione

$C_{22}H_{19}N_3O_4$. 389.40



15. COMMENTS

These two Prior Approval Supplements (PAS) to NDA No. 21-368 S-020 and NDA 21-368 S-

021 are efficacy supplements for the following indications:
• The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
• The treatment of ED and the signs and symptoms of BPH (ED/BPH)

Since these supplements are efficacy supplements, the emphasis of these two supplements will focus on the clinical aspect. As a result, the CMC review of this supplement will be minimal except for labeling. At the time of this review several minor labeling issue have yet to be resolved (minor PI edit and container/carton). When the final labeling is completed and acceptable we will enter a brief "Addendum" into DARRTS.

As of Sept 9, 2011, the four sections of the PI (Highlights, sections 3, 10 and 16) as reported below in the reviewer notes are acceptable, except we recommend that the words (b) (4) *be removed from the* (b) (4)

From a CMC perspective this supplement is recommended for approval from a CMC point of view pending final labeling and container/carton review and approval.

16. CONCLUSION AND RECOMMENDATION		
The supplement is recommended for approval from a CMC standpoint		
17. NAME	**18. REVIEWERS SIGNATURE**	**19. DATE COMPLETED**
Jeffrey B. Medwid, PhD	See appended electronic signature sheet	15-Sept-2011

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/s/

JEFFREY B MEDWID
09/14/2011

THOMAS F OLIVER
09/15/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 21-368 (S020 and S021)
Supporting document/s:	\\CDSESUB1\EVSPROD\NDA21368\21368.enx
Applicant's letter date:	12/6/10
CDER stamp date:	12/6/10
Product:	Cialis® (tadalafil)
Indication:	Benign Prostatic Hyperplasia (BPH);
	Erectile Dysfunction (ED) and BPH
Applicant:	Eli Lilly and Company
Review Division:	Division of Reproductive and Urologic Products
Reviewer:	Yangmee Shin, Ph.D.
Supervisor:	Lynnda Reid, Ph.D.
Division Director:	Scott Monroe, M.D.
Project Manager:	George Lyght

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21-368 are owned by Eli Lilly and Company or are data for which Eli Lilly and Company has obtained a written right of reference.
Any information or data necessary for approval of NDA 21-368 that Eli Lilly and Company does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21-368.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The sponsor seeks approval of tadalafil for two indications: treatment of men with signs and symptoms of benign prostatic hyperplasia (BPH) and for the treatment of men with ED and signs and symptoms of BPH (hereafter referred to as BPH/ED). The proposed dose is 5 mg, taken at approximately the same time every day.

Oral tadalafil has been approved to treat men with ED and patients with pulmonary arterial hypertension (PAH). In men with ED, tadalafil may be dosed as needed or once daily. For as-needed dosing, the starting dose is 10 mg and may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. For once daily dosing, the starting dose is 2.5 mg and may be increased to 5 mg based upon efficacy and tolerability. For patients with PAH, the recommended dose is 40 mg once daily.

1.2 Brief Discussion of Nonclinical Findings

No new toxicology studies were submitted with this application. The only additional nonclinical study included is an interim report evaluating the pharmacodynamic effect of tadalafil in prostate gland oxygenation in a spontaneously hypertensive rat (SHR) model. Tadalafil treatment reduced hypoxia-inducible factor 1α (HIF1α) and vasorelaxant endothelin-1 type B receptor (ETB) protein immunopositivity in SHR prostate sections when compared to WKY. Oxygenation was partially normalized after 1 day and completely restored to that of WKY after 7 days and 4 weeks. These results suggest that tadalafil treatment may improve prostate gland oxygenation in the SHR although a direct extrapolation to humans is uncertain.

Previous nonclinical studies submitted in support of the original marketing application of tadalafil are considered sufficient to support the safety of the new indications, given the exposure levels within the range of the approved Cialis® oral tablets.

1.3 Recommendations

1.3.1 Approvability

From a Pharmacology/Toxicology perspective, the previous nonclinical data submitted for the approval of the treatment of ED support the safety of the proposed indications of Cialis®.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The content of the sponsor's proposed labeling pertaining to nonclinical studies with the exception of the **Mechanism of Action** under **Clinical Pharmacology** section is identical with what is written in the previously approved Cialis® tablet.

The Division recommends that all data related to reproductive and developmental toxicology studies under the **Animal Toxicology and/or Pharmacology** section be moved to the appropriate sections under **Use in Specific Populations**.

Recommended labeling is detailed as follows (see annotated label in Appendix):

(b) (4)

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2 Drug Information

2.1 Drug

CAS Registry Number: 171596-29-5

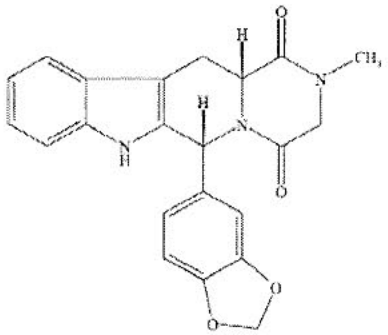
Generic Name: Tadalafil

Code Name: IC351, LY450190

Chemical Name: Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-12aR)-

Molecular Formula/Molecular Weight: $C_{22}H_{19}N_3O_4$/389.41

Structure or Biochemical Description



Pharmacologic Class: β-carboline phosphodiesterase (PDE) 5 inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 73,502; IND 54,553; NDA 21-368

2.3 Drug Formulation

Yellow film-coated tablets of 2.5, 5, 10 and 20 mg tadalafil containing lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose, talc, titanium dioxide, triacetin, iron oxide yellow/ (b) (4) iron oxide red/ (b) (4) and magnesium stearate as inactive ingredients.

(b) (4)

2.4 Comments on Novel Excipients

All inactive ingredients and excipients are found in previously approved drug products.

Comments on Impurities/Degradants of Concern

There are no impurities/degradants requiring qualification.

2.6 Proposed Clinical Population and Dosing Regimen

5 mg, taken at approximately the same time every day for

- Treatment of erectile dysfunction (ED) and signs and symptoms of benign prostatic hyperplasia (BPH)
- Treatment of the signs and symptoms of BPH

2.7 Regulatory Background

Tadalafil (Cialis®) was initially approved in the US in 2003 for the treatment of ED on an as needed basis at the recommended starting dose of 10 mg as an oral tablet, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability with the maximum dosing frequency is once per day. In 2008, tadalafil was approved for once daily use at the recommended doses of 2.5 or 5 mg based on efficacy and tolerability. Tadalafil (Adcirca®) was also approved for the treatment of PAH in 2009 at the recommended dose of 40 mg once daily with or without food.

The most frequent treatment-emergent adverse events associated with Cialis® use during the clinical studies included headache, dyspepsia, nasopharyngitis, back pain, upper respiratory tract infection, flushing, influenza, myalgia, cough, diarrhea, nasal congestion, pain in extremity, bronchitis, urinary tract infection, gastroesophageal reflux and abdominal pain.

Although It is not possible to determine whether the events are related directly to tadalafil, to sexual activity, to the patient's underlying risk factors or diseases, to a combination of these factors, or to other factors, adverse events of tadalafil including postmarketing experience based on the most recent labeling and the MICROMEDEX® included the following:

- Cardiovascular and cerebrovascular events: myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, angina, syncope, tachycardia, hypotension
- Dermatologic reactions: urticaria, Stevens-Johnson syndrome, erythroedema, flushing, itching, rash, sweating, exfoliative dermatitis, angioedema
- Neurologic disorders: seizure, migraine, dizziness, transient global amnesia, parethesia, hypesthesia, insomnia, vertigo, cerebral hemorrhage, somnolence
- GI effects: dysphagia, esophagitis, gastritis, loose stools, nausea, vomiting, dry mouth, xerostomia
- Respiratory events: dyspnea, epistaxis, pharyngitis, emphysema, pulmonary embolism
- Musculoskeletal: arthralgia, neck pain, pain in limb

- Ophthalmologic effects: visual field defect, edema of eyelid, retinal vein/artery occlusion, non-arteritic anterior ischemic optic neuropathy/atrophy, blurred/color vision, citreous detachment, conjunctivitis, eye pain
- Otologic events: sudden decrease or loss of hearing, tinnitus
- Hepatobiliary disorders: abnormal LFTs, increased GGTP
- Urogenital symptoms: priapism

3 Studies Submitted

3.1 Studies Reviewed

An interim report of a pharmacology study entitled "Effect of PDE5 Inhibition on Prostate Gland Oxygenation" was submitted and reviewed.

3.2 Studies Not Reviewed

A full nonclinical program for tadalafil in support of the original NDA approval for the ED indication was previously reviewed (see original NDA 21-368 review for details). These nonclinical program included general and safety pharmacology, PK/ADME, acute and chronic toxicology, genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies.

3.3 Previous Reviews Referenced

NDA 21-368; IND 73,502; IND 54,553

4 Pharmacology

4.1 Primary Pharmacology

Tadalafil inhibits a cGMP-hydrolyzing enzyme, PDE5 found in various tissues and organs including the corpus carvernosum, platelets, visceral/vascular/skeletal smooth muscle, heart, placenta, kidney, lung, liver, cerebellum and pancreas in vitro. Tadalafil was approximately 14-fold more potent for PDE5A (IC_{50}~1.1 nM) than for PDE11A1 (IC_{50}~15 nM) and 40-fold more potent for PDE5A than for PDE11A4 (IC_{50}~73 nM), which are found in testes, prostate, pituitary gland, skeletal muscle and other tissues. Tadalafil is 700-fold more potent for PDE5 than for PDE6 (IC_{50}~730 nM), an enzyme found in the retina, and >9000-fold more potent than for the other PDEs in assays using human recombinant PDEs. The metabolites of tadalafil, methylcatechol, catechol and the major human plasma metabolite, methylcatechol glucuronide also had potency and selectivity for PDE5A and PDE11A1 with IC_{50} values of approximately 290 nM, 36 nM and 14000-59000 nM for PDE5A or 1600 nM, 170 nM and 210000 nM for PDE11A1, respectively.

Tadalafil caused a dose-dependent relaxation of aortic rings in rats in the presence of endothelium, and enhanced the relaxation of human penile resistance arteries in the absence or presence of added NO donors or activators of NO-synthase, suggesting a role of the PDE5 inhibitor for enhancing cGMP levels and vasorelaxation. Tadalafil potentiated the inhibitory effect of SNP on platelet aggregation in a dose-dependent

manner. Tadalafil treatment also reduced HIF1α and vasorelaxant ETB protein immunopositivity in SHR prostate sections when compared to WKY rats. Oxygenation was partially normalized after 1 day and completely restored to that of WKY rats after 7 days and 4 weeks.

4.2 Secondary Pharmacology

Tadalafil had no effect on other receptors such as benzodiazepine, $GABA_A$, muscarinic, H1, 5-HT_2, D1, α1-adrenergic, α2-adrenergic and β-adrenergic receptors at concentrations up to 10 μM, but had an affinity for the D2 receptor at 1±0.3 μM. The methylcatechol and catechol derivatives of tadalafil did not compete with the same ligands at concentrations <3 μM.

4.3 Safety Pharmacology

Tadalafil caused emesis and increased heart rate at ≥10 mg/kg followed by tachycardia at ≥30 mg/kg in conscious dogs. Ptosis and depression of the pinnal reflex was noted at 200 mg/kg in rats following oral dosing. Decrease in mean arterial blood pressure was observed at ≥1 mg/kg in hypertensive or normotensive rats and ≥20 mg/kg in conscious dogs. Tadalafil, following cumulative intravenous doses of 0.1 to 3 mg/kg, produced dose-dependent decreases in blood pressure in anesthetized dogs secondary to decreased vascular resistance. In guinea pigs, an oral dose of 400 mg/kg produced significant reduction in heart rate and progressive bradycardia, concurrent with deteriorating clinical signs and weight loss resulting in deaths of animals. Intravenous injection of tadalafil potentiated ANF-induced diuresis and natriuresis in rats at ≥0.1 mg/kg.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Following a single oral administration of 10 mg/kg [^{14}C]-tadalafil, absorption was generally rapid in rats and dogs with T_{max} of 1-2 hours and 6 hours, respectively. Oral bioavailability was approximately 34-53% in rats and 10-18% in dogs. Oral plasma half-life in both rats and dogs could not be calculated due to the limited number of data points above the limit of quantification and a prolonged absorptive phase. In vitro binding of tadalafil to human, rat, dog and mouse plasma proteins was determined to be 94%, 92%, 87% and 85%, respectively.

In healthy subjects or in patients with ED, pharmacokinetics (PK) of tadalafil appear linear with respect to time and dose. Systemic exposure (AUC) increased proportionally over a dose range of 2.5- to 20 mg. C_{max} was achieved at a median time of 2 hours after dosing. Steady-state plasma concentrations were attained by Day 5, and are approximately 1.6-fold higher than the single-dose value suggesting accumulation on repeated dosing. Plasma $t_{1/2}$ was approximately 17.5 hours in healthy subjects.

Radiolabeled tadalafil was shown to be widely distributed in rats with the highest levels observed in the stomach, gastrointestinal (GI) tract, thyroid, lung and the liver, and to a much lesser extent in the brain. The high concentrations present in the GI contents are

consistent with data from PK studies, which indicated slow absorption of tadalafil after oral administration. The tissue half-lives of radioactivity were approximately 10 hours, except for whole blood (26 hours) and stomach wall (21 hours).

Exposure to pregnant rats on gestation Day 18 caused the highest concentrations of radioactivity in maternal adrenal gland, preputial gland and liver at 8 hours post-dose. Parent and/or metabolites of tadalafil were detected in the maternal placenta, and fetal adrenal gland, blood, brain, eye, kidney, liver and myocardium with substantially lower exposure at 8 hours post-dose, indicating placental transfer.

Tadalafil was predominantly metabolized by CYP3A4 in human liver microsomes. Unchanged tadalafil accounted for 43-51% in rat, 17-24% in dog and 26% in human plasma, suggesting extensive metabolism. The major route of metabolism of tadalafil was an initial opening of the methylenedeoxybenzyl ring to form the catechol metabolite followed by methylation to the methylcatechol and then by glucuronide conjugation to methylcatechol glucuronide. The major metabolite in mice, dogs and humans was methylcatechol glucuronide. Catechol glucuronide was the most abundant metabolite in rats.

The major route of excretion of tadalafil was via the feces in both rats and dogs. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

Slight- to moderate increases in hepatic enzyme activity and/or CYP450 content (e.g., CYP1A, CYP2B) were observed in mice, rats and dogs after oral doses of 400 mg/kg, indicating tadalafil as a inducer of CYP450 isoenzymes. Tadalafil was also a mechanism-based inactivator (CYP3A) in mice and dogs.

5.2 Toxicokinetics

Plasma concentrations of tadalafil were dose-dependent in animals, but the increases were less than proportional, especially at high doses used in the toxicology studies, suggesting saturation of absorption. A prolonged absorption phase was observed in all species at high doses. In rats and dogs, the plasma AUC values increased following repeated daily administration, indicating accumulation in the plasma. In mice, however, plasma AUC and C_{max} values generally decreased after about 1 month as compared to the initial dose, indicating enzyme induction. There was high intra-animal variability, particularly in dogs.

6 General Toxicology

6.1 Single-Dose Toxicity

Tadalafil did not cause mortality at up to the oral dose of 2000 mg/kg tested in mice and rats. The intravenous lethal dose was 100 mg/kg in mice and >62.5 mg/kg in rats. Deteriorating clinical signs including labored breathing, jerky movements, subdued behavior, prostration, tremor and convulsions were seen in treated animals, or in moribund animals with increased severity and frequency.

6.2 Repeat-Dose Toxicity

Repeat-dose toxicology studies were conducted in rats at up to 6 months via oral gavage and dogs at up to 1 year via oral capsules. The major target organs and tissues in animals included the following:

- Vascular system: vascular inflammation in multiple organs including the heart, liver, thymus, lungs and testes/epididymis
- Male reproductive system: epithelial degeneration/atrophy/inflammation in testes, epithelial vaculation/inflammation/aspermia in epididymides, hyperplasia/inflammation in seminal vesicle
- Hematopoietic system: hemorrhage/inflammation/necrosis in mesenteric lymph node/thymus, extramedullary hematopoiesis/necrosis in spleen, altered hematology parameters
- Liver: perivasculitis, pigmentation, vacuolation
- Urinary tract: mixed cell infiltration, tubular regeneration, epithelial hyperplasia, dilatation
- CNS: reduced activity, hunched posture
- Respiratory system: abnormal/labored/shallow breathing, congestion/edema in lungs
- Eye: cornea erosion/ulceration, lens degeneration
- GI tract: pigment, emesis, hemorrhage

Systemic exposures at the LOAEL or NOAEL for the unbound drug in pivotal studies are approximately 3-5 fold in rats ($AUC_{0\text{-}24h}$~1200-2200 ng·hr/mL at 10 mg/kg) and 2-19 fold in dogs ($AUC_{0\text{-}24h}$~1100-8800 ng·hr/mL at 25 mg/kg) compared to the human exposure at the MRHD of 20 mg ($AUC_{0\text{-}24h}$~460 ng·hr/mL).

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Negative

7.2 *In Vitro* Assays in Mammalian Cells

Negative

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Negative

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day that produce systemic exposures of unbound tadalafil approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, above the exposures in human males given the MRHD of 20 mg. The increased incidence of hepatocellular adenomas and/or carcinomas in both male mice and rats, and lung alveolar/bronchiolar carcinomas in female mice were not statistically significant.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Tadalafil had no significant effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg.

Embryonic Fetal Development

There was no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at exposures up to 11 times the human dose of 20 mg. A NOAEL for maternal toxicity (based on the reduced body weight gain) was determined to be 200 mg/kg/day and for embryo/fetal developmental toxicity to be 1000 mg/kg/day in rats. A NOAEL for both maternal and developmental toxicity was established as 1000 mg/kg/day in mice.

Prenatal and Postnatal Development

A statistically significant reduction in postnatal survival of pups (below historical background range) was observed in all treated groups in rats tested at up to 1000 mg/kg. Some f1 fetuses were found dead or euthanized in extremis due to impaired mobility, labored respiration and swaying while walking, dehydrated/lethargic, unkempt appearance, decreased defecation, dried red staining on the mouth/nose/forelimbs and/or dystocic. The NOEL for maternal toxicity was 200 mg/kg/day (based on decreased body weight gain), and for developmental toxicity was 30 mg/kg/day, which gives approximately 16- and 10-fold exposure multiples, respectively, of the human AUC for 20 mg.

10 Special Toxicology Studies

Tadalafil was a mild ocular and dermal irritant in an in vitro assay using New Zealand White rabbits.

11 Integrated Summary and Safety Evaluation

The sponsor is seeking approval of tadalafil for 1) the treatment of the signs and symptoms of BPH; and 2) for the treatment of ED and the signs and symptoms of BPH (BPH/ED) taken on a daily basis at the recommended dose of 5 mg. To support these indications, the sponsor conducted three pivotal clinical studies (two 12-week placebo-controlled studies and an open-label extension study for 52 weeks) for ED indication and one 12-week study for BPH/ED indication. The most common treatment-emergent AEs were headache, sinusitis, dyspepsia, back pain and hypertension.

No new toxicology studies were conducted in support of the BPH or BPH/ED indications. A pharmacology study designed to evaluate prostate gland oxygenation following tadalafil administration was conducted in an SHR model. Tadalafil treatment improved prostate gland oxygenation after 1 day, 7 days and 4 weeks in the SHR animal model, which is characterized by ischemia/hypoxia of the genitourinary tract.

As reflected in the approved labeling, tadalafil had significantly higher affinity for PDE11A isozyme than other PDE5 inhibitors. PDE11A catalyzes the hydrolysis of both cAMP and cGMP, while PDE5 is a cGMP-specific PDE. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenal cortex). In vitro, tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined. However, more recent studies report a role of PDE11A in various disease conditions including tumors (Nat Rev Endocrinol 7:64, 2011; J Clin Endocrinol Metab 96:E208, 2011; Mol Cell Endocrinol 336:162, 2011; Endoc Relat Cancer 17:R109, 2010; Best Pract Res Clin Endocrinol Metab 24:503, 2010; Endo Am J Surg Pathol 34:547, 2010; Best Pract Res Clin Endocrinol Metab 24:907, 2010; Cancer Res 69:5301, 2009; Clin Cancer Res 14:4016, 2008; Horm Metab Res 39:467, 2007; Nat Genet 38:794, 2006; Cancer Res 66:11571, 2006), asthma (J allergy Clin Immunol 126:871, 2010) and psychiatric diseases (PNAS 107:8457, 2010; Schizophr Res 119:266, 2010; Neuropsychiatr Dis Treat 5:163, 2009; Brain Res 1281:25, 2009; PNAS 103:15124, 2006). These studies found higher inactivation mutation of PDE11A genes associated with increased cAMP levels in certain tumor patients such as testicular (e.g., Sertoli cell, familial/bilateral testicular germ cell), prostate and adrenal (e.g., Carney complex, adrenal hyperplasia, primary pigmented nodular adrenocortical disease, Cushing syndrome) tumors known to be cAMP-responsive. The PDE11A mutations/variants that decreased or inactivated the production or activity of PDE11A in tumor patients suggest that PDE11A may act as a risk or genetic predisposition factor and/or modifier for tumors in tissues with high expression of PDE11A. In particular, the association of PDE11A with Carney complex, a multiple neoplasia syndrome that is inherited in an autosomal dominant manner and causes a variety of skin and endocrine tumors (e.g., adrenal cortex, pituitary, thyroid, gonad), indicates the major role of PDE11A in the endocrine steroidogenic tumorigenesis. It is currently unknown whether the chronic PDE11A inhibition that

results in increased cAMP may have any role in humans, particularly patients with predisposing factors such as adrenal malfunction or any other endocrine problems, considering the role of cAMP in tumorigenesis.

Tadalafil was incompletely absorbed in animals, especially at high doses tested. Plasma half-life could not be calculated due to the variable and prolonged absorptive phase. The less than proportional increase in total radioactivity to the dose levels suggests a saturation of absorption. The increase in plasma AUC values and prolongation of absorption phase corresponding to repeated administration also suggest accumulation of drug in plasma. These factors may have resulted in the high intra-animal variability of systemic exposure levels in animals. In humans, accumulation was also noted following repeated administration at therapeutic doses. Therefore, the prolonged half-life (17.5 hours) of tadalafil and the increased steady-state levels after multiple-dosing may lead to adverse effects of longer duration.

The target organ toxicity of tadalafil was similar to that of other PDE5 inhibitors. The major adverse effects of tadalafil were related to inflammatory responses in multiple tissues and organs. Although it is unknown whether the vascular inflammation is independent of the multi-systemic inflammatory responses or is secondary to the inflammatory process, arterial/vascular lesions were observed primarily in the heart, lung, thymus, brain, spinal cord, epididymides and stomach which consisted of medial fibrinoid hemorrhage/necrosis, neutrophilic/lymphocytic/sub-endothelial infiltration, edema and vascular inflammation. Vascular inflammation was noteworthy in mice, rats and dogs at unbound tadalafil exposures varying between 1 to 54 times the human exposures at the MRHD of 20 mg. These effects tend to occur without significant hemodynamic changes unlike those seen with sildenafil or vardenafil. In dogs, the arteritis resulted in mortality in 1- and 6-month studies. In a 1-year study using a different colony dogs, there were no significant findings of vascular inflammation. However, moderate-to-marked neutropenia and thrombocytopenia associated with inflammatory signs were observed in 2 females at ≥100 mg/kg (associated with perivasculitis in left coronary artery in one HD female). The sponsor stated that the hematologic findings are compound related, idiosyncratic and reversible, and not a result of a direct effect on bone marrow hematopoietic precursors, based on the lack of effects in early neutrophil precursors or megakaryocytes. The pathogenesis and significance of these findings in understanding potential underlying mechanisms responsible for causing the vascular injury and the potential risk in humans are unknown. Nor has sensitive and specific markers for the vascular injury been established. In humans, rare cases of hypersensitivity reactions including rash, urticaria, Stevens-Johnson syndrome, exfoliative dermatitis and angioedema have been reported in post-marketing reports in temporal association with the use of tadalafil although the relevance to the vascular toxicity is not determined.

Tadalafil caused non-reversible testicular effects in dogs resulting in a decrease in spermatogenesis at comparable exposures to the MRHD. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of

≥10 mg/kg/day. The clinical relevance of the testicular findings remains unknown. In humans, statistically significant decreases in mean sperm concentrations compared to placebo were observed given 10 mg for 6 months or 20 mg for 9 months.

The majority of the adverse effects seen in animals (e.g., liver, lung, CNS, CVS, eye, stomach, thyroid, testis) with tadalafil could be related to PDE5 inhibition. PDE5 is found in various parts of the body including the penis, testes, prostate, lung, platelet, heart, pancreas, visceral/vascular/skeletal smooth muscle, liver, eye and the brain regions. The wide distribution of PDE5 and the corresponding versatile effects of PDE5 inhibitors may be associated with the undesirable effects of tadalafil in off-target systems as well as for the beneficial effects in on-target systems. Inhibition of PDE5 may increase the level of cGMP in all sites where PDE5 is actively hydrolyzing cGMP, and thus, potentiate the effect of endogenous vasodilators via cGMP (e.g., NO, acetylcholine, adenosine, bradykinin). Numerous published studies suggest implication of the NO-cGMP pathway in PDE5 inhibitor-induced toxicity, given that the PDE5 inhibitors enhance NO-mediated response by elevating cGMP. In particular, NO is a potent biological mediator that displays a duality of function that can be both protective and deleterious depending on concentration, duration, type, localization, exposure conditions, etc. NO acts as an anti-inflammatory agent or an anti-oxidant and a pro-inflammatory mediator or pro-oxidant in a number of physiologic processes including neurotransmission, immune function, carcinogenesis and cardiovascular modulation. Overstimulation of the NO-cGMP pathway may result in untoward effects.

Tadalafil induced CNS-related clinical signs at high doses tested. A number of published studies suggest a possible implication of NO-cGMP in the PDE5-induced CNS effects, a modulation of seizure threshold (Eur J Pharmacol 587:129, 2008; Br J Pharmacol 147:935, 2006). NO functions as both an anticonvulsant and a proconvulsant depending on the type of seizure, source of NO, dose and the type of neurotransmitters involved (Pharmacol Rep 62:383, 2010; Epilepsia 51:1552, 2010; Eur J Pharmacol 617:79, 2009; Eur J Pharmacol 587:129, 2008; Br J Pharmacol 147:935, 2006; Neurosci Lett 376:116, 2005). A recent study showing EEG abnormalities in ED patients given tadalafil (Neurol Res 31:313, 2009) suggests perturbations of cerebrovascular vasoconstrictive response to oxygen status by PDE5 inhibitors (J Appl Physiol 106:1234, 2009). Similarly, increased NO production has been demonstrated in animals administered doses comparable to and/or higher than the MRHD of 20 mg associated with hearing loss, suggesting that excess NO-cGMP is involved in auditory effects (Biol Pharm Bull 31:1981, 2008; Hear Res 145:149, 2000; Ann NY Acad Sci 884:171, 1999). The PDE5 inhibitor-induced ocular effects could also be due to the NO-cGMP mediated vasodilatation (Drug Safety 32:1, 2009; Br J Ophthalmol 92:469, 2008; Invest Ophthalmol Vis Sci 49:720, 2008; Eye 22:144, 2008; Invest Opthalmol Vis Sci 49:720, 2008; Br J Ophthalmol 91:1551, 2007; Ophthalmology 109:584, 2002).

The effects of PDE5 inhibitors in the male reproductive system remain inconclusive with mixed results. Studies reported little, positive or negative effect of PDE5 inhibitors on semen parameters in vivo or in vitro (see BJU Int 106:1181, 2010; Curr Pharm Des 15:3506, 2009; Int J Impot Res 20:530, 2008; Asian J Androl 10:115, 2008; Eur Urol

53:1058, 2007, Andrologia 39:12, 2007 for details). Altered sperm motility and viability, and acrosome-reacted sperm were observed in humans, as well as in vitro studies (Curr Pharm Des 15:3506, 2009; Asian J Androl 10:115, 2008; Andrologia 39:12, 2007; Fertil Steril 88:860, 2007; Fertil Steril 87:1064, 2007; Am J Obstet Gynecol 182:1013, 2000), suggesting a role for PDE5 inhibitors on sperm acrosome reaction and capacitation process.

The following table summarizes exposure multiples of unbound tadalafil at the NOAEL for the major target organ toxicities observed in pivotal toxicology studies in animals compared to humans based on AUC.

Table 1. Summary of Exposure Multiples at the NOAEL for the Major Findings Observed in Pivotal Toxicology Studies in Animals Compared to Humans Based on AUC

Study Type	Species	Target Organ Toxicity	NOAEL (mg/kg)	Exposure Multiple*
General toxicity	Dog	Testicular degeneration, epididymal aspermia	Dog: <25 (M)	2-12
	Dog, Rat, Mouse	Vascular toxicity (inflammation, lymphoid necrosis/hemorrhage)	Dog: 100 Rat: <10 Mouse: 400	Dog: 3-45 Rat: <3 Mouse: 6
	Dog, Rat, Mouse	Hematotoxicity (neutropenia, thrombocytopenia, splenic hematopoiesis)	Dog: 400 (M), 25 (F) Rat: 60 (M), 400 (F) Mouse: 400	Dog: 5-22 (M), 2-19 (F) Rat: 5 (M), 33 (F) Mouse: 6
	Dog, Rat, Mouse	Clinical signs (abnormal breathing, decreased activity, hunched posture)	Dog: 400 Rat: 400 Mouse: 400	Dog: 4-40 Rat: 12-33 Mouse: 6
	Dog, Rat, Mouse	Other toxicity (liver, kidney, eye, stomach)	Dog: 100 Rat: 60 Mouse: 400	Dog: 3-45 Rat: 5-14 Mouse: 6
Carcinogenicity	Rat, Mouse	-	Rat: 400 Mouse: 400	Rat: 14-26 Mouse: 7-10
Reproductive & Developmental toxicity	Rat	Fertility	Rat: 400	Rat: 14-26
	Rat, Mouse	Embryonic/fetal development	Rat: 1000 Mouse: 1000	Rat: 11 mouse: 11
	Rat	Prenatal/postnatal development	Rat: 30	Rat: 10

*Mean $AUC_{0\text{-}24h}$~460 ng·hr/mL/day for 20 mg unbound tadalafil based on Study LVDN

12 Appendix/Attachments

The following annotated labeling is the DRUP's recommendations to the sponsor's proposed labeling. The revisions are limited to sections where the context has been altered (italicized in red) or deleted (strikethrough).

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

YANGMEE SHIN
08/05/2011

LYNNDA L REID
08/08/2011
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-368 **Applicant:** Eli Lilly and Company **Stamp Date:** 12/6/10

Drug Name: Cialis® **NDA/BLA Type:** sNDA (020 & 021)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		Based on the original NDA 21-368 No new toxicology studies provided (a new pharmacodynamic study included)
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		Based on the original NDA 21-368 No new toxicology studies provided
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		Based on the original NDA 21-368 No new toxicology studies provided
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		Based on the original NDA 21-368 No new toxicology studies provided
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		Based on the original NDA 21-368
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		Based on the original NDA 21-368
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		Based on the original NDA 21-368
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		Based on the original NDA 21-368

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Based on the original NDA 21-368 No new toxicology studies provided (minor changes in mechanism of action section recommended)
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		Manufacturing changes due to a transfer to a new site, but no significant changes to the previously approved regulatory commitments including solvents and reagents, raw materials specifications, analytical methods, drug substance specifications, critical in-process criteria, intermediate specifications and stability test conditions.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Yangmee Shin, Ph.D. 1/10/2011

Reviewing Pharmacologist/Toxicologist Date

Lynnda Reid, Ph.D.

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANGMEE SHIN
02/14/2011

LYNNDA L REID
02/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	21-368 (b) (4)
Drug Name:	Tadalafil®
Indication(s):	1. Treatment of signs and symptoms of Benign Prostatic Hyperplasia (BPH) 2. Treatment of Erectile Dysfunction (ED) and BPH
Applicant:	Eli Lilly and Company
Date(s):	Submission Date: 12-06-2010 PDUFA Date: 10-06-2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Xin Fang, Ph.D., Primary Reviewer
Concurring Reviewers:	Mahboob Sobhan, Ph.D., Team Leader
Medical Division:	Division of Reproductive and Urologic Products
Clinical Team:	Roger A. Wiederhorn, MD, Medical Reviewer Mark S. Hirsch, MD, Medical Team Leader
Project Manager:	George Lyght

Keywords: Clinical Studies, Cochran-Mantel-Haenszel, Logistic Regression

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LIST OF TABLES

1. EXECUTIVE SUMMARY

The data submitted in this application support the efficacy of tadalafil 5 mg once daily for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) in men. Tadalafil 5 mg once daily demonstrated statistically significant improvements in the international prostate symptom score (IPSS) and erectile function (EF) domain score of the international index of erectile function (IIEF), two primary endpoints evaluated to support the above indications. Tadalafil 2.5 mg did not demonstrate statistically significant improvement in the above symptoms.

From a statistical perspective, this application provided adequate data to support the efficacy of tadalafil 5 mg once daily in the treatment of signs and symptoms of both BPH and ED in men.

No major statistical issues were noted with regards to statistical analyses of the efficacy endpoints, except the secondary endpoint BII, which was not considered a valid patient reported outcome (PRO) based instrument. This review excluded pertinent efficacy data from 12 subjects in two of the three studies due to inconsistent IPSS (4 subjects) and IIEF-EF domain scores (8 subjects) between the case report forms (CRFs) and source files. The results of FDA analysis remained consistently similar to the sponsor's results. Handling of missing data in all three studies was addressed appropriately. Adjustment for multiplicity due to multiple dose comparisons was also handled as planned in the protocol.

2. INTRODUCTION

2.1 Overview

The applicant, Eli Lilly and Company, is seeking approval of Tadalafil 5 mg for the treatment of (1) signs and symptoms of benign prostatic hyperplasia (BPH), and (2) erectile dysfunction (ED) and BPH in men. Tadalafil has been approved for the treatment of erectile dysfunction since 2003 by the agency with the dosing strengths of 2.5 mg, 5 mg, 10 mg, and 20 mg.

The sponsor started the drug development for the two new indications under IND 73,502. Many issues in sponsor's protocols were resolved through the communications including five meetings and two special protocol assessments (SPA). In the three meetings during 2008-2010, the division notified the sponsor that the BPH impact index (BII) was not a valid patient reported outcome (PRO) instrument. After reviewing the submitted BII PRO instrument, both the medical and the SEALD reviewers recommended that BII was not a valid PRO instrument on Jan. 4, 2011 and Nov. 22, 2010, respectively. In the protocols for Studies LVHJ and LVHR multiplicity issues were found during the SPA. Subsequently, the sponsor resolved the multiplicity issues in the submission on Jan. 30, 2009 based on our comments dated Nov. 21, 2008 and Dec. 1, 2008. The proposed gatekeeping testing procedures in Studies LVHJ and LVHR were accepted in the statistical review dated Feb. 24, 2009.

To support the safety and efficacy of Tadalafil 5 mg, clinical data from two Phase-3 studies (LVHJ, LVHR) and one Phase 2/3 study (LVHG) were submitted. In addition, one Phase-3 study report (LVHB) and five Phase-2 study reports (LVHC, LVHK, LVHT, LVIA, and LVIA-OLE) were also submitted. Studies LVHG, LVHJ mainly supported BPH indication. Study LVHR supported the combined indication of ED and BPH.

The Phase-2 study LVIA and the Phase-3 study LVHB were conducted in Asia only and were considered as supportive. This review will focus on the efficacy data from the two Phase-3 studies and one Phase-2/3 study summarized in Table 1.

Table 1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Country (Number of Sites)	Study Population
LVHG	*Phase 2/3, randomized, placebo-controlled, double-blind, multinational*	*Screen/Washout ≤ 4 weeks* *Placebo Lead-in 4 weeks* *Double-blind 12 weeks*	*Planned 198* *Randomized* *Tadalafil 2.5 mg 209* *Tadalafil 5.0 mg 212* *Tadalafil 10 mg 216* *Tadalafil 20 mg 209* *Placebo 212*	*Australia (3), Canada (5) France (8), Germany (14) Greece (4), Italy (4) Mexico (6), Spain (5) Sweden (4), US (41)*	*Men ≥ 45 with BPH (>6 months, Total IPSS≥13)*
LVHJ	*Phase 3, randomized, double-blind, placebo-controlled, multinational*	*Screen/Washout ≤ 4 weeks* *Placebo Lead-in 4 weeks* *Double-blind 12 weeks*	*Planned 151* *Randomized* *Tadalafil 5.0 mg 161* *Placebo 164*	*Argentina (1), Germany (5), Italy (5), Mexico (5), US (12)*	*Men ≥ 45 with BPH (>6 months, Total IPSS≥13)*
LVHR	*Phase 3, randomized, placebo-control, double-blind, multinational*	*Screen/Washout ≤ 4 weeks* *Placebo Lead-in 4 weeks* *Double-blind 12 weeks*	*Planned 184* *Randomized* *Tadalafil 2.5 mg 198* *Tadalafil 5.0 mg 208* *Placebo 200*	*Canada (6), France (6) Germany (4), Greece (5) Italy (4), Mexico (5), Portugal (3), US (16) Russian Federation (5)*	*Men ≥ 45 with both BPH (>6 months, Total IPSS≥13) and ED (≥ 3 months)*

Note Sites without randomized subjects were excluded.

2.2 Data Sources

Study reports and additional information were submitted electronically. The data quality of the submission was within the acceptable limits. Analysis datasets and associated definition files were listed in Table 2.

Table 2. Data Sources

Study	File	Location
LVHG	Datasets	\\CDSESUB1\EVSPROD\NDA021368\ (b) (4) \m5\datasets\h6d-mc-lvhg\analysis\
	Definition	\\CDSESUB1\EVSPROD\NDA022560\ (b) (4) \m5\datasets\h6d-mc-lvhg\analysis\define.pdf
LVHJ	Datasets	\\CDSESUB1\EVSPROD\NDA021368\ (b) (4) \m5\datasets\h6d-mc-lvhj\analysis\
	Definition	\\CDSESUB1\EVSPROD\NDA022560\ (b) (4) \m5\datasets\h6d-mc-lvhj\analysis\define.pdf
LVHR	Datasets	\\CDSESUB1\EVSPROD\NDA021368\ (b) (4) \m5\datasets\h6d-mc-lvhr\analysis\
	Definition	\\CDSESUB1\EVSPROD\NDA022560\ (b) (4) \m5\datasets\h6d-mc-lvhr\analysis\define.pdf

2.3 Indication

Tadalafil 5 mg is indicated for the treatment of (1) signs and symptoms of benign prostatic hyperplasia (BPH) and (2) Erectile Dysfunction (ED) and BPH.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor created SDTM datasets from the analysis datasets in all 3 studies: LVHG, LVHJ, and LVHR (Submission Section 1.2: "Cialis BPH Note to Reviewer"). The randomizations in the three studies were conducted centrally via an interactive voice response system (IVR) and stratified by region, lower urinary tract symptoms (LUTS) severity and ED. Treatment assignments appear roughly balanced among the three stratification factors within each study. The datasets submitted in the three studies are sufficient for the efficacy and safety review.

3.2 Evaluation of Efficacy

3.2.1 BPH Indication

3.2.2 Studies LVHG and LVHJ

3.2.2.1 Design, Objectives and Endpoints

To support BPH indication two studies: LVHG, a phase 2/3 study and LVHJ, a Phase 3 study were conducted. The design of the studies was similar except in the number of arms. Therefore, unless otherwise noted, the study description will be similar for both studies.

Design and Objective: Study LVHG was a Phase 2/3 randomized, double-blind, placebo-controlled, multinational trial where 990 eligible men aged ≥45 with BPH-LUTS was randomized in a ratio of 1:1:1:1:1 to receive one of the five following treatments:

- Tadalafil 2.5 mg once daily
- Tadalafil 5 mg once daily
- Tadalafil 10 mg once daily
- Tadalafil 20 mg once daily
- Placebo once daily

Study LVHJ, which also followed the same design, randomized 302 eligible men aged ≥45 with BPH-LUTS in a ratio of 1:1 to receive either placebo once daily or tadalafil 5 mg once daily.

In both the studies, the randomization was stratified by the following three factors:

- Geographic region
- Baseline LUTS severity [moderate (IPSS <20), or severe (IPSS ≥20)] assessed at Visit 3
- History of ED at Visit 1 (yes or no)

The randomization assignment was determined by a computer-generated random sequence using interactive voice response system (IVRS).

Both studies had 3 periods: a screening/wash-out period for 1-4 weeks, a placebo ran-in period for 4 weeks, and a treatment period for 12 weeks.

The primary objective for both Studies LVHG and LVHJ was to demonstrate the efficacy of tadalafil 5 mg once daily at week 12 compared with placebo in improving the IPSS in men with signs and symptoms of BPH-LUTS.

Primary Efficacy Endpoint: In both studies, the primary efficacy endpoint was the change from baseline in the total IPSS (sum of the scores for IPSS Questions 1-7) at Week 12.

Secondary Efficacy Endpoints: The following secondary variables were also evaluated in both studies. The endpoints were the changes from baseline to Weeks 4, 8, and 12 in:

- IPSS storage (irritative) subscore, [$Q_2 + Q_4 + Q_7$]
- IPSS voiding (obstructive) subscore, [$Q_1 + Q_3 + Q_5 + Q_6$]
- IPSS nocturia [Q_7]
- IPSS Quality of Life (QoL) Index
- BPH Impact Index (BII)
- IIEF Erectile Function Domain [$Q_1 + Q_2 + Q_3 + Q_4 + Q_5 + Q_{15}$]
- Uroflowmetry parameter: peak flow rate (Q_{max})
- Uroflowmetry parameter: mean flow rate (Q_{ave})
- Uroflowmetry parameter: voided volume (V_{comp})

The following secondary endpoints were evaluated in Study LVHG only

- Total IPSS change
- LUTS Global Assessment Question (LUTS GAQ) score

The following secondary endpoints were evaluated in Study LVHJ only

- A modified version of the IPSS questionnaire score (mIPSS)
- The PGI-I subject-rated scores and the CGI-I clinician-rated scores
- IIEF intercourse Satisfaction Domain [$Q_6+Q_7+Q_8$]
- IIEF intercourse Overall Satisfaction Domain [$Q_{13}+Q_{14}$]
- Post void residual volume (PVR)

The pre-specified key secondary endpoints in Study LVHJ were:

- IIEF-EF domain after 12 weeks of treatment
- Total IPSS after 4 weeks of treatment
- BII after 12 weeks of treatment
- mIPSS after 1 week of treatment (visit 4)
- BII after 4 weeks of treatment

However, there were no key secondary endpoints in Study LVHG.

Determination of Sample Size: The sample size was calculated to test the null hypothesis of no difference between tadalafil 5 mg and placebo in terms of the total IPSS change from baseline to Week 12. The assumptions for the calculation were:

- A common standard deviation of 6 points
- The treatment difference of 2.0 points
- A two-sided alpha level of 0.05
- A power of 91% in Study LVHG and a power of 80% in Study LVHJ

- A dropout rate of 5% in Study LVHJ

Analysis Populations: In both studies, the primary analysis population for efficacy was the intent-to-treat (ITT) population including all subjects who were randomized and started study medication. Additional analyses were conducted on the per-protocol (PP) population, defined as those subjects who completed the 12 week treatment period and had administered ≥ 70% of prescribed doses.

Handling of Missing Data: In both studies, the missing questionnaire items in the IPSS were not imputed. The IIEF score of each domain was imputed at a specific visit if scores for < 30% of the component questions within that domain were missing at that visit. The missing IIEF domain score was then imputed using the mean of non-missing scores within that domain at that visit. Otherwise, the IIEF score of each domain was set to missing for that visit. After the above imputation, the missing values for efficacy endpoints were imputed using the last observation carried forward (LOCF).

Multiplicity Adjustment: In Study LVHG, the multiple comparisons between each of the 4 doses (2.5 mg, 5 mg, 10 mg, and 20 mg) and placebo were adjusted using Dunnett method.

In Study LVHJ, a fixed-sequence testing procedure was utilized to control the Type I error among the primary and multiple key secondary tests. The key secondary endpoints were assessed for statistical significance only if the result for the primary test was significant at a two-sided 0.05 significance level. The key secondary analyses were then performed in the following order at a two-sided significance level of 0.05 for each step. The test was stopped at the step in which the two-sided p-value was > 0.05.

- IIEF-EF domain after 12 weeks of treatment
- Total IPSS after 4 weeks of treatment
- BII after 12 weeks of treatment
- mIPSS after 1 week of treatment (Visit 4)
- BII after 4 weeks of treatment

Pool of Sites: There was no pooling of study sites. The randomization was not stratified by sites.

Statistical Methods: In general, the primary analysis was based on the ITT subjects with a non-missing post baseline total IPSS. Sensitivity analyses were performed using baseline observation carry forward (BOCF) imputation and repeated measure analysis.

In Study LVHG, sponsor's statistical analysis method included a stratified permutation test to test the hypothesis that tadalafil 5 mg resulted in a greater decrease in the total IPSS than placebo at a two-sided alpha level of 0.05. In addition, all doses were compared with placebo in an ANCOVA analysis. The ANCOVA model included fixed effects of geographic region, ED history, treatment and the baseline total IPSS as covariate. Adjustments for multiple comparisons between placebo and the 4 tadalafil doses were performed by Dunnett's test. The permutation tests and the ANCOVA analysis were also performed for the following secondary endpoints: IPSS total score, IPSS storage (irritative) sub-score, IPSS voiding (obstructive) sub-score, IPSS nocturia question, BII, IIEF-EF domain and uroflowmetry parameter (peak flow rate). The LUTS GAQ was analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization factors in subjects with non-missing responses at the final visit. A repeated measure mixed model was performed for total IPSS, IPSS storage (irritative) sub-score, IPSS voiding (obstructive) sub-score, IPSS nocturia question,

BII, IIEF-EF domain score and uroflowmetry parameters. The model included fixed effect of geographic region, ED history, treatment, visit, treatment-by-visit interaction and baseline value as covariate.

In Study LVHJ, analyses were performed on both intent-to-treat (ITT) and per-protocol (PP) populations. The ITT population was the primary analysis population including all randomized subjects who started study medication. The PP population included all ITT subjects who completed the 12-week treatment period and took at least 70% of the prescribed doses in the double-blind treatment period. The primary analysis of mean change in the total IPSS from baseline to endpoint was conducted using an ANCOVA model. The ANCOVA model included centered-baseline value as covariate and fixed effects of treatment group, region, centered-baseline-by-treatment interaction and treatment-by-region interaction. The interaction terms were tested at a significant level of 0.1. If an interaction was not significant, it was removed from the model. The ANCOVA model used in the primary efficacy analyses was also conducted on all key secondary efficacy variables. The above analyses were repeated for the per-protocol population. An additional sensitivity analysis using the same ANCOVA model with one additional fixed effect of ED history was conducted for the total IPSS in the primary analysis population. A repeated measure analysis was performed separately for the total IPSS, the BII and the IIEF-EF domain score. The repeated model included fixed effect of treatment, region, visit, visit-by-treatment interaction, centered-baseline-by-treatment interaction, treatment-by-region interaction and centered-baseline value as covariate. The centered-baseline-by-treatment interaction and treatment-by-region interaction was tested at a significant level of 0.1; if either of them was not statistically significant at the alpha level of 0.1, it was removed from the model. An unstructured covariance matrix was employed.

Reviewer's Comments on the Design: *Studies LVHG and LVHJ were adequately powered to test the superiority of tadalafil 5 mg compared to placebo at week 12 in the reduction of the total IPSS. But for the key secondary variables, Study LVHJ was not adequately powered to test all the corresponding key secondary hypotheses. Methods of handling missing data were appropriate.*

3.2.2.2 Results: Study LVHG

3.2.2.2.1 Subject Disposition

In study LVHG, a total of 1058 subjects randomized across 94 sites in 10 countries. No single site was predominant in terms of subject enrollment. The major reasons for discontinuation were adverse events (4.4%) and subject decision (4.3%) as shown in Table 3. The discontinuation rates due to adverse events appeared to be higher as dose increased. No clear trends across treatment groups in other discontinuation rates were observed. The total ITT population of 1056 subjects was well over the required 990 subjects, while the protocol population of 880 subjects was less than the required sample size for this study.

Table 3. Subject Disposition: Study LVHG

	Placebo (N=212)		Tadalafil 2.5 mg (N=209)		Tadalafil 5 mg (N=212)		Tadalafil 10 mg (N=216)		Tadalafil 20 mg (N=209)		Total (N=1058)	
	n	(%)	n	%	n	%	n	%	n	%	n	%
Randomized	212	(100.0)	209	(100.0)	212	(100.0)	216	(100.0)	209	(100.0)	1058	(100.0)
Complete	185	(87.3)	182	(87.1)	182	(85.9)	175	(81.0)	162	(77.5)	886	(83.7)
Discontinued	26	(12.3)	26	(12.4)	30	(14.2)	41	(19.0)	47	(22.5)	170	(16.1)
Adverse Event	5	(2.4)	4	(1.9)	12	(5.7)	11	(5.1)	14	(6.7)	46	(4.4)
Entry Criteria Not Met	2	(0.9)	6	(2.9)	7	(3.3)	8	(3.7)	4	(1.9)	27	(2.6)
Lack of Efficacy	1	(0.5)	1	(0.5)	2	(0.9)	1	(0.5)	2	(1.0)	7	(0.7)
Lost to follow up	5	(2.4)	3	(1.4)	0	(0.0)	4	(1.9)	6	(2.9)	18	(1.7)
Physician Decision	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	1	(0.5)	3	(0.3)
Protocol Violation	1	(0.5)	0	(0.0)	1	(0.5)	6	(2.8)	4	(1.9)	12	(1.1)
Sponsor Decision	3	(1.4)	4	(1.9)	0	(0.0)	5	(2.3)	0	(0.0)	12	(1.1)
Subject Decision	9	(4.3)	7	(3.4)	7	(3.3)	6	(2.8)	16	(7.7)	45	(4.3)
ITT Population	211	(99.5)	208	(99.5)	212	(100.0)	216	(100.0)	209	(100.0)	1056	(99.8)
Per Protocol Population	184	(86.8)	180	(86.1)	180	(84.9)	175	(81.0)	161	(77.0)	880	(83.2)

Note: A subject with two IDs of 118-2803 and 119-2906 was included in the ITT and Per Protocol population. His data were to be excluded for efficacy analysis due to the reason described in Section 3.2.2.2.3.

3.2.2.2.2 Subject demographic and baseline characteristics

The baseline characteristics such as age, race and body mass index were similar across the treatment groups as shown in Table 4. Baseline IPSS severity, ED history and subject allocation by region were also similar across treatment groups.

3.2.2.2.3 Primary Efficacy

The primary efficacy endpoint was the mean change from baseline in the total IPSS score at Week 12. The sponsor's result showed that tadalafil 5 mg provided statistically significant reduction in the total IPSS score compared with placebo (p-value <0.001). Sponsor's result also showed a dose response as evidenced by the reduction in the least squares mean changes in the total IPSS from baseline to week 12: -2.23 for placebo, -3.81 for tadalafil 2.5 mg, -4.83 for tadalafil 5 mg, -5.13 for tadalafil 10 mg and -5.17 for tadalafil 20 mg. However, our review focused only on the efficacy comparison for the intended tadalafil dose of 5 mg and placebo.

Two placebo subjects did not receive study drug and were excluded from ITT population. In addition, 14 ITT subjects (7 in placebo and 7 in tadalafil 5 mg) were excluded from the efficacy analysis for various reasons: one for multiple participation (tadalafil 20 mg at site 118 and placebo at site 119), one for a discrepancy IPSS between his case report form and source file (placebo), 12 subjects did not have post-baseline measurement (5 in placebo and 7 in tadalafil 5 mg).

Table 4. Subject Demographic and Baseline Characteristics: Study LVHG (ITT)

Parameters	Placebo (N=211)	Tadalafil 2.5 mg (N=208)	Tadalafil 5 mg (N=212)	Tadalafil 10 mg (N=216)	Tadalafil 20 mg (N=209)	Total (N=1056)
Age						
Main Age (SD)	61.7 (7.69)	62.0 (8.42)	61.9 (8.17)	62.2 (7.20)	62.6 (8.09)	62.1 (7.91)
Race						
African	3 (1.4)	3 (1.4)	7 (3.3)	5 (2.3)	5 (2.4)	23 (2.2)
Caucasian	179 (84.8)	184 (88.5)	179 (84.4)	186 (86.1)	176 (84.2)	904 (85.6)
East Asian	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
Hispanic	29 (13.7)	20 (9.6)	25 (11.8)	24 (11.1)	25 (12.0)	123 (11.7)
West Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.4)	4 (0.4)
BMI Mean (SD)	28.6 (4.40)	28.0 (4.00)	28.6 (3.83)	28.4 (4.26)	28.4 (4.70)	28.4 (4.25)
Mean Post Voided Residual (SD)	58.8 (62.78)	57.9 (60.70)	62.4 (63.43)	58.6 (58.09))	57.9 (62.31)	59.1 (61.38)
Baseline LUTS Severity						
Moderate (<20)	137 (64.93)	139 (66.83)	141 (66.51)	143 (66.20)	141 (67.46)	701 (66.38)
Severe (>=20)	74 (35.07)	69 (33.17)	71 (33.49)	72 (33.33)	68 (32.54)	354 (33.52)
Erectile Dysfunction						
Yes	142(67.30)	135(64.90)	144(67.92)	150(69.44)	145(69.38)	716 (67.80)
No	67(31.75)	71(34.13)	68(32.08)	64(29.63)	61(29.19)	331(31.34)
Unknown	1(0.47)	2(0.96)	0(0.00)	2(0.93)	3(1.44)	8(0.76)
Region						
Australia	4 (1.9)	5 (2.4)	5 (2.4)	6 (2.8)	4 (1.9)	24 (2.3)
Europe	71 (33.7)	70 (33.7)	72 (34.0)	72 (33.3)	72 (34.5)	357 (33.8)
North America	117 (55.5)	117 (56.3)	118 (55.7)	119 (55.1)	114 (54.6)	585 (55.4)
South America	19 (9.0)	16 (7.7)	17 (8.0)	19 (8.8)	19 (9.1)	90 (8.5)

We confirmed the sponsor's result using an ANCOVA model with and without Dunnett multiplicity adjustment as shown in Table 5. The ANCOVA model included fixed effects of treatment, region, and IPSS baseline value as covariate. Although the region had statistically significant effect, but the treatment-by-region interaction effect was not statistically significant at a two-sided alpha of 0.10, indicating no evidence of heterogeneous treatment differences across regions. The missing values were imputed by the last post-treatment observation carried forward (LOCF). The least squares means were -2.2 and -4.8 for placebo and tadalafil 5 mg, respectively. The treatment difference was -2.6 with the 95% confidence interval (CI) of -3.7 to -1.5. No effect of ED history seen when added to the ANCOVA model. The results were also similar based on the per-protocol population.

As a sensitivity analysis, a repeated measure analysis was performed. This model assumed missing at random (MAR) mechanism, and without the need for imputation for the missing values. The model included fixed effect of treatment, region, ED history, visit, treatment-by-visit interaction and total IPSS baseline value as covariate. The treatment difference in the total IPSS change from baseline was -2.7 for Week 12, which was consistent with the result shown in Table 5. In addition, results from BOCF provided similar results.

Table 5. Mean Change from Baseline for Primary Efficacy Endpoint at Week 12: Study LVHG (ITT, LOCF)

Endpoint	Placebo N=204	Tadalafil 5 mg N=205	Difference (95% C.I.)	P-value
Total IPSS				
Baseline (SD)	17.1 (6.37)	17.3 (5.97)		
Change from baseline [a]	-2.2	-4.8	-2.6 (-3.7, -1.5)	<.001

a: Least Square Mean from the ANCOVA model with fixed effects of treatment, region, and IPSS baseline value as covariate.

3.2.2.2.4 Secondary Efficacy

The key secondary endpoint was the mean change from baseline to week 12 in IIEF-EF domain score. The analysis of this endpoint was based on a subset of ITT subjects having a history of ED. The sponsor reported a non-decreasing dose response showing the estimated least squares means of 2.0 in placebo, 5.4 in tadalafil 2.5 mg, 6.8 in tadalafil 5 mg, 7.8 in tadalafil 10 mg, and 9.2 in tadalafil 20 mg.

Table 6 showed the efficacy results of our analysis using ANCOVA model that included fixed effects of treatment, region, and IIEF-EF baseline value as covariate. Although the region had statistically significant effect, but the treatment-by-region interaction effect was not statistically significant at a two-sided alpha of 0.10, indicating no evidence of heterogeneous treatment differences among regions. The least squares means of change from baseline at Week 12 were 2.2 for placebo and 6.9 for tadalafil 5 mg as shown in Table 6. The treatment difference at Week 12 was 4.7 (<0.001) with the 95% CI of 2.9 to 6.5. The ANCOVA model with additional fixed effect of IPSS severity provided consistent results. The analysis on per-protocol population gave similar results.

Table 6. Mean Change from Baseline for Secondary Efficacy Endpoint at Week 12: Study LVHG (ITT, LOCF)

	Placebo N=113	Tadalafil 5 mg N=113	Difference (95% C.I.)	P-value
IIEF-EF domain score				
Baseline Mean (SD)	17.3 (7.95)	15.3 (8.13)		
Change from baseline [a]	2.2	6.9	4.7 (2.9, 6.5)	<.001

a: Least Squares Mean from the ANCOVA model with fixed effects of treatment, region, and IIEF-EF baseline value as covariate.

The impact of the missing values on the IIEF-EF domain score was also investigated by repeated measure approach and the results were consistently similar between the two approaches. The results from BOCF also provided similar results.

3.2.2.2.5 Adjustment for Multiple Comparisons

There was no multiplicity adjustment needed for the primary test of superiority of tadalafil 5 mg over placebo. No multiplicity adjustment was made for the secondary efficacy endpoints.

3.2.2.2.6 Reviewer's Comment on the Efficacy Results

Tadalafil 5 mg resulted in a statistically significant decrease in the total IPSS at Week 12 compared with placebo. The treatment difference was -2.6 with a 95% confidence interval of -3.7 to -1.5. Results remained similar after accounting for missing values at week 12.

3.2.2.3 Results: Study LVHJ

3.2.2.3.1 Subject Disposition

A total of 325 subjects were randomized at 28 sites across 5 countries in study LVHJ. No single site was predominant in terms of enrollment. The total discontinuation rate was 7.7% as shown in Table 7. The majority of discontinuation was due to subject decision (1.8%), followed by ineligibility for not meeting criteria (1.5%). There was one death of an 81-year-old subject possibly related to tadalafil 5 mg. The direct reason for the death was an acute myocardial infarction (MI). Although some discontinuation rates were different between tadalafil 5 mg and placebo group, the magnitude of the discontinuation rate and the size of each discontinuation category did not appear to have a significant impact on the efficacy results. The primary analysis population of 325 subjects was well over the required 302 subjects needed as per protocol.

Table 7. Subject Disposition: Study LVHJ

	Placebo (N=164)		Tadalafil 5 mg (N=161)		Total (N=325)	
	n	(%)	n	%	n	%
Randomized	164	(100.0)	161	(100.0)	325	(100.0)
Complete	152	(92.7)	148	(91.9)	300	(92.3)
Discontinued	12	(7.3)	13	(8.1)	25	(7.7)
Adverse Event	1	(0.6)	2	(1.2)	3	(0.9)
Death	0	(0.0)	1	(0.6)	1	(0.3)
Entry Criteria Not Met	1	(0.6)	4	(2.5)	5	(1.5)
Lack of Efficacy	0	(0.0)	1	(0.6)	1	(0.3)
Lost to follow up	3	(1.8)	0	(0.0)	3	(0.9)
Physician Decision	0	(0.0)	2	(1.2)	2	(0.6)
Protocol Violation	3	(1.8)	1	(0.6)	4	(1.2)
Subject Decision	4	(2.4)	2	(1.2)	6	(1.8)
Primary Analysis Population	164	(100.0)	161	(100.0)	325	(100.0)
Per Protocol Population	152	(92.7)	148	(91.9)	300	(92.3)

3.2.2.3.2 Subject demographic and baseline characteristics

The baseline characteristics such as age, race, and body mass index were similar between the two treatment groups as shown in Table 8. The post voided residual in tadalafil 5 mg group was observed smaller than that in placebo group although the baseline LUTS severity was similar between the two treatment groups. This minor difference may be due to randomness.

3.2.2.3.3 Primary Efficacy

The primary efficacy endpoint was the mean change from baseline in the total IPSS score at Week 12.
We performed analysis using the equivalent ANCOVA model similar to the sponsor's analysis to evaluate the primary efficacy. The model included baseline value as covariate, treatment, region and treatment-by-baseline interaction as fixed effect. The model used the original baseline value as the covariate and the least squares means were evaluated at the average of the baseline values in the entire dataset. The least squares mean changes from baseline in the total IPSS were -3.6 and -5.6 for placebo and tadalafil 5 mg, respectively, as shown in Table 9. The treatment difference was -1.9 with the 95% CI of -3.2 to -0.6. Similar results were also observed using PP population.

Results based on LOCF, BOCF, and repeated measure analyses for missing values were also consistently similar.

Table 8. Subject Demographic and Baseline Characteristics: Study LVHJ (ITT)

Parameters		Placebo (N=164)	Tadalafil 5 mg (N=161)	Total (N=325)
Age (SD)		64.6 (10.03)	65 1 (8.43)	64.9 (9.26)
Race				
	American Indian/Alaska Native	8 (4.9)	9 (5.6)	17 (5.2)
	Asian	0 (0.0)	2 (1.2)	2 (0.6)
	Black or African American	5 (3.1)	3 (1.9)	8 (2.5)
	White	150 (91.5)	146 (96.7)	296 (91.1)
	Multiple	1 (0.6)	1 (0.6)	2 (0.6)
BMI Mean (SD)		28.4 (4.21)	27 1 (3.82)	27.7 (4.07)
Mean Post Voided Residual (SD)		63 3 (59.88)	44 9 (44.87)	54.2 (53.70)
Baseline LUTS Severity				
	Moderate (<20)	110 (67.1)	100 (62.1)	210 (64.6)
	Severe (>=20)	54 (32.9)	61 (37.9)	115 (35.4)
Erectile Dysfunction				
	Yes	112 (68.3)	112 (69.6)	224 (68.9)
	No	52 (31.7)	49(30.4)	101 (31.1)
Region				
	Europe	69 (42.1)	68 (42.2)	137 (42.2)
	Latin America	43 (26.2)	43 (26.7)	86 (26.5)
	United States	52 (31.7)	50 (31.1)	102 (31.4)

Table 9. Mean Change from Baseline for Primary Efficacy Endpoint at Week 12: Study LVHJ (ITT, LOCF)

Endpoint	Placebo N=164	Tadalafil 5 mg N=160	Difference (95% C.I.)	P-value
Total IPSS				
Baseline Mean (SD)	16.6 (5.99)	17.1 (6.06)		
Change from baseline [a]	-3.6	-5.6	-1.9 (-3.2, -0.6)	0.004

a: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IPSS baseline value as covariate.

3.2.2.3.4 Secondary Efficacy

The first key secondary endpoint was the change from baseline in the IIEF-EF domain score. Results based on similar ANCOVA showed that the least squares means were 2.0 and 6.7 for placebo and tadalafil 5 mg groups, respectively (Table 10). The treatment difference was 4.7 and the 95% CI for the difference was from 2.5 to 6.9. Similar results were observed using PP population.

Table 10. Mean Change from Baseline for Secondary Efficacy Endpoint at Week 12: Study LVHJ (ITT Subset with an ED History, LOCF)

	Placebo N=84	Tadalafil 5 mg N=88	Difference (95% C.I.)	P-value
IIEF-EF domain Score				
Baseline Mean (SD)	16.8 (8.68)	14.3 (8.35)		
Change from baseline [a]	2.0	6.7	4.7 (2.5, 6.9)	<.001

a: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and IIEF-EF baseline value as covariate.

As noted earlier, the secondary endpoint based on BII score was not recommended by the Division, and therefore, not evaluated in this review.

Since tadalafil 5 mg statistically significantly improved both the total IPSS and the IIEF-EF domain scores at a two-sided alpha of 0.05, the second key secondary endpoint (the change from baseline of the total IPSS at Week 4) was tested at the same alpha level according to the protocol specified testing sequence. Table 11 showed the least squares means of -3.5 and -5.3 for placebo and tadalafil 5 mg group, respectively. The treatment difference was -1.8 with the 95% CI of -3.0 to -0.6. The p-value for this difference was 0.003. The model including the treatment-by-region effect provided consistent results. Similar results were observed for PP population.

Table 11. Primary Efficacy Endpoint (IPSS) Analysis at week 4: Study LVHJ (ITT, LOCF)

	Placebo N=162	Tadalafil 5 mg N=158	Difference (95% C.I.)	P-value
Total IPSS				
Baseline Mean (SD)	16.6 (5.99)	17.1 (6.06)		
Change from baseline [a]	-3.5	-5.3	-1.8 (-3.0, -0.6)	0.003

a: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IPSS baseline value as covariate.

3.2.2.3.5 Adjustment for Multiple Comparisons

A fixed-sequence testing procedure was used in this study for multiplicity adjustments among the primary and the key secondary efficacy endpoint. Results remained statistically significant after the adjustment.

3.2.2.3.6 Reviewer's Comment on the Efficacy Results

Based on the efficacy data from Study LVHJ, tadalafil 5 mg once daily demonstrated a statistically significant decrease in the total IPSS score compared with placebo at both Weeks 4 and 12. Similarly, results were also statistically significant for the IIEF domain score at Week 12.

3.2.3 ED/BPH indication

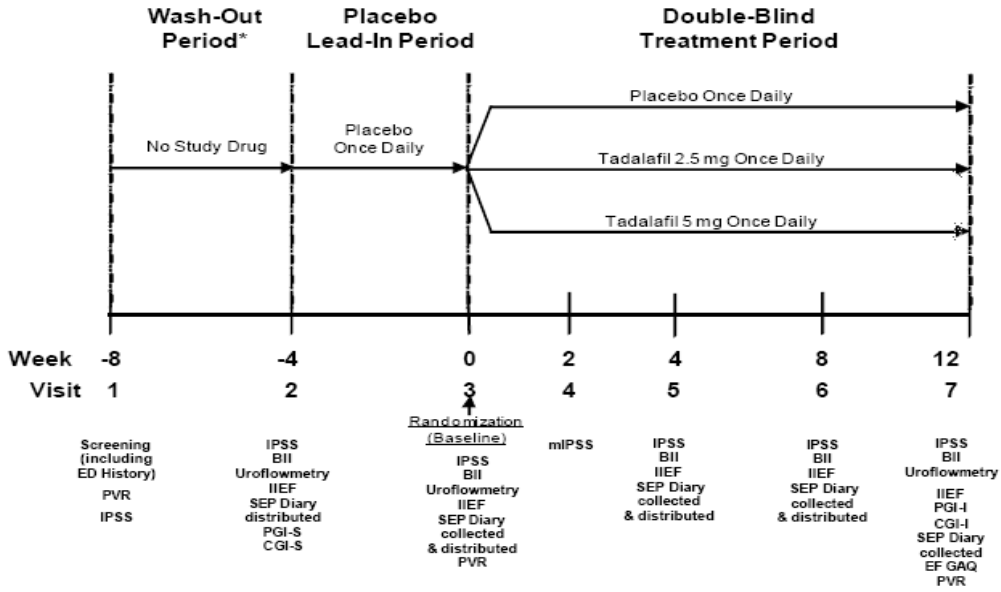
3.2.3.1 Study LVHR

3.2.3.2 Design, Objectives and Endpoints

Objectives and Design: Study LVHR was a randomized, double-blind, placebo-controlled, parallel-group, multinational trial (Table 1). The primary objective was to establish the efficacy of tadalafil once daily for 12 weeks compared with placebo in improving both the total IPSS and the IIEF Erectile Function (EF) Domain score in men with both ED and BPH. A total of 552 men aged at least 45 with both BPH-LUTS (> 6 months) and history of ED (≥3 months) were randomized in a 1:1:1 ratio to receive placebo, tadalafil 5 mg, or tadalafil 2.5 mg. The randomization was stratified by the following 3 factors:

- Baseline LUTS severity (IPSS <20 or IPSS ≥20) at Visit 3
- Baseline ED severity (the IIEF-EF Domain score of 17-30, 11-16, or 1-10 at Visit 3)
- Region (North America [defined as US and Canada], Mexico, or Europe).

As per protocol, the study had 3 periods as illustrated in Figure 1.



*Subjects not taking prohibited BPH, overactive bladder (OAB), or ED treatments may return to the study site for Visit 2 as soon as screening results are reviewed.

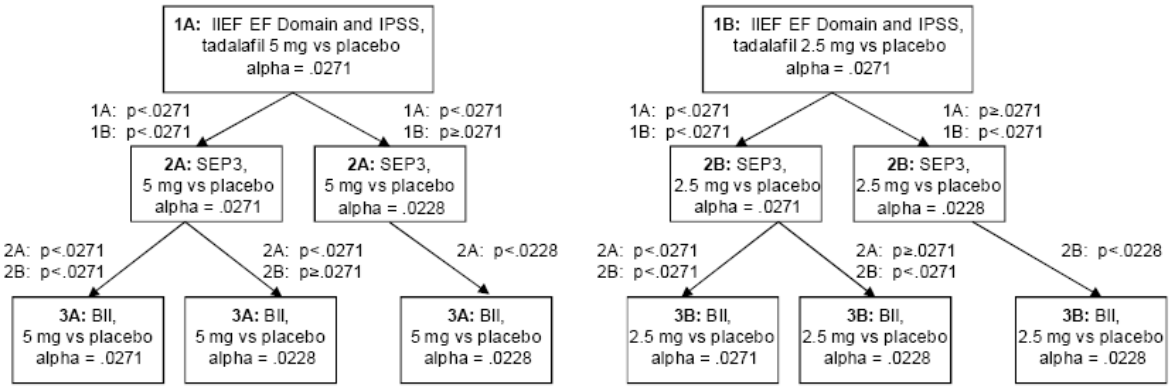
Abbreviations: BII = BPH (benign prostatic hyperplasia) Impact Index; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; ED = erectile dysfunction; EF = erectile function; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; GAQ = Global Assessment Questions; mIPSS = Modified International Prostate Symptom Score; N = number of subjects; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity; PVR = postvoid residual volume; SEP = Sexual Encounter Profile.

Figure 1: Study Periods (from Sponsor's Figure LVHR.9.1)

Primary Efficacy Endpoints: There were two co-primary efficacy endpoints: the changes from baseline to Week 12 in the total IPSS and the IIEF-EF Domain score.

Secondary Efficacy Endpoint: The two key secondary efficacy endpoints were the changes from baseline to Week 12 in the mean BII score and the mean percentage of "Yes" responses to the SEP3 (successful intercourse)

Determination of Sample Size: The sample size was calculated to test two null hypotheses of no differences in the mean change from baseline to the end of therapy in the total IPSS and the IIEF-EF Domain score between tadalafil and placebo. These two null hypotheses were to be tested together with the two key secondary endpoints. The alpha level for each test sequence was decided as two-sided 0.0271 based on a Dunnett-Bonferroni gatekeeping procedure illustrated by Figure 2 below.



Abbreviations: BII = Benign Prostatic Hyperplasia (BPH) Impact Index, EF = erectile function, IIEF = International Index ofErectile Function, IPSS = International Prostate Symptom Scale, SEP3 = Sexual Encounter Profile Question 3.

Figure 2. Sponsor's Dunnett-Bonferroni Gatekeeping Procedure

A total of 552 men, for 184 men per treatment group, were decided to be enrolled based on the following:

- Placebo-adjusted mean difference in the total IPSS of 1.9 points with a standard deviation of 6.0
- Placebo-adjusted mean difference in the IIEF-EF Domain score of 2.6 points with a standard deviation of 8.0
- A non-evaluable rate of 5%
- A power of 80%

Analysis Population: The primary analysis (PA) population included all subjects who were randomized and started study medication. The treatment for each subject was the randomized treatment. The per-protocol (PP) population included all PA subjects who competed the 12-week treatment period and took ≥ 70% of the prescribed doses in the double-blind study period.

Handling of Missing Data: The missing values at week 12 were imputed by post-baseline data using the method of last observation carried forward [LOCF]. Repeated measure analyses of variance were also conducted to evaluate the sensitivity of LOCF method. If a response to an IPSS or BII questionnaire item was missing, then the item response was set to missing. The IIEF score of each domain was imputed if fewer than 30% of the component questions within that domain score were missing for a subject. The missing questions were imputed with the mean of the non-missing questions for that domain for that subject.

Pool of Sites: Study sites were not pooled.

Multiplicity Adjustment: A Dunnett-Bonferroni gatekeeping procedure was used to address the multiplicity of tests as illustrated in Figure 2. The 3-step algorithm was:

- Step 1: The 2 dose-placebo comparisons (2.5, 5 mg vs. placebo) were performed for the total IPSS and the IIEF-EF Domain score at a two-sided alpha level of 0.0271.
- Step 2: The dose-placebo comparisons corresponding to the doses which were significant in Step 1 were performed for the first secondary endpoint (SEP3) at an alpha level illustrated in Figure 2.
- Step 3: The dose-placebo comparisons corresponding to the does which were significant in Step 2 were performed for the second secondary endpoint (BII) at an alpha level illustrated in Figure 2.

Statistical Methods: The primary analysis was based on the PA population defined above, which is essentially the ITT population. The primary and two key secondary endpoints were analyzed using an ANCOVA model. The model included fixed effects of treatment, region, and centered-baseline value as covariate. Interaction terms for centered-baseline value-by-treatment and region-by-treatment were evaluated and included in the model if any of these terms was significant at an alpha level of 0.10. The above analyses were repeated on the PP population.

A repeated measure analysis of variance was conducted for both the primary and secondary variables. The repeated time points of post-baseline measurement were Weeks 4, 8, and 12. The model included fixed effects of treatment, region, visit, visit-by-treatment interaction, centered-baseline-by-treatment interaction (if significant at 0.01), region-by-treatment interaction (if significant at 0.01) and centered-baseline value as covariate. If the model did not converge, then a compound symmetric covariance structure was used. Otherwise, ad hoc analyses with alternative model terms and covariance matrices were to be examined to identify a model that converged.

Reviewer's Comments on the Design:

The multiplicity adjustment by Dunnett-Bonferroni's gate-keeping procedure was appropriate. The study power for the secondary endpoints was not considered during the sample size calculation, and therefore, conclusions for these endpoints were less robust.

3.2.3.3 Results: Study LVHR

3.2.3.3.1 Subject Disposition

At 54 sites across 9 countries, a total of 606 subjects were randomized approximately equally to the treatment groups as shown in Table 12. No single site was predominant in terms of subject enrollment. The number of enrollment ranged from 1 to 44. A total of 80 subjects discontinued the study. The major reasons for the discontinuation were subject decision (3.1%), entry criteria not met (2.8%), protocol violation (2.3%), and lack of efficacy (2.0%). Although the discontinuation rates were not similar across the treatment groups, the magnitude of the discontinuation did not appear to impact the efficacy results. The primary analysis population of 606 subjects was well over the planned 552 subjects, while the per-protocol population of 525 subjects was also in the acceptable range.

3.2.3.3.2 Subject demographic and baseline characteristics

The subject baseline characteristics such as age, race, body mass index, and post voided residual were similar across the treatment groups as shown in Table 13. Other baseline characteristics, including baseline LUTS severity, baseline ED severity, and region, were also approximately equally distributed across the treatment groups.

Table 12. Subject Disposition: Study LVHR

	Placebo (N=200)		Tadalafil 2.5 mg (N=198)		Tadalafil 5 mg (N=208)		Total (N=606)	
	n	(%)	n	%	n	%	n	%
Randomized	200	(100.0)	198	100.0)	208	100.0)	606	100.0)
Complete	170	(85.0)	172	(86.9)	184	(88.5)	526	(86.8)
Discontinued	30	(15.0)	26	(13.1)	24	(11.5)	80	(13.2)
Adverse Event	3	(1.5)	2	(1.0)	6	(2.9)	11	(1.8)
Death	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Entry Criteria Not Met	3	(1.5)	8	(4.0)	6	(2.9)	17	(2.8)
Lack of Efficacy	8	(4.0)	1	(0.5)	3	(1.4)	12	(2.0)
Lost to follow up	1	(0.5)	1	(0.5)	3	(1.4)	5	(0.8)
Physician Decision	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Protocol Violation	6	(3.0)	6	(3.0)	2	(1.0)	14	(2.3)
Subject Decision	8	(4.0)	7	(3.5)	4	(1.9)	19	(3.1)
Primary Analysis Population	200	(100.0)	198	(100.0)	208	(100.0)	606	(100.0)
Per Protocol Population	170	(85.0)	172	(86.9)	183	(88.0)	525	(86.6)

Table 13. Subject Demographic and Baseline Characteristics: Study LVHR (ITT)

Parameters	Placebo (N=200)	Tadalafil 2.5 mg (N=198)	Tadalafil 5 mg (N=208)	Total (N=606)
Age				
Main Age (SD)	62.9 (8.22)	62.2 (7.56)	62.5 (8.43)	62.6 (8.08)
Race				
American Indian or Alaska Native	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Asian	2 (1.0)	6 (3.0)	6 (2.9)	14 (2.3)
Black or African American	8 (4.0)	9 (4.6)	6 (2.9)	23 (3.8)
White	190 (95.0)	181 (91.4)	194 (93.3)	565 (93.2)
Multiple	0 (0.0)	1 (0.5)	2 (1.0)	3 (0.5)
BMI Mean (SD)	28.6 (4.80)	27.7 (3.86)	28.0 (4.18)	28.1 (4.30)
Mean Post Voided Residual (SD)	55.5 (60.46)	53.0 (51.24)	51.1 (60.91)	53.2 (57.72)
Baseline LUTS Severity				
Moderate (<20)	122 (61.0)	123 (62.1)	124 (59.6)	369 (60.9)
Severe (>=20)	78 (39.0)	74 (37.4)	84 (40.4)	236 (38.9)
Baseline ED Severity				
Mild (17-30)	93 (46.5)	104 (52.5)	99 (47.6)	296 (48.8)
Moderate (11-16)	49 (24.5)	46 (23.2)	54 (26.0)	149 (24.6)
Severe (1-10)	58 (29.0)	48 (24.2)	55 (26.4)	161 (26.6)
Region				
Europe	84 (42.0)	78 (39.4)	87 (41.8)	249 (41.1)
Mexico	22 (11.0)	27 (13.6)	27 (13.0)	76 (12.5)
North America	94 (47.0)	93 (47.0)	94 (45.2)	281 (46.4)

3.2.3.3.3 Primary Efficacy

Two co-primary endpoints considered in this study were the changes from baseline in (1) the total IPSS and (2) the IIEF-EF domain score. We performed a statistical analysis using an ANCOVA model equivalent to the sponsor's analysis. The model used the original baseline value as the covariate compared to the sponsor's centered baseline. The least squares means were evaluated at the average of the baseline values in the entire dataset. As per protocol, a gatekeeping multiple testing procedure was used to control the type-I error rate in the tests for the two tadalafil doses. The first step was to test the improvement of the co-primary endpoints in each of the two tadalafil doses compared with placebo at a two-sided alpha of 0.0271 as described in Figure 2 in Section 3.2.2.2. The second step was to be performed within each dose sequence if the treatment

differences in both two co-primary endpoints were statistically significant. Otherwise, the test would be stopped (Figure 2).

In general, subjects with missing baseline values or no post-baseline primary efficacy measurement were excluded from the primary efficacy analysis. In addition, 3 subjects (2 in tadalafil 2.5 mg, and 1 in placebo) were excluded from the primary IPSS analysis due to IPSS discrepancies between their CRFs and source files. Eight subjects (5 in tadalafil 2.5 mg, 1 in tadalafil 5 mg, and 2 in placebo) were excluded from the primary IIEF-EF analysis due to IIEF discrepancies between their CRFs and source files.

Tadalafil 5 mg statistically significantly improved the total IPSS and the IIEF-EF domain score for the patients with both BPH and ED as shown in Table 14. The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, region, and total IPSS baseline value as covariate. The ANCOVA model for the change from baseline IIEF-EF score included fixed effects of treatment, region, treatment-by-baseline interaction, and IIEF-EF baseline value as covariate. The least squares means for the total IPSS were -3.8 and -6.1 for placebo and tadalafil 5 mg, respectively. The treatment difference for the total IPSS was -2.3 with the 95% CI of -3.5 to -1.2. The least squares means for the IIEF-EF domain score were 1.9 and 6.5 for placebo and tadalafil 5 mg, respectively. The treatment difference for the IIEF-EF domain score was 4.6 with the 95% CI of 3.3 to 5.9.

Table 14. Mean Change from Baseline for Co-primary Efficacy Endpoints for Tadalafil 5 mg at Week 12: Study LVHR (PA), LOCF)

		Placebo	5 mg Tadalafil	Difference (95% C.I.)	P-value
Total IPSS					
	N	193	206		
	Baseline Mean (SD)	18.2 (5.33)	18.5 (5.78)		
	Change from baseline [a]	-3.8	-6.1	-2.3 (-3.5, -1.2)	<.001
IIEF-EF Domain Score					
	N	188	202		
	Baseline Mean (SD)	15.6 (6.87)	16.5 (7.22)		
	Change from baseline [b]	1.9	6.5	4.6 (3.3, 5.9)	<.001

a: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and total IPSS baseline value as covariate.
b: Least squares mean from the ANCOVA modelwith fixed effects of treatment, region, treatment-by-baseline interaction, and IIEF-EF baseline value as covariate.

Results after imputing for missing values using LOCF, BOCF, and repeated measure analysis were similar.

Tadalafil 2.5 mg did not statistically significantly improve the total IPSS for the patients with both BPH and ED as shown in Table 15. Since the p-value for the treatment difference in the total IPSS for tadalafil 2.5 mg was 0.211 much greater than 0.0271, tadalafil 2.5 mg did not show a statistically significant improvement in the total IPSS. The second test for tadalafil 2.5 mg was not performed according to the gatekeeping testing procedure.

3.2.3.3.4 Secondary Efficacy

Tadalafil 5 mg statistically significantly improved the success rate of the SEP3 (erection long enough to have successful intercourse) as shown in Table 16. The ANCOVA model included fixed effects of treatment,

region, treatment-by-baseline interaction, and SEP3 baseline value as covariate. According to the gatekeeping multiple testing procedures, the test on the SEP3 was performed sequentially at a two-sided alpha of 0.0228. The least squares means were 15.3% and 33.9% for placebo and tadalafil 5 mg, respectively. The treatment difference in the success rate of the SEP3 between tadalafil 5 mg and placebo was 18.7% with the 95% CI of 11.9% to 25.4%.

Table 15. Mean Change from Baseline for Primary Efficacy Endpoints for Tadalafil 2.5 mg at Week 12: Study LVHR (PA, LOCF)

		Placebo	2.5 mg Tadalafil	Difference (95% C.I.)	P-value
Total IPSS					
	N	193	189		
	Baseline Mean (SD)	18.2 (5.33)	18.2 (5.62)		
	Change from baseline [a]	-3.8	-4.5	-0.7 (-1.9, 0.4)	0.211
IIEF-EF Domain Score					
	N	188	186		
	Baseline Mean (SD)	15.6 (6.87)	16.6 (6.95)		
	Change from baseline [b]	1.9	5.3	3.4 (2.1, 4.8)	<.001

a: Least squares mean from the ANCOVA model with fixed effects of treatment, region, and total IPSS baseline value as covariate.
b: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and IIEF-EF baseline value as covariate.

Table 16. Mean Change from Baseline for Secondary Efficacy Endpoint at Week 12: Study LVHR (PA, LOCF)

		Placebo N=187	5 mg Tadalafil N=199	Difference (95% C.I.)	P-value
SEP3 (percentage of yes)					
	Baseline Mean (SD)	36.3 (38.7)	42.7 (40.0)		
	Change from baseline [a]	15.3	33.9	18.7 (11.9, 25.4)	<.001

a: Least squares mean from the ANCOVA model with fixed effects of treatment, region, treatment-by-baseline interaction, and SEP3 baseline value as covariate.
Note: The post-treatment SEP3 success rate was calculated based on the last visit. The sponsor calculated this rate cumulatively based on the period from the first post-treatment visit to the last visit. In sponsor's report, the LS mean changes from baseline were 12.0 and 31.7 for placebo and tadalafil 5 mg, respectively. The treatment different was 19.7% with the 95% CI of 14.2 to 25.2.

As noted in Table 16, we used a different method to calculate the SEP3 success rate. Although the sponsor's results were reproduced, we need to look at other methods for consistency of the results.

Results after imputing for missing values using LOCF, BOCF, and repeated measure analysis were similar.

3.2.3.3.5 Adjustment for Multiple Comparisons

The multiplicity for the tests was adjusted using the gatekeeping multiple testing procedures illustrated in Section 3.2.2.2.

3.2.3.3.6 Reviewer's Comment on the Efficacy Results in Study LVHR

Tadalafil 5 mg showed a statistically significant improvement in the total IPSS, the IIEF-EF domain score, and success rate in the SEP3. Tadalafil 2.5 mg did not provide a statistically significant improvement in the total IPSS.

3.3 Evaluation of Safety

Evaluation of safety is reported in the clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subjects whose data were excluded from the primary and the secondary analyses were also excluded from the pertinent subgroup analyses. The ANCOVA models used in subgroup analysis were similar to the models in the corresponding primary analyses, which were different from the sponsor's models. We did not disagree with the sponsor's approach, but need to look at other methods for consistency of the results.

For gender, the subgroup analysis was not performed since all study subjects were male.

For Race, Caucasian was the predominant subgroup. Among all ITT subjects, the proportion of Caucasian was 85.6%, 91.1%, and 93.2% in Studies LVHG, LVHJ, and LVHR, respectively. Sparse sample in other race was observed. There was no need to perform statistical analysis in race subgroups with sparse data. The statistical inferences in Studies LVHG, LVHJ, and LVHR were mainly applied to Caucasian.

For age subgroup (tadalafil 5 mg and placebo) who had at least one change from baseline total IPSS value, there were 262 (61.9%), 172 (52.9%), and 240 (60.3%) subjects aged ≤ 65 in studies LVHG, LVHJ, and LVHR, respectively. Likewise, there were 379 (89.6%), 274 (84.3%), and 367 (92.2%) subjects aged <75 in studies LVHG, LVHJ, and LVHR, respectively. Age group did not appear to have a significant impact on the treatment difference in the total IPSS as shown in Tables 17-19. Similar results were observed for the IIEF-EF domain score in Table 20.

For geographic region (tadalafil 5 mg and placebo) among subjects who had at least one change from baseline total IPSS as shown in Tables 21-23, there were 228 (53.9%), 30 (7.1%), 142 (33.6%), and 9 (2.1%) subjects in North America, South America, Europe, and Australia, respectively in Study LVHG; There were 102 (31.4%), 136 (41.8%), and 86 (26.5%) subjects in US, Europe, and Latin America, respectively in Study LVHJ; There were 183 (46.0%), 169 (42.5%), and 48 (12.1%) subjects in North America, Europe, and Mexico, respectively in Study LVHR. The treatment differences in the total IPSS between tadalafil 5 mg and placebo were observed very smaller in Latin America and Mexico compared with those in Europe, North America/US and Australia. However, the sample sizes in Latin America and Mexico were too small to draw a valid statistical conclusion. Table 24 showed that there was no significant regional impact observed for the treatment differences in the IIEF-EF domain score.

Due to small sample sizes in the subgroups, all the above subgroup analyses were considered exploratory.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major statistical issues were noted regarding the statistical analyses of the efficacy data in this application. This review did not evaluate one of the secondary endpoint: BII, since it was not considered a valid PRO based instrument by the Division. In study LVHG and LVHR, 12 subjects had inconsistent IPSS (4) and the IIEF-EF domain scores (8) between their CRFs and source files. These subjects were excluded from the FDA efficacy analysis, and the results remained consistently similar. Handling of missing data in all studies was addressed appropriately. There was no pre-specified multiplicity adjustment for the secondary endpoints in the phase 2/3 study (LVHG). However, the protocol pre-specified the multiple testing procedures in both phase-3 studies.

In Study LVHG, tadalafil 5 mg statistically significantly decreased the total IPSS score at Week 12 compared with placebo. The treatment difference between tadalafil 5 mg and placebo was -2.6 with the 95% confidence interval of -3.7 to -1.5. In Study LVHJ, tadalafil 5 mg also statistically significantly decreased the total IPSS compared with placebo at both Weeks 4 and 12. At Week 4, the treatment difference in the total IPSS between tadalafil 5 mg and placebo was -1.8 with the 95% CI of -3.0 to -0.6. At Week 12, the treatment difference in the total IPSS between tadalafil 5 mg and placebo was -1.9 with the 95% CI of -3.2 to -0.6. In the patients with additional ED history, tadalafil 5 mg also statistically significantly increased the IIEF-EF domain score compared with placebo. At Week 12, the treatment difference in the IIEF-EF domain score was 4.7 with the 95% CI of 2.5 to 6.9.

In Study LVHR, tadalafil 5 mg showed statistically significant improvement in the total IPSS, the IIEF-EF domain score, and the SEP3 success rate compared with placebo. The treatment difference in the total IPSS between tadalafil 5 mg and placebo was -2.3 with the 95% CI of -3.5 to -1.2. The treatment difference in the IIEF-EF domain score between tadalafil 5 mg and placebo was 4.6 with the 95% CI of 3.5 to 5.9. The treatment difference in the SEP3 success rate between tadalafil 5 mg and placebo was 18.7% with the 95% CI of 11.9% to 25.4%.

5.2 Conclusions and Recommendations

Data from Studies LVHG and LVHJ demonstrated that tadalafil 5 mg once daily statistically significantly improved the total IPSS score in men with BPH-LUTS at Week 12, compared with placebo.

Data from Study LVHR also demonstrated that tadalafil 5 mg once daily statistically significantly improved the total IPSS, increased the IIEF-EF domain score and the successful intercourse rate (SEP3), compared with placebo at Week 12. Data from all ITT subjects and data from ED subgroup in Study LVHJ also demonstrated that tadalafil 5 mg statistically significantly improved the total IPSS and the IIEF-EF domain score compared with placebo, respectively.

From a statistical perspective, data from all three studies: LVHG, LVHJ and LVHR supports the efficacy of tadalafil 5 mg once daily in the treatment of men with BPH or men with both BPH and ED, compared with placebo.

APPENDICE: Subgroup Analysis Tables 19-24

Table 17. Total IPSS by Age Subgroup in Study LVHG at Week 12 (ITT, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=211	Tadalafil 5 mg N=212	Placebo	Tadalafil 5 mg		
Age ≤ 65	17.1 (6.75) N=132	17.1 (6.01) N=130	-2.7	-5.0	-2.3 (-3.7, -1.0)	<.001
Age >65	17.1 (5.65) N=72	17.6 (5.93) N=75	-1.4	-4.6	-3.3 (-5.1, -1.4)	<.001
Age < 75	17.0 (6.44) N=192	17.1(5.90) N=187	-2.1	-5.1	-2.9 (-4.0, -1.8)	<.001
Age ≥ 75	17.8 (5.24) N=12	19.7 (6.40) 18	-3.5	-3.0	0.5 (-4.1, 5.0)	0.840

Note: The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, region, and total IPSS baseline value as covariate.

Table 18. Total IPSS by Age Subgroup in Study LVHJ at Week 12 (ITT, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=164	Tadalafil 5 mg N=161	Placebo	Tadalafil 5 mg		
Age ≤ 65	16.8 (6.17) N=86	17.2 (6.67) N=86	-4.4	-6.0	-1.6 (-3.5, 0.3)	0.095
Age > 65	16.3 (5.80) N=78	17.1 (5.31) N=74	-2.8	-4.9	-2.1 (-3.8, -0.4)	0.014
Age < 75	16.3 (6.01) N=137	17.1 (6.27) N=137	-3.8	-5.7	-1.9 (-3.3, -0.4)	0.010
Age ≥ 75	17.9 (5.80) N=27	17.1 (4.74) N=23	-2.6	-4.8	-2.2 (-5.5, 1.1)	0.187

Note: The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, region, treatment-by-baseline interaction and total IPSS baseline value as covariate.

Table 19. Total IPSS by Age Subgroup in Study LVHR at Week 12 (PA, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=200	Tadalafil 5 mg N=198	Placebo	Tadalafil 5 mg		
Age ≤ 65	18.4 (5.81) N=117	19.1 (6.08) N=123	-3.5	-6.3	-2.7 (-4.2, -1.2)	<.001
Age > 65	18.0 (4.51) N=76	17.4 (5.18) N=83	-4.1	-5.7	-1.6 (-3.4, 0.2)	0.073
Age < 75	18.3 (5.47) N=176	18.6 (5.83) N=191	-3.7	-6.0	-2.3 (-3.5, -1.1)	<.001
Age ≥ 75	17.4 (3.60) N=17	16.1 (4.58) N=15	-5.2	-8.8	-3.5 (-7.7, 0.6)	0.093

Note: The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, region, and total IPSS baseline value as covariate.

Table 20. IIEF-EF Domain Score by Age Subgroup in Study LVHR at Week 12 (PA, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=200	Tadalafil 5 mg N=198	Placebo	Tadalafil 5 mg		
Age ≤ 65	16.9 (6.50) N=112	17.6 (6.97) N=121	1.8	6.1	4.3 (2.7, 6.0)	<.001
Age > 65	13.8 (7.06) N=75	15.0 (7.36) N=81	1.9	7.0	5.2 (3.0, 7.3)	<.001
Age < 75	16.2 (6.73) N=170	16.7 (7.15) N=187	1.9	6.3	4.5 (3.1, 5.8)	<.001
Age ≥ 75	10.0 (5.93) N=17	14.1 (7.94) N=15	3.1	9.5	6.4 (1.3, 11.5)	0.016

Note: The ANCOVA model for the change from baseline IIEF-EF domain score included fixed effects of treatment, region, treatment-by-baseline interaction and baseline IIEF-EF domain score as covariate.

Table 21. Total IPSS by Region Subgroup in Study LVHG at Week 12 (ITT, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=211	Tadalafil 5 mg N=212	Placebo	Tadalafil 5 mg		
North America	17.8 (5.85) N=113	18.1 (6.02) N=115	-2.2	-4.5	-2.3 (-3.7, -0.9)	0.002
South America	10.2 (7.37) N=17	15.0 (10.26) N=13	-1.0	-2.8	-1.8 (-6.3, 2.7)	0.430
Europe	17.5 (5.88) N=70	16.6 (4.56) N=72	-3.1	-6.1	-3.1 (-5.0, -1.1)	0.002
Australia	20.5 (8.89) N=4	14.0 (6.56) N=5	0.7	-4.8	-5.4 (-11.5, 0.7)	0.078

Note: The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, and total IPSS baseline value as covariate.

Table 22. Total IPSS by Region Subgroup in Study LVHJ at Week 12 (ITT, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=164	Tadalafil 5 mg N=161	Placebo	Tadalafil 5 mg		
United States	19.0 (5.91) N=52	19.3 (5.88) N=50	-3.3	-6.5	-3.2 (-5.7, -0.6)	0.0161
Europe	16.7 (5.33) N=69	17.1 (5.13) N=67	-3.8	-6.1	-2.3 (-4.2, -0.4)	0.020
Latin America	13.5 (5.84) N=43	14.5 (6.71) N=43	-3.8	-3.8	0.01 (-2.40, 2.43)	0.991

Note: The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, region, treatment-by-baseline interaction and total IPSS baseline value as covariate.

Table 23. Total IPSS by Region Subgroup in Study LVHR at Week 12 (PA, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=200	Tadalafil 5 mg N=198	Placebo	Tadalafil 5 mg		
North America	18.0 (5.05) N=89	18.5 (5.99) N=93	-2.4	-6.1	-3.7 (-5.4, -2.0)	<.001
Europe	18.0 (5.04) N=82	17.6 (4.94) N=87	-4.9	-6.3	-1.4 (-3.0, 0.2)	0.080
Mexico	20.0 (7.16) N=22	21.3 (6.86) N=26	-6.0	-6.4	-0.3 (-4.5, 3.8)	0.872

Note: The ANCOVA model for the change from baseline IPSS total score included fixed effects of treatment, region, and total IPSS baseline value as covariate

Table 24. IIEF-EF Domain Score by Region Subgroup in Study LVHR at Week 12 (PA, LOCF)

	Baseline Mean (SD)		LS Mean change from baseline		Difference (95% C.I.)	P-value
	Placebo N=200	Tadalafil 5 mg N=198	Placebo	Tadalafil 5 mg		
North America	15.4 (7.61) N=85	15.9 (8.12) N=91	1.2	5.5	4.4 (2.2, 6.5)	<.001
Europe	15.8 (6.36) N=81	17.0 (5.99) N=85	2.3	7.6	5.3 (3.5, 7.2)	<.001
Mexico	16.0 (5.78) N=22	17.1 (7.66) N=26	2.8	6.4	3.5 (0.3, 6.8)	0.034

Note: The ANCOVA model for the change from baseline IIEF-EF domain score included fixed effects of treatment, region, treatment-by-baseline interaction and baseline IIEF-EF domain score as covariate.

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/s/

XIN FANG
09/15/2011

MAHBOOB SOBHAN
09/15/2011

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 21-368 **Applicant: Eli Lilly and Company** **Stamp Date: 12-06-2011**

Drug Name: Cialis® **NDA/BLA Type: sNDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	√			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.	√			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

There are no review issues noted at this time.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint / Analysis	Sponsor's findings
H6D-MC-LVHG	*Phase 2/3, randomized, placebo-controlled, double-blind, multinational*	*Planned 198* *Randomized* *Tadalafil 2.5 mg 209* *Tadalafil 5.0 mg 212* *Tadalafil 10 mg 216* *Tadalafil 20 mg 209* *Placebo 212*	*Primary endpoint the change in IPSS total score from baseline to Week 12* *Primary analysis a permutation test + ANCOVA model*	*Median;* *Tadalafil 2.5 mg -3, p=0.0043* *Tadalafil 5 mg -4, p<0.001* *Tadalafil 10 mg -5, p<0.001* *Tadalafil 20 mg -5, p<0.001* *Placebo; -2* *LS mean;* *Tadalafil 2.5 mg -3.81, p =0.005* *Tadalafil 5 mg -4.83, p<0.001* *Tadalafil 10 mg -5.13, p<0.001* *Tadalafil 20 mg -5.17, p<0.001* *Placebo -2.23*
H6D-MC-LVHJ	*Phase 3, randomized, double-blind, placebo-controlled, multinational*	*Planned 151* *Randomized* *Tadalafil 5.0 mg 161* *Placebo 164*	*Primary endpoint the change in IPSS total score from baseline to Week 12* *Primary analysis ANCOVA model*	*LS mean;* *Tadalafil 5 mg -5.6, p=0.004* *Placebo -3.6*
H6D-MC-LVHR	*Phase 3, randomized, placebo-control, double-blind, multinational*	*Planned 184* *Randomized* *Tadalafil 2.5 mg 198* *Tadalafil 5.0 mg 208* *Placebo 200*	*Co-primary endpoints the change from baseline to Week 12 in* *--IPSS total score* *--IIEF EF domain score* *Primary analysis ANCOVA model*	*LS mean for IPSS total;* *Tadalafil 2.5 mg -4.6, p =0.181* *Tadalafil 5 mg -6.1, p<0.001* *Placebo -3.8* *LS mean for IIEF EF domain;* *Tadalafil 2.5 mg 5.2, p<0.001* *Tadalafil 5 mg 6.5, p<0.001* *Placebo 1.8*
H6D-MC-LVHS	*Phase 3, randomized,* double-blind, placebo-controlled	*Planned 150* *Randomized* *Tadalafil 5.0 mg 158* *Placebo 160*	*Primary endpoint proportion of men with BPH-LUTS experiencing treatment-emergent dizziness* *Primary analysis one-side Fisher's exact test*	*Proportion of men with dizziness;* *Tadalafil 5 mg* + α blocker *7.0%, p=0.403* *Placebo* + α blocker *5.7%*

Xin Fang, Ph.D. — Jan. 31, 2011

Reviewing Statistician — Date

Mahboob Sobhan, Ph.D. — Jan. 31, 2011

Supervisor/Team Leader — Date

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/s/

XIN FANG
01/31/2011

MAHBOOB SOBHAN
01/31/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
SUPPLEMENT REVIEW Addendum

NDA: 021368	Submission Dates: Dec. 3, 2010
Brand Name	Cialis
Generic Name	Tadalafil
Primary Reviewer	CAPT E. Dennis Bashaw, Pharm.D.
Secondary Reviewer	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Lilly
Submission Type	Efficacy Supplemental NDAs #20 and 21
Formulation; Strength(s)	Film coated tablet; 5 mg
Indication	S-20 The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) S-21 The treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (ED/BPH)

Addendum

Since the execution of this review and its placement in DARRTS (September 16th, 2011), there has been additional communication with the sponsor regarding labeling. As of today September 27th, 2011, the sponsor has agreed to all of the Clinical Pharmacology based labeling recommendations. Based on their agreement, the Division of Clinical Pharmacology-3 considers all of the review issues closed and the application to be acceptable under the provisions of 21CFR320.

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/s/

EDWARD D BASHAW

09/27/2011

As I am the primary author of these supplements, I have delegated secondary sign-off to Dr. Myong-Jin Kim as the Repro/Uro Clin Pharm Team Leader

MYONG JIN KIM

09/27/2011

OFFICE OF CLINICAL PHARMACOLOGY SUPPLEMENT REVIEW

NDA: 021368	Submission Dates: Dec. 3, 2010
Brand Name	Cialis
Generic Name	Tadalafil
Primary Reviewer	CAPT E. Dennis Bashaw, Pharm.D.
Secondary Reviewer	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Lilly
Submission Type	Efficacy Supplemental NDAs #20 and 21
Formulation; Strength(s)	Film coated tablet; 5 mg
Indication	S-20 The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) S-21 The treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (ED/BPH)

Executive Summary

Tadalafil (LY450190, CIALIS®, ADCIRCA®) is an orally administered, potent, and selective inhibitor of the phosphodiesterase type 5 (PDE5) enzyme. According to the sponsor, in vitro studies show that tadalafil is a more potent inhibitor of the PDE5 isoenzyme than of the other phosphodiesterase isoenzymes. It is currently available in the US under two brand names for different discrete populations:

CIALIS® is indicated for erectile dysfunction (ED).

ADCIRCA® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

The two supplements being reviewed here (20, 21) are seeking additional indications for Cialis:

Supplement 20: The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)

Supplement 21: The treatment of ED and the signs and symptoms of BPH (ED/BPH)

For the Clinical Pharmacology development of these supplements the sponsor conducted one new trial (LVHN)[1] and included the results of an additional NON-IND trial (LVIA) in response to a pre-NDA meeting request to provide additional information on the use of tadalafil in Asian subjects.

Recommendation

The results of the submitted trials did not reveal any significant changes in the pharmacokinetics of tadalafil. The application is acceptable from a Clinical Pharmacology standpoint provided that appropriate labeling is developed to incorporate the information into the package insert.

Post-Marketing Commitments

None

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Study LVHN

The results of Study LVHN demonstrated that there was no statistically significant difference (approximately 10-15%) in the AUC0-24 and Cmax of tadalafil between the elderly (70 to 76 years old) and young (48 to 59 years old) subjects with BPH enrolled following single- and multiple-dose administration of tadalafil 20 mg once daily for 10 days. The doses used in study LVHN represent a significant increase over the anticipated clinical dose of 5 mg once a day. While the sponsor did not specifically study subjects with BPH/ED, as these populations are unlikely to exhibit marked metabolic or distributional differences, a separate study in the BHP/ED population is not required.

The results of this study are somewhat in conflict with the current label as a previous study using healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. While these findings are at odds here, part of the explanation is likely due to the fact that the "young subjects" in this study are "young" in only a relative sense. The subjects in this trial were between the ages of 48-59, a significantly different population than the 19-45 age group mentioned in the label. Thus it is quite possible, assuming that the reduction in clearance is age associated, that relative to the 19-45yr old age group there was a decrease in clearance in the elderly that was not significant when compared to the older 48-59yr old "younger" group used in this trial. While it is true that the "young subjects" in this study had normal renal function, this does not mean that there was not such an age related change in clearance, just that the

[1] These studies are described in more detail in the Summary of Important Clinical Pharmacology and Biopharmaceutics Findings below.

mechanism may be more complex than that assumed under the standard filtration model of drug elimination. Such conclusions of course are speculative short of a larger population based trial.

It should be noted that the sponsor also included in study LVHN 3 younger subjects without BPH (45 to 60 years of age) but with creatinine clearance 51 to 80 mL/min [Cockcroft-Gault formula) to elucidate if any age-related pharmacokinetic differences might be attributable to altered renal function (rather than age alone.) However the small number of subjects enrolled with renal impairment precludes any meaningful findings with regard to this issue and in fact do not clarify the issue to any meaningful extent.

From a Clinical Pharmacology perspective the sponsor has adequately demonstrated the pharmacokinetics in the target population of BPH. While a separate study was not done in the BPH/ED population, as there would not be expected to be any differences (pharmacokinetically) in the populations, this is acceptable. As for the age issue, while there are conflicting findings across the LVHN study and the approved label with regards to clearance based changes, there does not seem to a significant enough safety concern to raise it to the level of a post-marketing study.

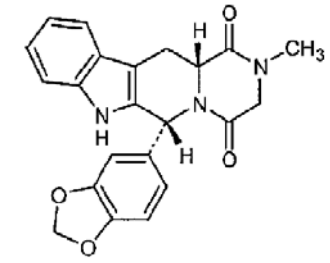
Study LVIA

Study H6D-JE-LVIA (LVIA) was a non-IND Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-design, to evaluate the efficacy and safety of tadalafil 2.5 and 5 mg administered once daily in Japanese male subjects ≥45 years of age with BPH. Overall, 141 subjects administered 2.5 mg tadalafil having 410 observations and 134 subjects receiving 5 mg with 386 observations were available for the PK analysis.

As this was a double-blind trial, plasma sampling was extremely limited in this study. Such that direct comparison of the pharmacokinetics between this trial (LVIA) the study LVHN cannot be directly made and only a descriptive summary was provided by the sponsor without a formal Pharmacometric analysis of the data. As this was a non-IND study and as the ethnic variability of Asian populations has been previously addressed in both clinical and pharmacokinetic trials, no further review of this study is included in this review.

Question Based Review
General Attributes

Tadalafil (CAS [171596-29-5]) is chemically identified as pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-and is also identified as GF196960X, IC351, or LY450190 It has been marketed in the United States since 2003.



What studies were submitted in support of Clinical Pharmacology?

The Clinical Pharmacology portion of these supplements included two new in vivo Clinical Pharmacology Studies, one in the target population:

LVHN[2] A Study to Evaluate the Pharmacokinetics of Tadalafil Administered Once Daily in Young and Elderly BPH Subjects

And another specifically focused on addressing concerns about the data available in the Japanese population:

LVIA A Study to Evaluate the Efficacy and Safety of Tadalafil Administered Once Daily for 12 Weeks in Japanese Men With Signs and Symptoms of BPH (Benign Prostatic Hyperplasia)

What is the Overview of Previously Conducted Clinical Pharmacology Studies?

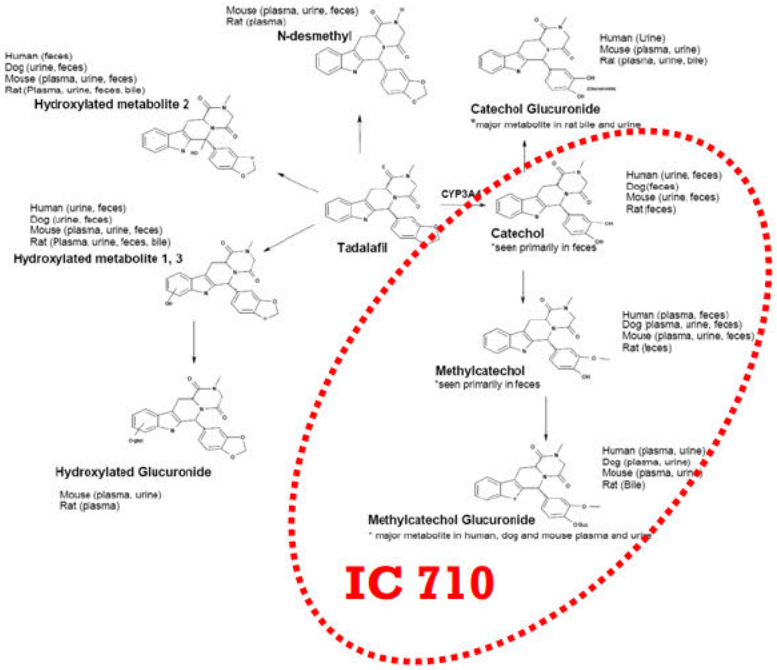
In general, the previous clinical pharmacology development program adequately covered the proposed once-daily 5mg dose for the treatment of BPH and BPH/ED. The original clinical pharmacology program established the PK and resultant PD properties of tadalafil 10 and 20 mg as ED therapy for as-needed use and included studies assessing intrinsic and extrinsic factors including drug-drug interactions (at doses up to 20mg). A

[2] Lilly uses a somewhat convoluted numbering system. Throughout the submission, The first three characters (X0X) are a project-specific code. The project-specific code for the tadalafil BPH program is H6D; therefore, all study names begin with that code. The next two characters are for internal tracking purposes. The last four characters are assigned in a sequential fashion (LVHR, LVHS, etc) to designate a specific planned protocol. Because not all planned protocols are necessarily conducted, there may be breaks in the sequence of the last four letters. Since the last four characters are unique to each tadalafil protocol, the studies frequently are referenced using only those four characters (for example, Protocol/Study LVHG). However, the longer alpha-numeric system is also used interchangeably by the sponsor.

QT study using a 100mg dose (designed to represent the worse case scenario with concurrent CPY3A4 inhibitors) did not show any significant change in QTc (mean 3.5msec).

It should be noted, that four dose strengths of the tadalafil tablet formulations have been used in clinical and clinical pharmacology studies (2.5, 5, 10, and 20 mg). (b) (4) Two studies were previously reviewed to support the as-needed dosing regimen (NDA 21-368). They were conducted in healthy male subjects to determine the relative bioavailability across the 2.5-, 5-, and 10-mg tablets using a single dose of 10 mg (H6D-EW-LVBX [LVBX]), and for the 10- and 20-mg tablets using a single dose of 20 mg (H6D-EW-LVDL). The 2.5-, 5-, and 10-mg tablets and the 10- and 20-mg tablets were bioequivalent. Therefore, these tablet strengths can be used interchangeably to achieve the same total oral dose and systemic exposure for the purposes of labeling.

Tadalafil is cleared extensively by oxidative metabolism to produce the catechol metabolite (IC711), and CYP3A4 is the predominant enzyme in the oxidative metabolism of tadalafil (ADME 34). This oxidative metabolite is rapidly further metabolized to form the methylcatechol and the methylcatechol glucuronide conjugate with the methylcatechol glucuronide as the major metabolite in human plasma and urine. Pharmacokinetic assessment has shown that the methylcatechol is present at levels generally <10% of the total methylcatechol level. Systemic exposure to total methylcatechol at steady state (also referred to as total IC710), representing the methylcatechol glucuronide and any unconjugated methylcatechol, is approximately 30% higher than for tadalafil. This metabolite is not selective for phosphodiesterase type 5 (PDE5) and is at least 13,000-fold less potent for PDE5 than tadalafil.

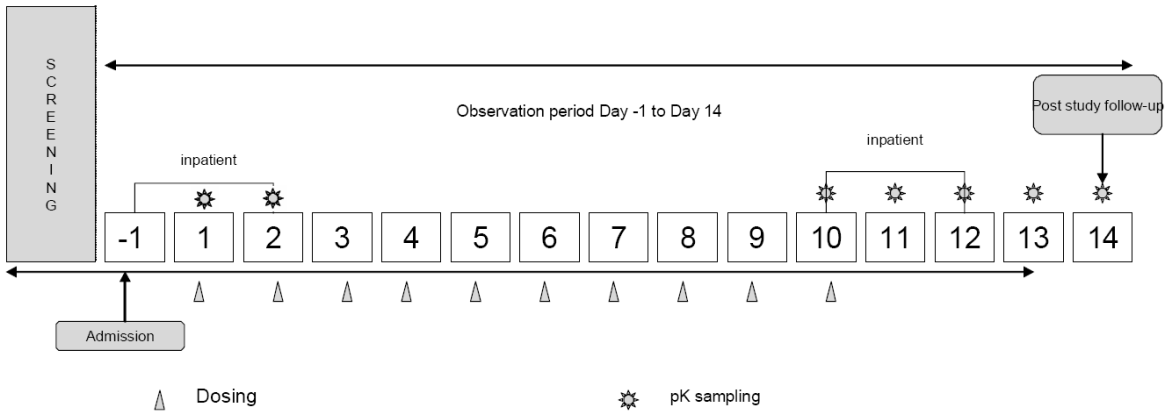


As part of the analysis of the PK of tadalafil, both tadalafil and IC 710 levels were determined and reported, however, to date only information on tadalafil levels have been reported in the package insert.

Study Summaries

LVHN A Study to Evaluate the Pharmacokinetics of Tadalafil Administered Once Daily in Young and Elderly BPH Subjects

This was a multicenter, parallel-group, open-label study in 12 elderly (70 to 76 years of age) and 12 young (48 to 59 years of age) subjects with BPH to assess the single and multiple-dose PK and cardiovascular dynamics of tadalafil in a more elderly population than previously included in ED or clinical pharmacology trials.



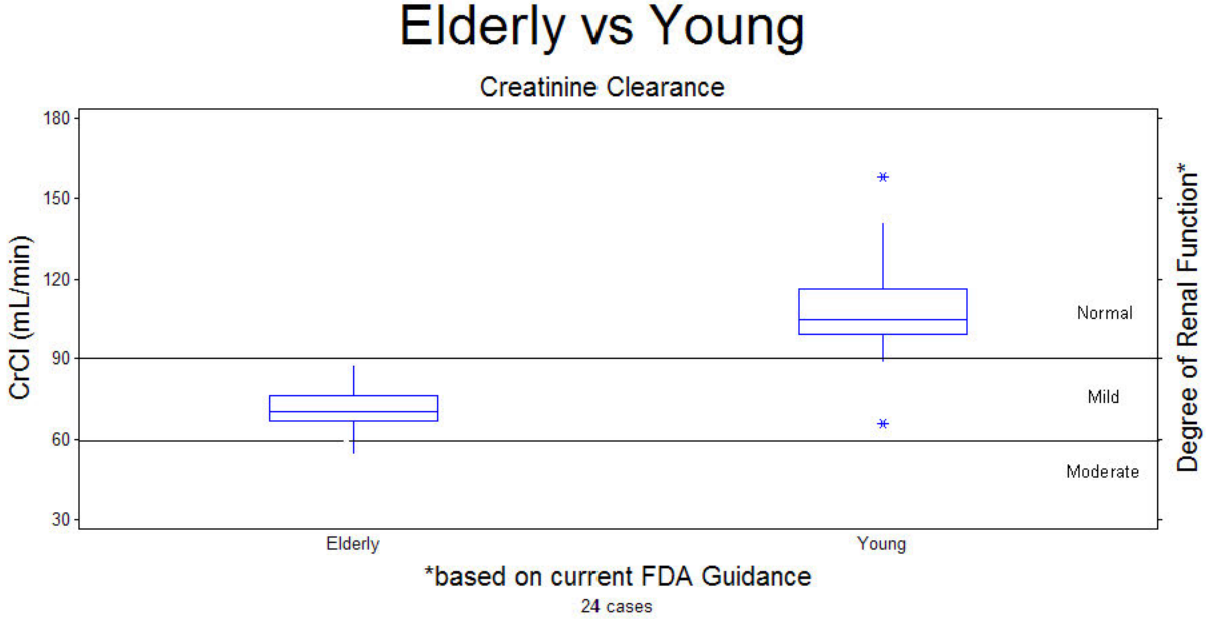
This study also recruited 3 additional younger subjects without BPH (45 to 60 years of age) but with mild renal impairment (creatinine clearance 51 to 80 mL/min [Cockcroft-Gault formula]) to elucidate if any age-related PK differences might be attributable to altered renal function rather than age alone. This definition of mild renal impairment is at odds with the current definition contained the 2010 Draft FDA Guidance Document entitled: *Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling.* We will base our recommendations on these current cut-points for renal function.

The sponsor limited the primary analyses to the PK and hemodynamic data from original 24 subjects (12 elderly and 12 young) having BPH. Subjects received tadalafil 20 mg once daily for 10 consecutive days. Given the small number of subjects (3) with "mild" renal impairment it is unlikely that this data would yield any significant findings.

DEMOGRAPHIC SUMMARY

		Age (years)	Body weight (kg)	BMI (kg/m^2)	CGCL (mL/min)	Total IPSS score
Elderly subjects with BPH	Mean (SD)	73 (2.2)	82.2 (11.65)	27.6 (2.80)	71 (8.9)	20 (5.9)
	Min-max	70-76	58.2-102	23.0-30.7	55-87	13-34
Normal renal function with BPH (N=11)						
Young subjec	Mean (SD)	53 (6.0)	87.2 (9.68)	27.2 (2.31)	112 (20.4)	19 (5.6)
	Min-max	42-58	73.4-107	21.7-30.3	89-158	12-30
Mild renal impairment						
Overall (BPH/Not BPH; N=4)						
	Mean (SD)	55 (6.9)	70.5 (7.89)	24.9 (2.22)	68 (4.3)	NC
	Min-max	45-60	63.6-80.9	23.1-27.7	64-74	NC
Not BPH (N=3)						
	Mean (SD)	54 (7.8)	67.0 (4.57)	23.9 (1.44)	68 (5.1)	NC
	Min-max	45-60	63.6-72.2	23.1-25.6	64-74	NC

As can be seen in the figure below, there was generally a break between the renal function classification of the elderly and young subjects with BPH. Interestingly 1 subject in the young group, (a 59yr old Caucasian) had a CrCl of 66 and thus had mild renal insufficiency, while 1 subject in the elderly group (a 76yr old Caucasian) had a CrCl of 55 or moderate insufficiency.



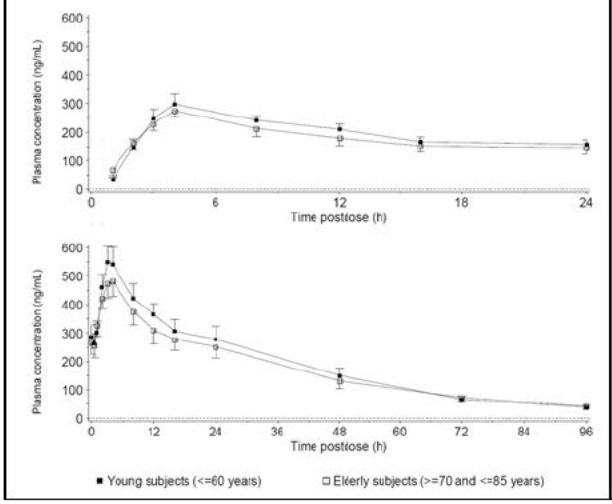
Venous blood samples (5 mL) were collected for the determination of plasma concentrations of tadalafil and total methylcatechol metabolite (total IC710) on:

- Day 1: at predose, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 hours postdose
- Day 10: at predose, 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72 and 96 hours postdose

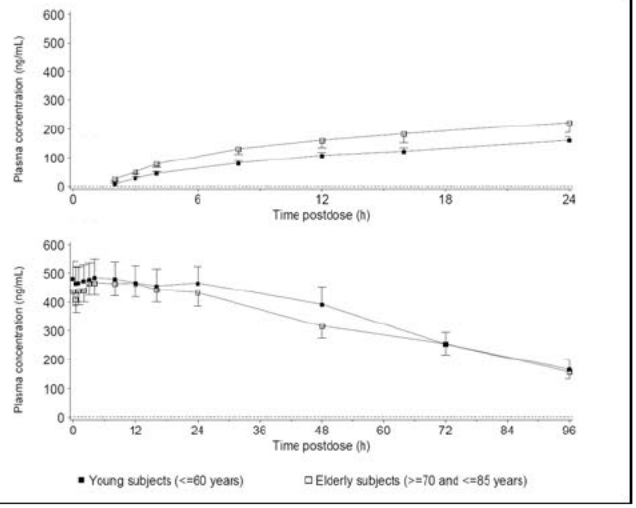
Actual blood sampling times were used in the calculation of pharmacokinetic parameters. Plasma samples that were reported to be below the lower quantitation limit (BQL) and occurred prior to the first quantifiable concentration were assigned a value of 0 ng/mL. Mean concentrations were graphically represented at a specific time point if at least 2/3 of the subjects had quantifiable concentrations and were within 5% of the scheduled sampling time.

The Mean plasma concentrations of both tadalafil and IC 710 are presented below for both day 1 and day 10.

Arithmetic mean (± SEM) plasma concentration-time profiles of tadalafil following single and multiple doses of 20-mg tadalafil in elderly and young subjects with BPH (upper panel Day 1 [0 to 24 hours]: lower panel Day 10 [0 to 96 hours]).



Arithmetic mean (± SEM) plasma concentration-time profiles of total IC710 following single and multiple doses of 20-mg tadalafil in elderly and young subjects with BPH (upper panel Day 1 [0 to 24 hours]: lower panel Day 10 [0 to 96 hours]).



Mean pharmacokinetic parameters from this study are consistent with the previous studies conducted with tadalafil in the ED population. While there are differences in the derived PK parameters both groups overlap to a significant degree for both tadalafil and IC 710.

Mean Tadalafil Pharmacokinetic Values

Tadalafil	Elderly Subjects* (mild renal insufficiency)		Young Subjects* (normal renal function)	
	Day 1	Day 10	Day 1	Day 10
AUC_{0-24}(ng*hr/mL)	3900 (39%)	7360 (40%)	4500 (26%)	8280 (41%)
Cmax (ng/mL)	273 (32%)	472 (33%)	328 (23%)	536 (35%)
Tmax (hrs)	4 (2-8)	3.52 (2-4)	4 (3-8)	3.5 (2-4)
Clss/F (L/hr)	--	2.72 (40%)	--	2.41 (41%)
T1/2 (hrs)	--	25.7 (32%)	--	23.6 (20%)

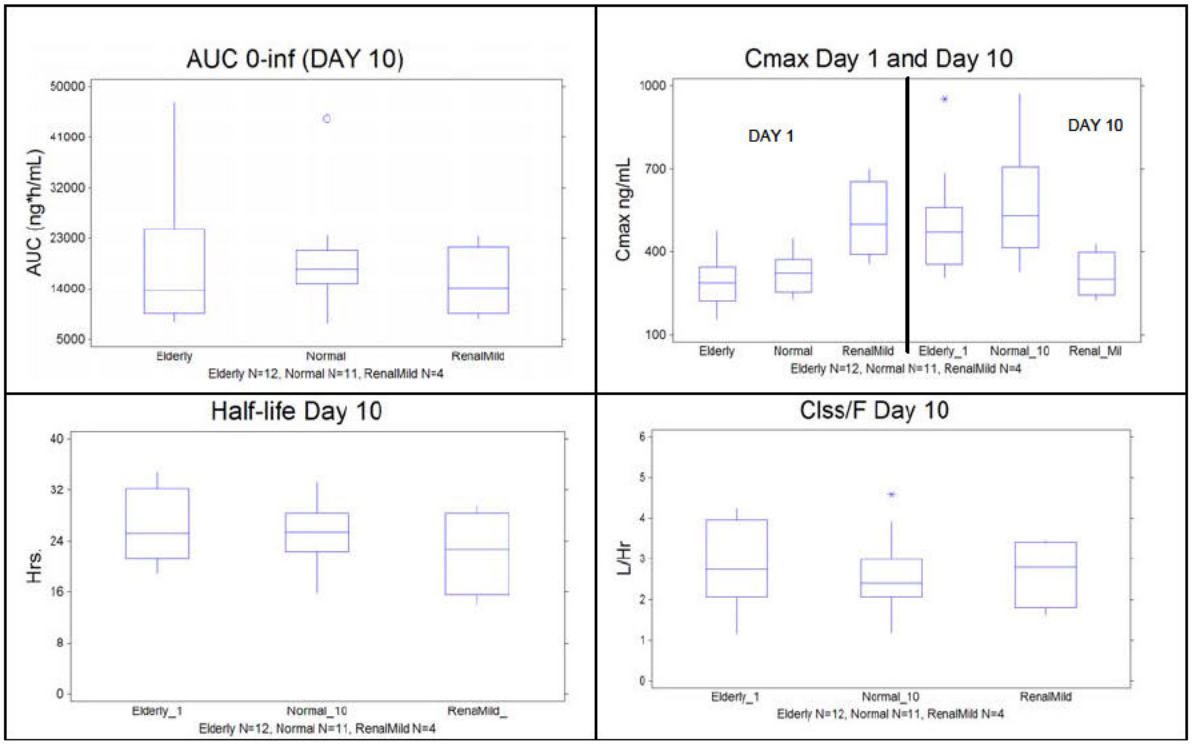
*N=12 for Elderly, N=10 for Young

Mean IC 710 Pharmacokinetic Values

IC 710	Elderly Subjects* (mild renal insufficiency)		Young Subjects* (normal renal function)	
	Day 1	Day 10	Day 1	Day 10
AUC_{0-24} (ng*hr/mL)	3020 (54)	10300 (32)	2150 (30)	9780 (33)
Cmax (ng/mL)	198 (52)	488 (32)	151 (27)	445 (34)
Tmax (hrs)	23.9 (23.3-24)	4 (0-24)	23.9 (23.9-24)	4 (0-24)

*N=12 for Elderly, N=10 for Young

A more detailed comparison of standard pharmacokinetic parameters are presented below between these parameters in a graphical format. The group entitle "Mild Renal" represents the three added subjects with "mild" insufficiency without BPH and the 1 subject discussed earlier (the 59yr old Caucasian) with moerate insufficiency:



Examination of the data in this manner shows the high degree of overlap present in the data. While the AUC values of the elderly subjects are highly variable, this relative degree of variability is consistent with the variability also seen in clearance and for the most part overlaps that of the normal subjects. The data for the mildly impaired renal subjects is included here for completeness, but the small number of subjects present (n=4) makes drawing any conclusions impossible. A brief discussion of renal effects is presented below to augment this limited data.

Cross-Study Evaluation of Renal Function

The pharmacokinetics of tadalafil were previously characterized in subjects with normal renal function (creatinine clearance 86-162 mL/min), mild (creatinine clearance 51-71 mL/min) or moderate (creatinine clearance 31 to 88 mL/min) renal impairment (Study H6D-EW-LVAJ). Systemic tadalafil exposure in subjects with mild or moderate renal impairment was doubled compared to that in healthy subjects following single tadalafil doses of 5 and 10-mg. The Cmax in patients with mild and moderate renal impairment was approximately 1.2-fold of that in healthy subjects. Apparent oral clearance (CL/F) was reduced in the renally impaired subjects, which resulted in a longer apparent t1/2. Although exposure to tadalafil was modestly increased in renally impaired subjects as compared to normal subjects, Cmax, AUC, and t1/2 were not significantly different between the mild and moderately renally impaired subjects. These findings are presented in the current labeling for Cialis in multiple sections of the label as described below:

> **8.7 Renal Insufficiency**
>
> In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with moderate renal impairment. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. *[See Dosage and Administration (2.3) and Warnings and Precautions (5.7)].*

Even in the face of what would normally be considered a definitive analysis, the sponsor undertook an exploratory cross-study analysis combining data from LVHN and LVAJ was undertaken. Although a conclusive absence of any relationship between renal function and tadalafil CL/F cannot be ascertained based upon the present data, no overt differences between the results reported in LVAJ and those provided herein (LVHN) are observed. Individuals appear to have comparable exposures when stratified by renal function, irrespective of age. While neither agreeing nor disagreeing this conclusion, the need for this analysis is not readily apparent to this reviewer given the current labeling which appears to be definitive in this regards and the small number of renally impaired subjects enrolled in this trial.

What is clear is that the FDA has since revised it's guidance for renal insufficiency and has established the followint cut-points:

Stage	Description[b]	eGFR[c] (mL/min/1.73m^2)	CLcr[d] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

The labeling needs to be revised by the sponsor to reflect these changes in renal function assessment as the terms mild, moderate, and severe are less definitive and subject to interpretation.

Safety-Orthostatic Hypotension

As PDE5 agents work through arterial muscle vasodilatation, one of the consistent concerns is the degree and severity of orthostatic hypotension. Safety vital signs measurements were performed at screening and on Day -1, in addition to the pharmacodynamic assessments.

In this study two young subjects experienced adverse events of orthostatic hypotension. For both subjects, the episodes of orthostatic hypotension were considered to be mild in severity and possibly related to tadalafil, but were adjudged by the clinical site and the sponsor to be of no clinical concern.

Subject 2010 (51yrs old) experienced orthostatic hypotension at approximately 1 and 3 hours after tadalafil administration on Day 1, which lasted for approximately 1 hour and 5 minutes, respectively. Additional vital signs and ECG assessments were performed following the first incidence of orthostatic hypotension, the results of which were not clinically significant.

Subject 2011 (43yrs old) experienced orthostatic hypotension at approximately 4 hours postdose on Day 1, which lasted for 1 minute, and on Day 10, at approximately 4 hours after tadalafil administration which lasted *for approximately 11 days*.

(b) (4)

These reports are puzzling. For subject 2010 the reported incidences of hypotension occur early in the plasma level time course and are unlikely to be due to true orthostatic hypotension thru a drug mediated mechanism. As if the subject had orthostatic hypotension at this low a level, then they would have had severe hypotension when the peak levels occurred. One wonders if this is related to either fear over study procedures (negative white coat anxiety?) or other effects? The highly unusual nature of the findings and its time course argues **against** it being a drug related effect. In comparison for subject 2011, the symptoms occurring as they do at or approximating the peak plasma concentrations are at least conceptually compelling, but the duration of the second incidence of 11 days is frankly unbelievable to this reviewer (as they relate to true drug specific ADRs). In addition the associated plasma concentration is not within the upper quartile for the normal subjects Cmax at day 10, thus it is difficult to assign a direct causation here in this subject.

There is, however, sufficient evidence present in this trial to demonstrate that 20mg to tadalafil can cause hypotension in both young and elderly subjects.

Table LVHN.7.6. Statistical Analysis of Haemodynamic Data Following Single and Multiple Doses of Tadalafil on Days 1 and 10 in Elderly and Young Subjects with BPH

Parameter	LS mean		Mean difference (95% CI)
	Elderly	Young	(Elderly-Young)
Day 1			
Maximum drop from baseline in standing systolic BP (mmHg)	24.1	14.5	9.6 (-0.7, 19.9)
Maximum drop from baseline in supine systolic BP (mmHg)	20.8	13.0	7.8 (-0.4, 16.1)
Maximum drop from baseline in standing diastolic BP (mmHg)	11.9	9.83	2.1 (-4.1, 8.2)
Maximum drop from baseline in supine diastolic BP (mmHg)	10.7	7.42	3.2 (-2.2, 8.7)
Maximum increase from baseline in standing heart rate (bpm)	12.8	14.7	-1.9 (-10.0, 6.2)
Maximum increase from baseline in supine heart rate (bpm)	10.3	13.2	-3.0 (-9.5, 3.5)
Day 10			
Maximum drop from baseline in standing systolic BP (mmHg)	23.1	14.0	9.1 (0.3, 17.9)
Maximum drop from baseline in supine systolic BP (mmHg)	20.7	16.5	4.2 (-6.8, 15.1)
Maximum drop from baseline in standing diastolic BP (mmHg)	11.5	10.7	0.8 (-5.3, 6.9)
Maximum drop from baseline in supine diastolic BP (mmHg)	9.42	8.83	0.6 (-4.8, 5.9)
Maximum increase from baseline in standing heart rate (bpm)	12.2	15.9	-3.8 (-14.1, 6.6)
Maximum increase from baseline in supine heart rate (bpm)	11.5	17.8	-6.3 (-14.4, 1.8)

Baseline is predose on Day 1 or Day 10, as appropriate
Model: Blood pressure = Group + Random Error

While this data does not support an increased hypotensive risk (day1 to day 10) it also shows that over the observation interval there is no apparent sign of tachyphylaxis to the hypotension.

Labeling

The Clinical Pharmacology section of the label is essentially unchanged except for the inclusion of a new paragraph in the Mechanism of Action section(12.1) and a new sub-section entitled "*Patients with BPH"* under Pharmacokinetics (12.3). The revised text is presented below in blue (with underlining), current text with no underlining, and deletions in red with strikeout.

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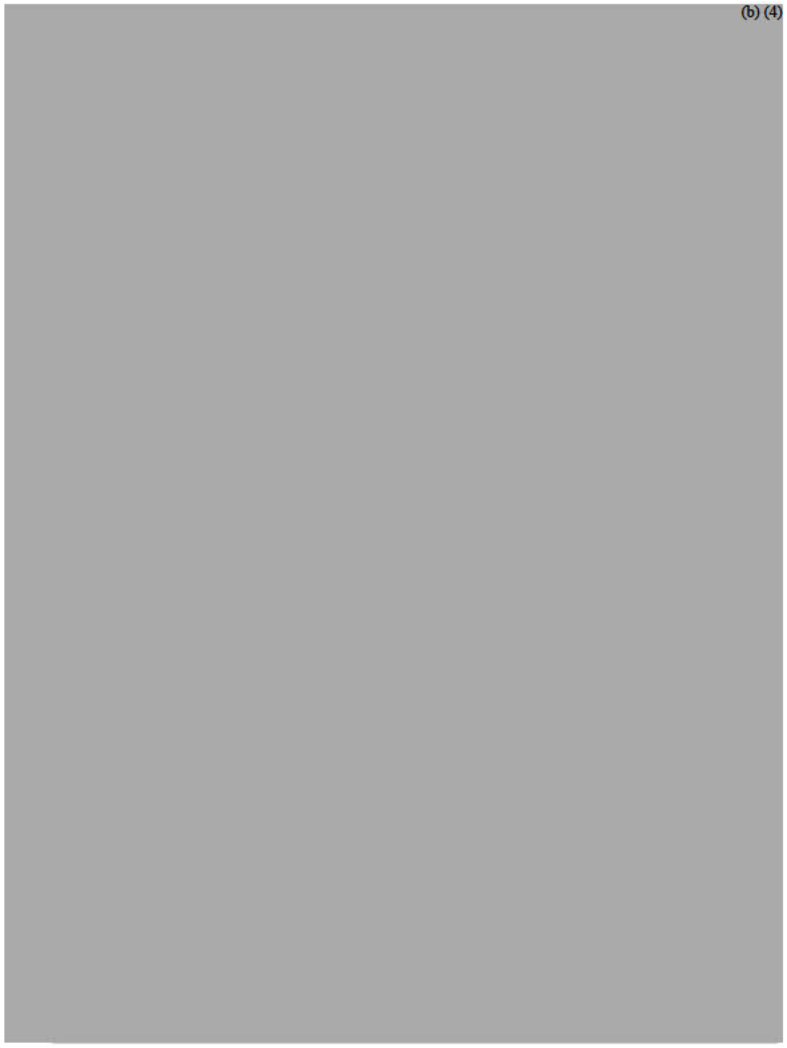
Individual Study Review

LVHN A Study to Evaluate the Pharmacokinetics of Tadalafil Administered Once Daily in Young and Elderly BPH Subjects

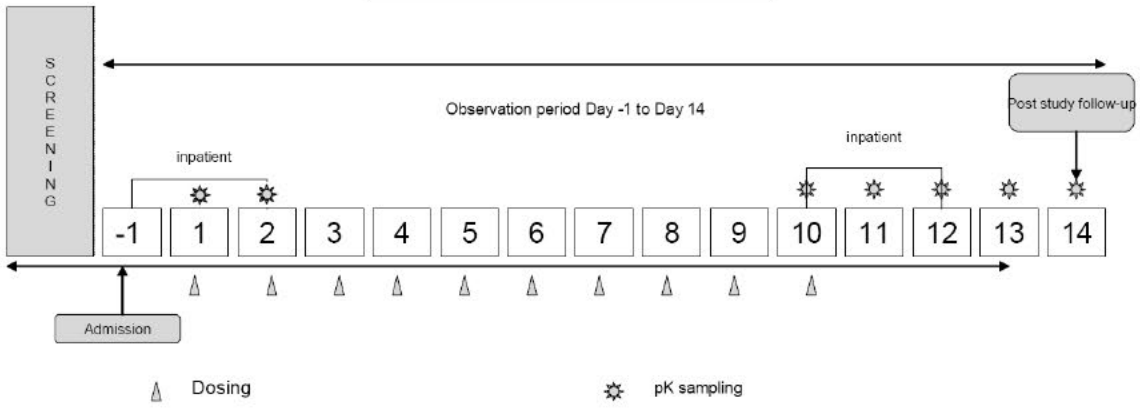
This was a multicenter, parallel-group, open-label study in 12 elderly (70 to 76 years of age) and 12 young (48 to 59 years of age) subjects with BPH to assess the single and multiple-dose PK and cardiovascular dynamics of tadalafil in a more elderly population than previously included in ED or clinical pharmacology trials.



A total of 27 subjects (10 elderly BPH subjects with mild renal impairment, 2 elderly BPH subject with moderate renal impairment, 10 young BPH subjects with normal renal function, 2 young BPH subjects with mild renal impairment, and 3 healthy subjects with mild renal impairment) participated in the study. All subjects completed the study and received tadalafil as daily 20-mg doses from Day 1 to Day 10. Following screening, subjects were admitted to the study site 1 day before dosing and remained in the inpatient study unit through the morning of day 3 for blood sampling. Subjects were then discharged with daily dosing until day 10 (the last dosing day). They were re-admitted to

the study site for additional blood sampling through the washout phase (days 10-14) following which they were discharged from the study. The following is a schematic overview of the trial design:

Study Schema for Study LVHN



Venous blood samples (5 mL) were collected for the determination of plasma concentrations of tadalafil and total methylcatechol metabolite (total IC710) on:

- Day 1: at predose, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 hours postdose
- Day 10: at predose, 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72 and 96 hours postdose

Actual blood sampling times were used in the calculation of pharmacokinetic parameters. Plasma samples that were reported to be below the lower quantitation limit (BQL) and occurred prior to the first quantifiable concentration were assigned a value of 0 ng/mL. Mean concentrations were graphically represented at a specific time point if at least 2/3 of the subjects had quantifiable concentrations and were within 5% of the scheduled sampling time.

Pharmacodynamic Assessments

Hemodynamic data were collected at predose (within 30 minutes prior to dosing), and at 1, 2, 3, 4, 12, and 24 hours postdose on Day 1; and at predose (within 30 minutes prior to dosing), and 1, 2, 3, 4, 12, 24, 48, 72 and 96 hours postdose on Day 10. All hemodynamic assessments included systolic blood pressure, diastolic blood pressure, and heart rate and were made with the subject both in supine and standing position (supine: after 5 minutes in the supine position, the subject then sat for 1 minute and stood for 2 minutes prior to standing measurements). These measurements were repeated if the clinical situation demanded it. On days where pharmacokinetic and pharmacodynamic assessments were performed, the order of tests was vital signs and then pharmacokinetic sampling.

Analytical

(b) (4)

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The analytical method was adequately validated. Prior to pharmacokinetic data analysis, a review of the data by the sponsor revealed a protocol violator, subject 3006 who had positive tadalafil concentrations upon study entry. The affected Day 1 profile shown below:

Following a post-study interview the subject admitted to self-medicating with tadalafil prior to study entry (subject was unsure of the timing of dosing relative to the study). This subject's positive predose plasma tadalafil concentrations were included in the calculation of his pharmacokinetic parameters by the sponsor; however, the pharmacokinetic parameters calculated for Subject 3006 were excluded from the descriptive summary of pharmacokinetic parameters and statistical analyses. All safety and pharmacodynamic data for Subject 3006 were included in the summary statistics.

A Note on Renal Function Measurement

Since the time that the development began, the definition of renal function (via Cockroft-Gault) has undergoine revision. The current cutpoints are reproduced from the FDA Renal Guidance Document that was issued in 2010

Stage	Description[b]	eGFR[c] ($mL/min/1.73m^2$)	CLcr[d] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

The sponsor used a different set of cutpoints that resulted in there being 1 subject in the elderly group moving from the mild to the moderate renal function category. While not a dramatic effect, it does have an impact on the labeling and how it is presented. Wherever possible we are using the cutpoints established here for regulatory purposes.

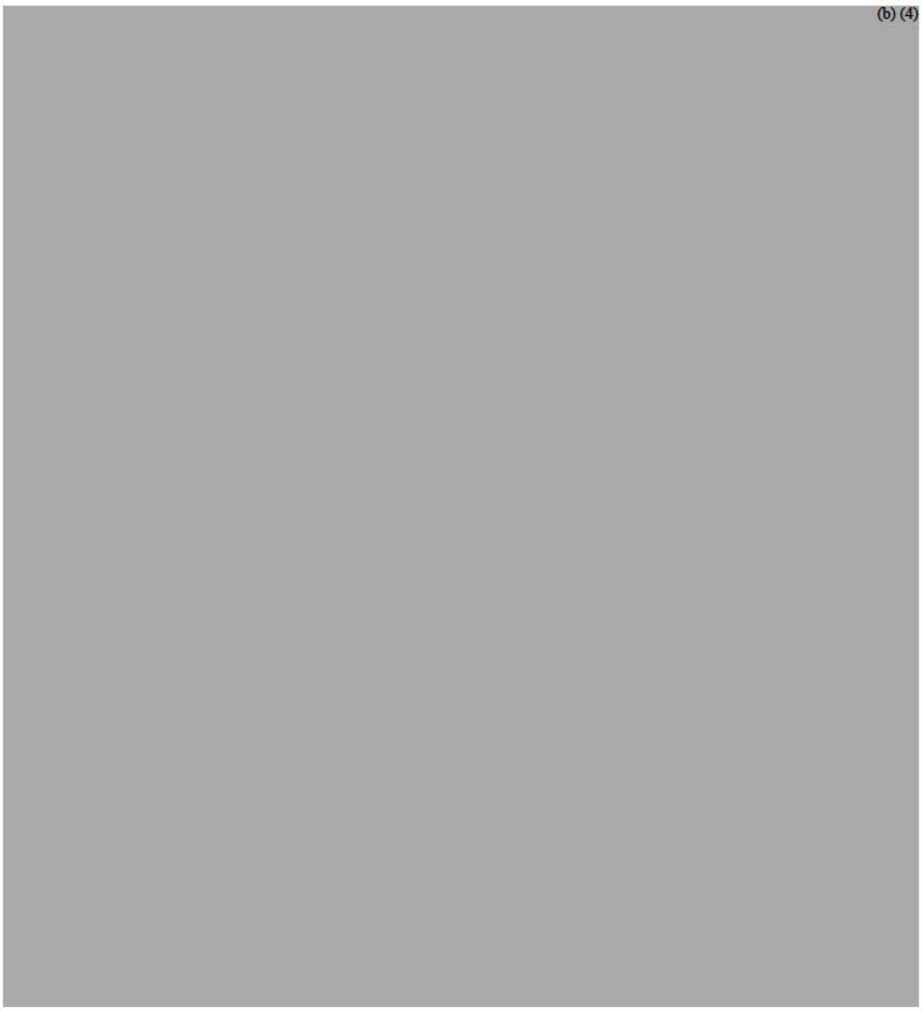
Table LVHN.7.1. Geometric Mean (CV%) Pharmacokinetic Pa Tadalafil in Elderly and Young Subjects with Normal Renal Function Following Single and of 20-mg Tadalafil on Days 1 and 10

	Elderly subjects		Young subjects	
Parameter of tadalafil	Day 1 (N=12)	Day 10 (N=12)	Day 1 (N=10)	Day 10 (N=10)
AUC(0-24) (ng.h/mL)	3900 (39)	7360 (40)	4500 (26)	8280 (41)
C_{max} (ng/mL)	273 (32)	472 (33)	328 (23)	536 (35)
t_{max} [a] (h)	4.00 (2.00, 8.00)	3.52 (2.00, 4.03)	4.00 (3.00, 8.00)	3.50 (2.00, 4.00)
$t_{½}$ (h)	NA	25.7 (21)	NA	23.6 (20)
CL_{ss}/F (L/h)	NA	2.72 (40)	NA	2.41 (41)
$V_{z,ss}/F$ (L)	NA	101 (25)	NA	82.2 (31)
RA_{AUC}	NA	1.89 (13)	NA	1.84 (21)
RA_{Cmax}	NA	1.73 (15)	NA	1.63 (18)

[a] Median (min-max) data
RA_{AUC} = AUC(0-24) on Day 10 / AUC(0-24) on Day 1
RA_{Cmax} = C_{max} on Day 10 / C_{max} on Day 1
NA = not applicable

3

[3] Elderly (10 BPH subjects with mild renal impairment +2 with moderate renal impairment using the revised definition of renal function from the 2010 FDA guidance) vs. "Young" (normal renal function)



Lower limit of quantification (1.000 ng/mL)

Table LVHN.7.2. Geometric Mean (CV%) Pharmacokinetic Parameters of Total IC710 in Elderly and Young Subjects with BPH Following Single and Multiple Doses of 20-mg Tadalafil on Days 1 and 10

	Elderly subjects		Young subjects	
Parameter of total IC710	Day 1 (N=12)	Day 10 (N=12)	Day 1 (N=10)	Day 10 (N=10)
AUC(0-24) (ng.h/mL)	3020 (54)	10300 (32)	2150 (30)	9780 (33)
C_{max} (ng/mL)	198 (52)	488 (32)	151 (27)	445 (34)
t_{max} [a] (h)	23.93 (23.30, 24.05)	4.00 (0.00, 24.00)	23.92 (23.87, 24.05)	4.00 (0.00, 24.00)
RA_{AUC}	NA	3.42 (61)	NA	4.54 (46)
RA_{Cmax}	NA	2.46 (51)	NA	2.94 (38)
MR_{AUC}	NA	1.40 (33)	NA	1.18 (29)

[a] Median (min-max) data

RA_{AUC} = AUC(0-24) on Day 10 / AUC(0-24) on Day 1

RA_{Cmax} = C_{max} on Day 10 / C_{max} on Day 1

MR_{AUC} = AUC(0-24) total IC710 / AUC(0-24) Tadalafil

NA = not applicable

Table LVHN.7.3. Statistical Analysis of the Effect of Age on the Pharmacokinetics of Tadalafil in Subjects with BPH

Parameter of tadalafil	Day	Geometric LS mean (95% CI) Elderly	Young	Ratio of geometric LSmeans (elderly:young)	90% CI for the ratio (elderly:young)
AUC(0-24)	1	3899	4461	0.87	0.68, 1.13
(ng.h/mL)	10	7359	8336	0.88	0.68, 1.14
C_{max}	1	273	317	0.86	0.69, 1.07
(ng/mL)	10	472	534	0.88	0.71, 1.10
t_{max} [a]	1	4.00	4.00	0.00	-0.07, 0.00
(h)	10	3.52	4.00	0.00	0.00, 0.03

Model: log(PK)= SUBJECT + DAY + GROUP + GROUP x DAY + RANDOM ERROR

[a] Median of differences (elderly-young) and associated 90% CI for median of differences for t_{max}

LS = Least squares

CI = Confidence interval

Table LVHN.7.4. Statistical Analysis of the Effect of Age on the Pharmacokinetics of Total IC710 in Subjects with BPH

Parameter of total IC710	Day	Geometric LS mean (95% CI) Elderly	Young	Ratio of geometric LSmeans (elderly:young)	90% CI for the ratio (elderly:young)
AUC(0-24)	1	3023	2205	1.37	1.04, 1.80
(ng.h/mL)	10	10330	10524	0.98	0.75, 1.29
C_{max}	1	198	156	1.27	0.97, 1.67
(ng/mL)	10	488	476	1.03	0.78, 1.34
t_{max} [a]	1	23.9	23.9	0.00	-0.05, 0.02
(h)	10	4.00	4.00	0.00	-4.00, 4.00

Model: log(PK)= SUBJECT + DAY + GROUP + GROUP x DAY + RANDOM ERROR

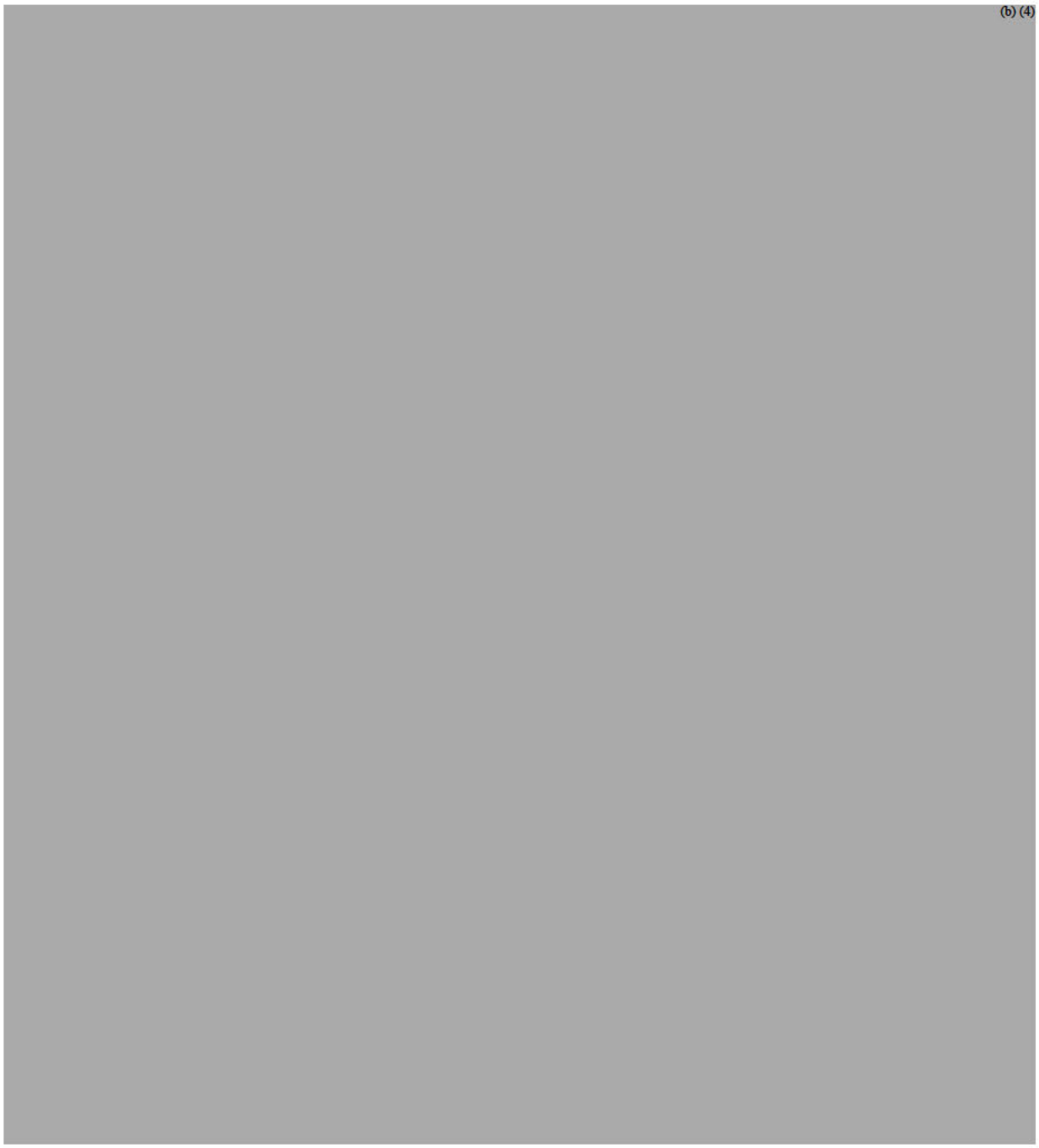
[a] Median of differences (elderly-young) and associated 90% CI for median of differences for t_{max}

LS = Least squares

CI = Confidence interval

Cross-Study Evaluation of Renal Function

As mentioned in the Summary of Clinical Pharmacology Findings, Study LVAI was a safety and efficacy study in Japanese subjects. The study had limited PK sampling with 141 subjects administered 2.5 mg tadalafil having 410 observations and 134 subjects receiving 5 mg with 386 observations were available for the PK analysis. From these data, a population pk model was developed and estimates of drug clearance were obtained, along with measurements of CrCl. These results were combined with the current dataset and presented below.



The results here are highly dependent upon the quality of the model used for the estimate of CL/F for LVAJ. As such, it is neither reassuring nor alarming. The conclusion drawn by the sponsor is that there is no difference in drug clearance and renal function between Japanese and the current study population, however, this conclusion, based as it is on a post-hoc cross study analysis is not definitive and the current labeling in this regards is adequate.

Labeling and Renal Function

As to the issue of age and renal function, the current label contains the following language:

8.7 Renal Insufficiency

In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with moderate renal impairment. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. *[See Dosage and Administration (2.3) and Warnings and Precautions (5.7)].*

This is somewhat at odds with what we have seen in this study where there was minimal (<15%) difference in AUC or Cmax following dosing for 10 days in a population that was both aged and had mild (10) and moderate (2) renal insufficiency. Part of this difference is likely due to the fact that the studies in the label actually used a young population (19-45yrs old) vs. the "young" population (42-58yrs old) used here. This is not an insignificant difference in age between what is categorized as "young" subjects, while both groups are under age 65, the disparity in ages between the two groups is significant. While not totally discounting the difference, the data from this study do not really provide enough concern for a post-marketing study. It is also unclear how the differences in renal function play out here, as the drug is predominately found in the feces (61%) and not the urine (36%). It is also possible that renal transport rather than renal filtration factors could be complicating the issue. Given that the study here is of reasonable size, and that the current label does not recommend dose adjustment in the mild to moderate population, no alteration in the labeling is recommended based on the results of this study.

CIALIS for Once Daily Use

- Mild (creatinine clearance 51 to 80 mL/min): No dose adjustment is required.
- Moderate (creatinine clearance 31 to 50 mL/min): No dose adjustment is required.
- Severe (creatinine clearance <30 mL/min and on hemodialysis): CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use In Specific Populations (8.7)].*

Adverse Events

Table LVHN.8.1. Summary of Treatment-Emergent Adverse Events

Population	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])	
Elderly subjects (N=12)	10 [83%]	Mild	53	10 [83%]	Mild	45
		Moderate	21		Moderate	19
		Severe	0		Severe	0
		Total	74		Total	64
Young subjects (overall) (N=15)	15 [100%]	Mild	76	15 [100%]	Mild	62
		Moderate	22		Moderate	17
		Severe	0		Severe	0
		Total	98		Total	79
Young subjects (normal renal function with BPH) (N=11)	11 [100%]	Mild	62	11 [100%]	Mild	52
		Moderate	15		Moderate	13
		Severe	0		Severe	0
		Total	77		Total	65
Young subjects (mild renal impairment overall [BPH/not BPH]) (N=15)	4 [100%]	Mild	19	4 [100%]	Mild	15
		Moderate	11		Moderate	8
		Severe	0		Severe	0
		Total	30		Total	23
Young subjects (not BPH) (N=3)	3 [100%]	Mild	19	3 [100%]	Mild	16
		Moderate	8		Moderate	8
		Severe	0		Severe	0
		Total	27		Total	24
Overall (N=27)	25 [93%]	Mild	129	25 [93%]	Mild	107
		Moderate	43		Moderate	36
		Severe	0		Severe	0
		Total	172		Total	143

N = Number of subjects studied

[a]Adverse events considered to be possibly or probably related to study drug

Table LVHN.8.2. Frequency of Drug-Related Adverse Events Reported on at Least Two Occasions

	Number of subjects with adverse events [number of adverse events]		
MedDRA preferred term	Elderly subjects (N=12)	Young subjects (N=15)	Overall (N=27)
Myalgia	6 [16]	6 [15]	12 [31]
Headache	6 [13]	10 [17]	16 [30]
Dyspepsia	5 [11]	7 [9]	12 [20]
Pain in extremity		4 [8]	4 [8]
Back pain	4 [5]	1 [1]	5 [6]
Diarrhoea	3 [6]		3 [6]
Nausea		4 [6]	4 [6]
Vomiting		3 [4]	3 [4]
Nasal congestion	1 [1]	2 [2]	3 [3]
Chest pain	2 [4]		2 [4]
Orthostatic hypotension		2 [4]	2 [4]
Fatigue	1 [1]	1 [1]	2 [2]
Chest discomfort		1 [3]	1 [3]
Hyperhidrosis		1 [2]	1 [2]

N = Number of subjects studied

Pharmacodynamics and Blood Pressure

DAY 1

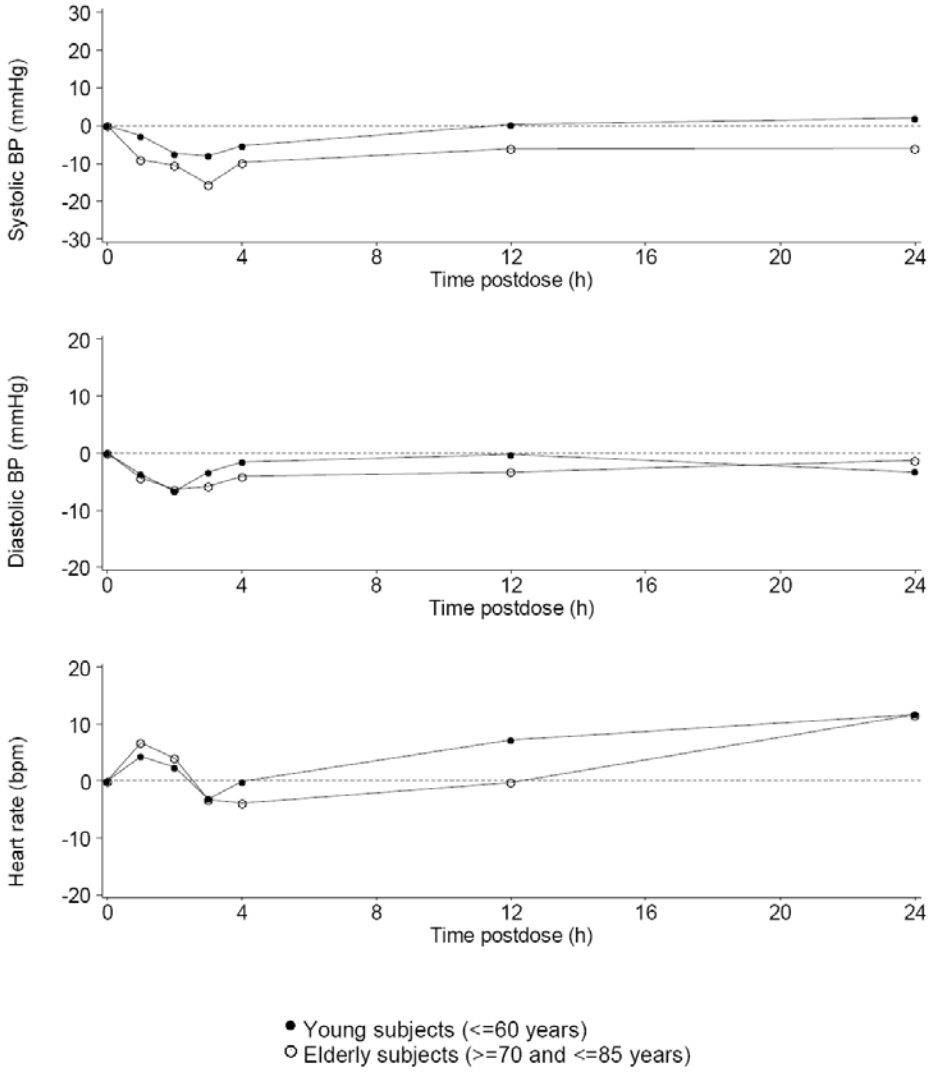


Figure LVHN.7.10. Mean changes from baseline (Day 1, predose) in standing blood pressure and heart rate following single doses of 20-mg tadalafil on Day 1 in elderly and young subjects with BPH.

Pharmacodynamics and Blood Pressure
DAY 10

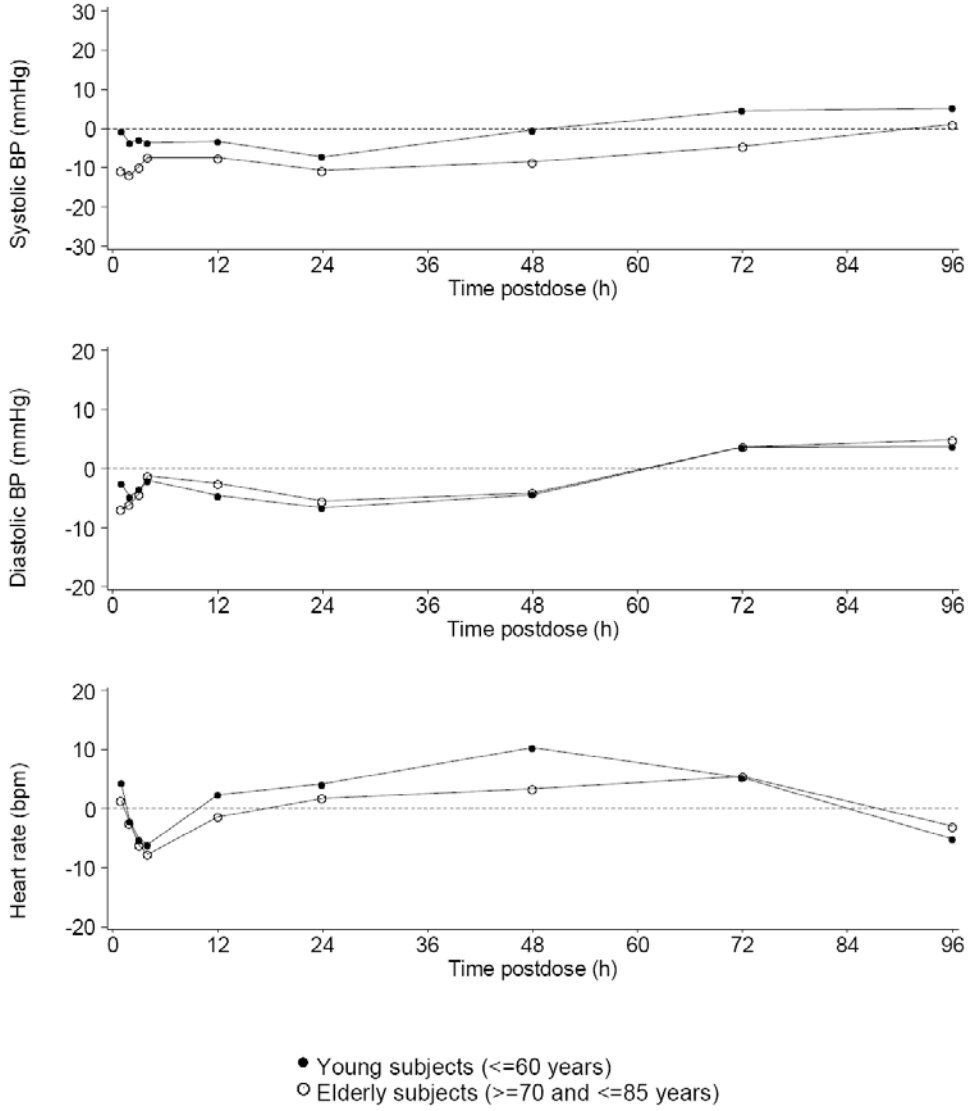


Figure LVHN.7.11. **Mean changes from baseline (Day 1, predose) in standing blood pressure and heart rate following multiple doses of 20-mg tadalafil on Day 10 in elderly and young subjects with BPH.**

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/s/

EDWARD D BASHAW

09/16/2011

Although I am the Division Director, I was also the primary reviewer on this application and I have delegated secondary sign-off to the Repro-Uro Clin Pharm TL, Dr. Myong-Jin Kim

MYONG JIN KIM

09/16/2011

NDA/BLA Number: 021368 S-20/21 **Applicant: Eli Lilly** **Stamp Date: 12/6/2010**

Drug Name: Tadalafil **NDA/BLA Type: Efficacy supplement**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?		x		
Criteria for Assessing Quality of an NDA					
	Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	x			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?		x		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?		x		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			Supplement is focused on use in the elderly
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Not a pediatric indication.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
13	On its face, is the clinical pharmacology and	x			

	biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?				
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	x			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
17	Was the translation from another language important or needed for publication?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**021368 S-20/21**	**Brand Name**	**Cialis**
OCP Division	**Division of Clinical Pharmacology 3**	**Generic Name**	**Tadalafil**
Medical Division	**Division of Reproductive and Urologic Products**	**Drug Class**	**PDE-5 Inhibitor**
OCP Primary Reviewer	**Capt. E. Dennis Bashaw, Pharm. D.**	**Indication(s)**	**(s-20)Treatment of signs and symptoms of Benign Prostatic Hyperplasia (BPH) (s-21) Treatment of Erectile Dysfunction (ED) and signs and symptoms of BPH**
OCP Secondary Reviewer	**Myong-Jin Kim, Pharm. D.**	**Dosage Form**	**Tablet 2.5, 5, 10, and 20mg**
		Dosing Regimen	**QD**
Date of Submission	**12/6/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**5/01/2011**	**Sponsor**	**Eli Lilly**
PDUFA Due Date	**10/6/2011**	**Priority Classification**	**Standard**
Division Due Date	**8/6/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	2	2	1 pivotal pk, 1 supportive trial in Japanese subjects with sparse sampling
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1	1	As noted above 1 supportive study had results from Japanese subjects.
gender:				
pediatrics:				
geriatrics:	x			The indication is (primarily) a geriatric/elderly indication.

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Fileability and QBR comments

	"X" if yes	**Comments**
Application fileable?	**x**	
Comments sent to firm?		No
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology Review

NDA: 021368 S020/21
Compound: **Tadalafil**
Sponsor: **Eli Lilly**

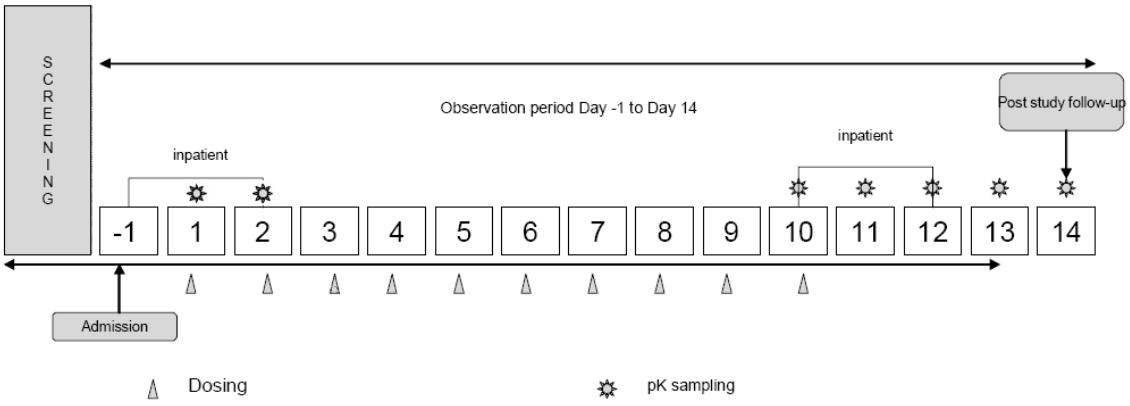
Date: **2/1/2011**
Reviewer: **Dennis Bashaw**

Background: Tadalafil, a selective inhibitor of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) is approved to treat men with erectile dysfunction (ED) under New Drug Application (NDA) 021368 and patients with pulmonary arterial hypertension (PAH) under NDA 022332.

This application seeks approval of tadalafil for the treatment of men with signs and symptoms of benign prostatic hyperplasia (BPH)-*supplement 20* and for the treatment of men with ED and signs and symptoms of BPH (BPH/ED)-*supplement 21*.

The majority of the clinical pharmacology information obtained during the tadalafil ED (as-needed and once-daily) clinical development program is applicable to the present applications (BPH and BPH/ED), including pharmacokinetics, pharmacodynamics, and intrinsic and extrinsic factors affecting pharmacokinetics. To directly support the BPH indication, 1 additional clinical pharmacology study using a 20-mg dose (CSR LVHN) was conducted. Additional supportive data was provided from a study conducted in that was performed to support Japanese registration that contained sparse PK sampling.

Bioavailability: Study CSR LVHN was a multicenter, balanced, parallel-group, open-label study evaluating multiple oral doses of 20-mg tadalafil in elderly and young male subjects with lower urinary tract symptoms secondary to BPH. Subjects received an oral dose of 20-mg tadalafil once a day on 10 consecutive days (Days 1 to 10). Subjects remained in the research unit from Day -1 until Day 2, and from Day 10 until Day 12. Sequential pharmacokinetic samples were collected on Days 1 and 2, and on Days 10 to 14.



Drug interactions: The sponsor did not conduct any in vitro drug metabolism, in vitro drug-drug interaction studies, or in vivo drug interaction trials. The need for such information will be considered during NDA review.

Pediatrics: Not applicable.

Clinical vs. to-be-marketed formulation: Tadalafil was provided as commercially available Cialis® (20-mg tablets: lot numbers: A226547 (b) (4), A244531 (b) (4) and A335320 and A362242 (b) (4)

Method validation: According to the sponsor, blood samples for the determination of plasma concentrations of tadalafil and total methylcatechol metabolite (IC710) were assayed using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods at (b) (4) A summary of the analytical findings was appended to the study report and a separate more detailed method development report was submitted in the Bioanalytical section of the ENDA.

Recommendation: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 021368 S-20/21 is fileable.

Comments for sponsor:

None at the present time.

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/s/

EDWARD D BASHAW
02/03/2011

MYONG JIN KIM
02/04/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 21368 supp 020 and 021
APPLICANT	Eli Lilly and Company
PRODUCT NAME	CIALIS (tadalafil)
SUBMISSION DATE	6 Dec 2010
PDUFA DATE	6 Oct 2011 (Clinical Efficacy)
SEALD SIGN-OFF DATE	29 Sep 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed 22 Sep 2011 have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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LAURIE B BURKE
09/29/2011

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 21368 supp 020 and 021
APPLICANT	Eli Lilly and Company
PRODUCT NAME	CIALIS (tadalafil)
SUBMISSION DATE	6 Dec 2010
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/s/

LAURIE B BURKE
09/29/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

PATIENT LABELING REVIEW

Date:	**September 26, 2011**
To:	Scott Monroe, MD., Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)** Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Focused Review of Patient Labeling (Patient Package Insert)
Drug Name:	CIALIS (tadalafil)
Dosage Form and Route:	Tablets for Oral Use
Application Type/Number:	NDA 21368
Supplement Number:	• 020 • 021
Applicant:	Eli Lilly and Company
OSE RCM #:	2011-343

1 INTRODUCTION

Cialis (tadalafil) Tablets was originally approved on November 21, 2003 for the treatment of males with Erectile Dysfunction (ED). On December 03, 2010 the applicant submitted a Prior Approval Labeling Supplement (PAS) for CIALIS (tadalafil) Tablets for use in the treatment of males with symptoms of benign prostatic hyperplasia (BPH) and the treatment of males with ED and symptoms of BPH.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) provide a focused review of the Applicant's proposed Patient Package Insert (PPI) for CIALIS (tadalafil) Tablets.

2 MATERIAL REVIEWED

- Draft CIALIS (tadalafil) PPI received on December 06, 2010 and sent to DRISK on September 22, 2011.
- Draft CIALIS (tadalafil) PI received on December 06, 2010, revised by the reviewing division throughout the review cycle, and sent to DRISK on September 22, 2011.
- Approved CIALIS (tadalafil), dated February 01, 2010.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Per the request of DRUP, DRISK provided a focused PPI review for the new indication of BPH and ED with BPH only. DRISK did not review or provide comments to the CIALIS PPI in its entirely. We recommend bringing all ED drug PPI's up to current patient labeling standards in the future.
- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
09/26/2011

LASHAWN M GRIFFITHS
09/26/2011

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 21368; supplements 020 and 021
APPLICANT	Eli Lilly and Company
PRODUCT NAME	CIALIS (tadalafil)
RECEIVED DATE	December 6, 2010
PDUFA DATE	October 6, 2011 (Clinical Efficacy)
SEALD REVIEW DATE	September 22, 2011
SEALD LABELING REVIEWER	Jeanne Marie Delasko, RN, MS Labeling Initiatives Specialist

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. **[JMD Comment: Waiver previously granted by DRUP.]**

☐ There is no redundancy of information.

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

☐ A horizontal line must separate the HL and Table of Contents (TOC).

☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***."

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☒ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  [JMDComment: Must insert in month/year format, the date of supplement approval for each RMC. There are <u>11</u> RMC listed in HL with "mm/yyyy" instead of the date of supplement approval for each RMC. Please correct.]

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

  ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**

  ☒ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval. **[JMDComment: The revision date should be "10/2011"** (b) (4) **Please update at time of approval.]**

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JEANNE M DELASKO
09/22/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	September 14, 2011
Reviewer:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, Pharm.D., Team Leader Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Cialis (Tadalafil) Tablet, 2.5 mg, 5 mg, 10 mg, and 20 mg
Application Type/Number:	NDA 021368/S-020 and S-021
Applicant/sponsor:	Eli Lilly and Compnay
OSE RCM #:	2011-343-1

1 INTRODUCTION

This review evaluates the revised blister and container labels as well as carton labeling for Cialis (Tadalafil) Tablets submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant on OSE Review #2011-343, dated July 7, 2011.

2 MATERIALS REVIEWED

The revised blister and container labels and carton labeling submitted to the FDA on September 1, 2011 (See Appendix A) and OSE Review #2011-343, dated July 7, 2011, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling address all of DMEPA's concerns. However, the revised blister labels still contain days of the week, a statement "last tablet", and clockwise arrows above the tablets organized in a circular manner. Although blister label's design is not ideal, we did not any medication errors related to the product's blisters. Thus, we have find the revised blister labels acceptable and have no additional comments to the Applicant at this time. However, we will continue monitoring medication errors involving Cialis.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

YELENA L MASLOV
09/14/2011

ZACHARY A OLESZCZUK
09/14/2011

CAROL A HOLQUIST
09/14/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: September 2, 2011

To: George Lyght
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Matthew Falter, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 021368; S-020 & S-021**
DDMAC labeling comments for Cialis (tadalafil) Tablets for oral use

Background

This consult is in response to DRUP's February 15, 2011 request for DDMAC's review on labeling materials for Cialis (tadalafil) Tablets for oral use (Cialis) for a new indication. DDMAC has reviewed the following labeling materials for Cialis:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Patient Package Insert (PPI)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on August 26, 2011. In addition, we have considered the Cialis PI and PPI (approved February 2010), Jalyn PI and PPI (approved June 2010) Avodart PI and PPI (approved June 2011), and Rapaflo PI and PPI (approved March 2010) in our review of the draft Cialis labeling.

We offer the following comments:

PI & PPI

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
  (301) 796-3821, or janice.maniwang@fda.hhs.gov

- Matthew Falter (Consumer directed materials)
  (301) 796-2287, or matthew.falter@fda.hhs.gov

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/s/

JANICE L MANIWANG
09/02/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 021368 BLA#	NDA Supplement #:S- 020 BLA STN #	Efficacy Supplement Type SE- 1
Proprietary Name: Cialis Established/Proper Name: tadalafil Dosage Form: tablet Strengths: 5 mg		
Applicant: Eli Lilly and CO. Agent for Applicant (if applicable):		
Date of Application: 12-03-2010 Date of Receipt: 12-06-2010 Date clock started after UN:		
PDUFA Goal Date: October 6, 2011	Action Goal Date (if different):	
Filing Date: 02-04-2011	Date of Filing Meeting: 01-26-2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of signs and symptoms of benign prostatic hyperplasia (BPH)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☑ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☑ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted

Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐

Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 073502	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	Yes			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	Yes			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	Yes			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		No		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	Yes			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☑ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☑ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		No		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		No		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		No		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			NA	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		No		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			NA	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	Yes			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		No		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			Na	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☑ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**Yes**			
Index: Does the submission contain an accurate comprehensive index?	**Yes**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**Yes**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☑ legible ☑ English (or translated into English) ☑ pagination ☑ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	Yes			
Are all establishments and their registration numbers listed on the form/attached to the form?	Yes			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	Yes			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	Yes			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	Yes			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	Yes			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			NA	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**NA**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	Yes			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	Yes			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		No		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			NA	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		No		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☑ Package Insert (PI) ☑ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☑ Carton labels ☑ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	Yes			
Is the PI submitted in PLR format?[4]	Yes			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	Yes			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	Yes			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	Yes			
OTC Labeling	☑ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	Yes			DSI
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s): September 25, 2008** ***If yes, distribute minutes before filing meeting***	Yes			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** April 13, 2010 ***If yes, distribute minutes before filing meeting***	Yes			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		No		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 26, 2011

BLA/NDA/Supp #: NDA 021368/S-020 and NDA 02368/S-021

PROPRIETARY NAME: Cialis

ESTABLISHED/PROPER NAME: tadalafil

DOSAGE FORM/STRENGTH: tablet 5 mg

APPLICANT: Eli Lilly and Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)

BACKGROUND:
Tadalafil is already approved to treat men with erectile dysfunction (ED) under NDA 021368 and also for patients with pulmonary arterial hypertension (PAH) under NDA 022332.

Eli Lilly held a Pre-IND meeting on January 17, 2006, with the Division of Reproductive and Urologic Products (DRUP) to discuss their development plans for tadalafil for the treatment of BPH. IND 073502 was opened for those studies. Eli Lilly's End of Phase 2 meeting was held with DRUP on September 25, 2008. Eli Lilly then had a Pre-NDA meeting April 13, 2010, to discuss submission plans for their supplemental NDAs for once daily use of tadalafil for BPH and combined BPH/ED use. DRUP provided Eli Lilly with minutes on May 12, 2010 as well as "Additional Discussion Items" on August 24, 2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	George Lyght	Y
	CPMS/TL:	Margaret Kober	Y
Cross-Discipline Team Leader (CDTL)	Mark Hirsch		Y
Clinical	Reviewer:	Roger Wiederhorn	Y
	TL:	Mark Hirsch	Y
Social Scientist Review (*for OTC*	Reviewer:		

products)			
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Denis Bashaw, Director Chongwoo Yu	N Y
	TL:	Myong-Jin Kim	N
Biostatistics	Reviewer:	Xin Fang	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yangmee Shin	Y
	TL:	Lynnda Reid	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Jeffrey Medwid	N
	TL:	Donna Christner	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Roy Blay	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Karen Townsend	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	Y
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☑ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☑ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☑ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: ☑ NO ☐ To be determined Reason:

o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☑ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☑ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☑ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☑ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☑ YES ☐ NO ☑ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**: None	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: George Benson, MD **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☑	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☑ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☑ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE A LYGHT
08/12/2011

MARGARET M KOBER
08/12/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 21, 2011

TO: George Lyght, R.Ph., Regulatory Project Manager
Roger Wiederhorn, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Branch Chief (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 21-368/S-020 and -021

APPLICANT: Eli Lilly & Co.

DRUG: Tadalafil (Cialis®)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) and the treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (ED/BPH)

CONSULTATION
REQUEST DATE: February 9, 2011

DIVISION ACTION
GOAL DATE: October 6, 2011

PDUFA DATE: October 6, 2011

I. BACKGROUND:

The applicant submitted this application for the use of Cialis® to support an indication for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) and the treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (ED/BPH). The following three pivotal studies were submitted in support of the indication.

Study H6D-MC-LVHR:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Tadalafil 2.5 and 5 mg Once-Daily Dosing for 12 Weeks for the Treatment of Erectile Dysfunction and Signs and Symptoms of Benign Prostatic Hyperplasia in Men With Both Erectile Dysfunction and Benign Prostatic Hyperplasia.

The primary efficacy measures are the change from baseline (Visit 3) to the end of therapy or Week 12 (Visit 7) in the Total IPSS and the IIEF EF Domain score. The former is the sum of the responses to the seven component questions with IPSS scores ranging from 0 to 35 with higher scores representing a greater severity of BPH-LUTS symptoms. The latter is the sum of the responses to the six component questions with scores ranging from 1 to 30 with higher numerical scores representing better erectile function.

Study H6D-MC-LVHG:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design,
5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia.

The primary efficacy measure is the IPSS which represents the sum of the responses to the seven component questions with IPSS scores ranging from 0 to 35 with higher scores representing a greater severity of BPH-LUTS symptoms.

Study H6D-MC-LVHJ:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia.

The primary efficacy measure is the IPSS which represents the sum of the responses to the seven component questions. IPSS scores range from 0 to 35 with higher scores representing a greater severity of BPH-LUTS symptoms.

The following sites were selected for inspection because of their enrollment of relatively large numbers of subjects.

II. RESULTS (by Site):

Name of CI, Location	**Protocol #/ # of Subjects/**	**Inspection Dates**	**Final Classification**
Site #115 Mohamed Bidair, M.D. 6699 Alvarado Road, Suite 2207 San Diego, CA 92120 Ph: (619) 229-2626	LVHR/ 30/	16-28 Mar 2011	VAI. Pending Final Classification.
Site #101 Eugene Dula, M.D. West Coast Clinical Research 5525 Etiwanda Ave. (818) 996-4242	LVHR/ 29/	1-14 Apr 2011	VAI. Pending Final Classification.
Site #101 Franklin Gaylis, M.D. Franklin D. Gaylis MedResearch 8851 Center Drive, Suite 501 La Mesa, CA 91942 (619) 697-2456	LVHG/ 50/	14-26 Apr 11	VAI. Pending Final Classification.
Site #102 James McMurray, M.D. 303 Williams Ave., S.W., Suite 411 Huntsville, AL 35801 (256) 553-1687	LVHJ/ 21/	5-6 Apr 2011	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Site #115
   Mohamed Bidair, M.D.
   6699 Alvarado Road, Suite 2207
   San Diego, CA 921208

   a. What was inspected: At this site, 58 subjects were screened for the study (one subject re-screened), and 22 completed the study (Subject 3733 was not counted having declined final laboratory testing). The records of 20 subjects were audited. The records audited included, but were not necessarily limited to, informed consent forms, inclusion/exclusion criteria, primary and secondary efficacy endpoints, protocol deviations, adverse events, concomitant medications, eCRFs, drug accountability records, IRB correspondence, and Uroflow calibration records. Subject records were compared to CRF entries.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection. Deviations observed included a lack of prompt reporting to the IRB of unanticipated problems (at least one Safety Report was delayed in its submission to the IRB). Subjects 3748, 3750 and 3756 were randomized to the study despite meeting exclusion criteria. All three were subsequently terminated early as documented in the line listings. Drug disposition records were not accurate for Subjects 3703, 3737, and 3742 though the discrepancies appear confined to internally generated drug logs. Sponsor–provided logs appear to properly document drug disposition. There were discrepant responses for several subjects between source data and eCRFs for specific questionnaire items and for the amounts of study article returned.

The following table of discrepant responses was forwarded to DRUP for review:

Subject #	Visit #	Question #	I-PSS-subject	I-PSS- eCRF	IEFF-subject	IEFF-eCRF	SEP-source	SEP-eCRF
3707	7	6	Less than one-half the time	About half the time				
3733	6	3			Some times	Most times		
3745	2	4			Most times	Almost always or always		
3745	2	5			Slightly difficult	Not difficult		
3745	2	3					Yes	No
3756	3	5	Less than 1 time in 5	More than half the time				

c. Assessment of data integrity These discrepancies in responses between questionnaires and the eCRFs were brought to the attention of Drs. Wiederhorn and Hirsch of DRUP on July 14, 2011. Dr. Wiederhorn responded via e-mail the same day that the observed discrepancies for Subjects 3707 and 3756 would be unlikely to change the efficacy conclusions regarding the use of the 2.5 mg dose of tadalafil. In addition, as primary efficacy was determined by assessment of difference scores between Visit 3 and Visit 7, for the majority of subjects with discrepant diary and eCRF scores the discrepancy would not impact primary efficacy analysis.

Dr. Bidair's written response dated April 6, 20011, outlined his commitment and specific actions for improving study practices to prevent such observations from occurring in future studies.

Other than the discrepancies in questionnaire responses discussed in detail above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Site #101
   Eugene Dula, M.D.
   West Coast Clinical Research
   5525 Etiwanda Ave.

   a. What was inspected: At this site, 74 subjects were screened for the study, 29 were enrolled, and 23 completed the study. The records of 20 subjects were audited. Records reviewed included, but were not necessarily limited to, a comparison of source documents with electronic Case Report Forms (eCRFs), informed consent forms, IRB and CRO correspondence, inclusion/exclusion criteria, the primary and secondary efficacy endpoints, adverse event reporting, concomitant medication records, laboratory tests, and test article accountability.

   b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection. A comparison of subject responses made on the IIEF and/or I-PSS questionnaires with the corresponding entries on the eCRFs revealed numerous discrepancies including, but not necessarily limited to, an absence of source documentation, date and time discrepancies regarding sexual encounters, and study article intake. Responses to specific questions within the IIEF and/or I-PSS comprised the primary efficacy endpoint. Discrepancies between these responses as recorded by the subjects on the questionnaires and the corresponding entries on the eCRFs would have the potential to affect the co-primary endpoint evaluations for these subjects. Such discrepancies were observed for subjects 1101, 1142, 1148, 1151, 1156, 1159, and 1173.

   The above findings were discussed extensively in a teleconference held on July 12, 2011, between Drs. Roger Wiederhorn, reviewing medical officer for DRUP, Mark Hirsch, Team Leader for DRUP, and Roy Blay, OSI reviewer. Of particular importance to the medical review team were the observed discrepancies in responses to those questions in the IIEF and the I-PSS which constituted the domains of the co-primary efficacy endpoints. As previously noted, discrepant responses between the source documents as completed by study subjects and the corresponding information recorded on eCRFS could have the potential to affect the evaluation of the co-primary efficacy endpoints. Dr. Hirsch noted that Subjects 1101, 1142, 1148, 1151, 1159, and 1173 were discrepant with respect to questions on the IIEF, and Subject 1156 was discrepant with respect to a question on the I-PSS. Dr. Hirsch said that he would ask the DRUP statistician to perform a new analysis for the corresponding endpoint, excluding the data for the six subjects with discrepant responses on the IIEF. With respect to Subject 1156, because the discrepancy was particularly small and only involved one subject at one visit, Dr. Hirsch said that it was their preference to retain this subject in the analysis of the I-PSS endpoint.

   The following table indicates how the responses differed between those of the subject on the source documents and what was subsequently recorded on the eCRF. As noted above, DRUP will do a re-analysis excluding the discrepant

responses on the IIEF for six subjects to determine any effect on study outcome.

Subject	Question #	Visit #	IIEF-subject	IIEF-eCRF	I-PSS-subject	I-PSS-eCRF
1101	4	6	Almost always or always	Almost never or never		
1142	1	6	Almost never or never	Almost always or always		
1142	2	6	Almost never or never	Almost always or always		
1148	4	5	Almost always or always	Did not attempt		
1148	QOL	5			Mostly dissatisfied	Mixed-about equally satisfied and dissatisfied
1151	2	3	Almost never or never	Almost always or always		
1151	3	3	Almost never or never	Almost always or always		
1151	4	3	Almost never or never	Almost always or always		
1151	1				About half the time	More than half the time
1156	5	6			About half the time	Less than half the time
1159	1	3	Almost always or always	Sometimes		
1159	2	3	Most times	Few Times		
1159	3	3	Almost always or always	Most times		
1159	4	3	Most times	Sometimes		
1159	5	3	Difficult	Slightly difficult		
1173	1	6	Most times	Almost never or never		

Dr. Dula's written response attributes these discrepancies to human error, in particular to the "…click and scroll features of electronic systems..." If the grades /classifications are part of a continuum of potential responses selected as part of a drop-down menu operated by the click and scroll features of a mouse, then the root cause of these discrepancies with regards to their number and nature may be more readily appreciated.

c. Assessment of data integrity: The observations in this inspection, and, in particular, the discrepancies with the potential to affect the co-primary endpoints have been discussed at length with the review division (DRUP). DRUP re-analyzed the IIEF data, excluding the discrepant data. This re-analysis, per discussion with Dr. Wiederhorn, indicated that the primary efficacy endpoint was not affected by the exclusion of the discrepant data. In addition, as primary efficacy was determined by assessment of difference scores between Visit 3 and Visit 7, for the majority of subjects with discrepant diary and eCRF scores the discrepancy would not impact primary efficacy analysis. Other deviations were isolated in nature and would not appear to have a significant impact on data integrity. Other than the discrepancies in questionnaire responses discussed in detail above, the study appears to have been conducted adequately, and the balance of data generated by this site appear acceptable in support of the respective indication.

3. Site #101
   Franklin Gaylis, M.D.
   Franklin D. Gaylis MedResearch
   8851 Center Drive, Suite 501
   La Mesa, CA 91942

   a. What was inspected: At this site, 83 subjects were screened and 50 were enrolled in the study. An audit of 22 subjects' records was conducted. All informed consent forms were reviewed. Other records reviewed included, but were not necessarily limited to, inclusion/exclusion criteria, primary and selected secondary efficacy endpoints, discontinuations, protocol deviations, subject randomization, Uroflow and ECG printouts, laboratory data, adverse events, concomitant medications, and drug accountability. Source documentation was compared to eCRFs.

   b. General observations/commentary: A Form FDA 483 was issued. Observations included, but were not necessarily limited to the following: Subject 1104 was enrolled into the study despite meeting the exclusion criterion of a positive leukocyte esterase test. Subjects 1103, 1109, 1119, and 1130 had PSA samples drawn less than 48 hours after their last ejaculations (this occurred one time at one visit for each subject). Subjects 1133, 1175, and 1183 were missing various laboratory results for Visits 6, 8, and 12, respectively. Subject 1124 discontinued from the study stating that the study medication caused a rise in blood pressure. This adverse event was not reported on the CRF; however, no evidence of resulting subsequently related events were noted in source records or the CRF. Subject 1133 experienced right side abdominal pain possibly related to the study drug according to source documents; however, the CRF stated that the pain was not related to the study drug. Subject 1102's BPH Impact Index was completed on the source document but not reported on the CRF. Subject 1130's responses on the I-PSS at Visit 8 are discrepant with those reported on the CRF. The subject's total score on the source document was 8; however, the total was 12 on the CRF.

   c. Assessment of data integrity While enrollment of a single ineligible subject at the site seems unlikely to significantly impact safety and efficacy analyses, the review division may wish to consider excluding data from Subject 1104 from per protocol analyses. In addition, the review division may wish to consider the impact, if any, regarding the correct I-PSS score for Subject 1130 on its evaluation of the respective endpoint. The other deviations noted appear to be isolated in nature and are unlikely to significantly impact primary safety or efficacy analyses. In addition, it does not appear that the rights, safety, or welfare of subjects was compromised. With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Site #102
   James McMurray, M.D.
   303 Williams Ave., S.W., Suite 411
   Huntsville, AL 35801

   a. What was inspected: At this site, 24 subjects were screened, three were screen failures, twenty completed the study, and one subject withdrew from the study. The records of all 24 subjects were reviewed. The audit included, but was not necessarily limited to, the following parameters: informed consent, IRB, sponsor, and monitor correspondence, test article accountability, and electronic Case Report Forms.

   b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. No significant regulatory violations were noted.

   c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Bidair, Dula, Gaylis, and McMurray were inspected in support of this NDA. No significant regulatory violations were noted at Dr. McMurray's site and the final classification for the inspection is No Action Indicated (NAI).

Regulatory violations were noted at the sites of Drs. Bidair, Dula, and Gaylis and the preliminary classifications for each of these inspections is Voluntary Action Indicated (VAI). Noteworthy were discrepancies observed between the source document questionnaires and the corresponding CRFs at Dr. Bidair's site for Subjects 3707, 3733, 3745, and 3756, and at Dr. Dula's site for Subjects 1101, 1142, 1148, 1151, 1159, and 1173. However, as primary efficacy was determined by assessment of difference in Total IPSS and the IIEF EF Domain scores between Visit 3 and Visit 7 in Study LVHR, discrepant documentation would impact primary efficacy outcome for Subjects 3707 and 3756 from Dr. Bidair's site and Subjects 1151 and 1159 at Dr. Dula's site. At Dr. Gaylis's site, only Subject 1130 (enrolled in Study LVHG) exhibited such a discrepancy. These discrepancies have been discussed with the DRUP reviewing medical officer, Dr. Wiederhorn and the Team Leader, Dr. Hirsch. Dr. Wiederhorn indicated that the discrepancies observed at Dr. Bidair's and Dr. Dula's sites would be unlikely to affect the assessment of the primary efficacy outcome. Similarly, at Dr. Gaylis's site, the exclusion of data from Subject 1130 for a single discrepant response would be unlikely to affect the primary efficacy outcome.

Notwithstanding the observations detailed above, the studies appear to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
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/s/

ROY A BLAY
07/21/2011

JEAN M MULINDE
07/22/2011

LAUREN C IACONO-CONNORS
07/22/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date:	June 27, 2011
Application Type/Number:	NDA 021368/S-020 and S-021
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator
Subject:	Label and Labeling Review
Drug Name(s):	Cialis (Tadalafil) Tablets, 2.5 mg, 5 mg, 10 mg, and 20 mg
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2011-343

CONTENTS

1 INTRODUCTION

This review evaluates the container label, carton and package insert labeling, as well as packaging for Cialis (Tadalafil) Tablets for the potential to contribute to medication errors. The labels and labeling were submitted under Efficacy Supplements, 020 and 021, which allow for a new indication for treatment of Benign Prostatic Hyperplasia (S-020) as well as the combination of Erectile Dysfunction and Benign Prostatic Hyperplasia (S-021). This review responds to the Division of Reproductive and Urologic Products (DRUP) February 15, 2011, request.

1.1 REGULATORY HISTORY

Cialis (NDA 021368) was approved on November 21, 2003 for the treatment of erectile dysfunction. After approval of the product, DMEPA completed one labeling review (OSE Review #2007-2565), dated December 21, 2007. The review was related to the Efficacy Supplement-011, which provided for 2.5 mg strength and a once daily dosing regimen for 2.5 mg and 5 mg tablets. The review focused on the blister label and carton labeling and recommended these labels and labeling not be approved. However, in case of approval, the review recommended a multitude of changes to the labels and labeling such as removing days of the week from the blister pack, deleting the phrase "Once daily" from the principle display panel, revising "Usual Dosage" statement, ensuring sufficient differentiation between 2.5 mg and 5 mg labels, and deleting unnecessary information. It is unknown whether the Applicant received DMEPA's recommendations.

On December 6, 2010, the Applicant submitted Efficacy Supplements 020 and 021 to expand Cialis's indication for the treatment of of Benign Prostatic Hyperplasia (S-020) as well as the combination of Erectile Dysfunction and Benign Prostatic Hyperplasia (S-021). The proposed dose for the new indications is 5 mg administered orally once daily at approximately the same time of each day. Thus, the marketed strengths and packaging configuration for Cialis will remain the same for the new indications.

2 METHODS AND MATERIALS

Since Cialis has been marketed since 2003, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Cialis's labels and labeling.

Additionally, DMEPA evaluated the proposed container labels, carton and package insert labeling for Cialis using Failure Mode and Effects Analysis[1] (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 CIALIS ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SELECTION OF CASES

The AERS search conducted on May 4, 2011 for Cialis used the following search terms: MedDRA High Level Group Terms (HLGT) "Medication Errors" and "product Quality Issues" along with the active ingredient name of "Tadalafil", the trade name "Cialis" and the verbatim terns "Tada% and "Cial%" and no date limitations were used in the search.

Duplicate reports were combined into cases. Those cases, not pertaining to medication errors related to the labels and labeling of Cialis (i.e., intentional overdoses, recreational use, or accidental ingestion by a child) and cases pertaining to adverse events and allergic reactions were

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

excluded from further analysis. All cases of medication error related to the labels and labeling were evaluated and grouped by the type of error. Each case was evaluated for the root cause.

2.2 LABELS, LABELING, AND PACKAGING RISK ASSESSMENT

The Applicant submitted the container labels for Cialis 5 mg, 10 mg, and 20 mg and prescribing information labeling for Efficacy Supplement-020 on December 3, 2010. The Applicant submitted prescribing information labeling for Efficacy Supplmement-021 with incorporated changes from Supplement-020 on December 6, 2010. Additionally, the Applicant submitted blister card labels for Cialis 2.5 mg and Cialis 5 mg on August 11, 2009 and carton labeling for these strengths on March 18, 2011. Thus, the following container labels, blister labels, and carton labeling were submitted by the Applicant (See Appendix A for the container labels, blister card labels, and carton labeling):

- Blister Card labels: 2.5 mg and 5 mg
- Carton Labeling 2.5 mg and 5 mg
- Container Labels: 5 mg, 10 mg, and 20 mg

Additionally, DMEPA checked the Applicant's Annual Report submitted to the FDA on July 20, 2010 to identify whether the product has child resistant packaging.

3 RESULTS

The following sections describe the results of the DMEPA's medication error searches and labeling evaluation.

3.1 CIALIS ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE RESULTS

In total DMEPA evaluated six cases. Five cases involved wrong administration technique (n=5), one case involved overdose (n=1), and one case involved wrong drug (n=1). Thus, the number of errors (n=7) exceeded the number of cases (n=6). The following Sections describe the cases in detail.

3.1.1 Wrong Administration Technique (n=5)

Five cases (n=5) reported wrong administration technique. Four cases (n=4) reported dividing tablets and one case (n=1) reported chewing tablets.

Dividing tablets (n=4)

Three cases (n=3) reported dividing the tablet in half and administering half of the tablet. One foreign case from Republic of Korea occurred in 2011 (ISR #7416302-0). The remaining two US cases from 2004 and 2006 (ISR #4535588-3 and 5088611-4) reported dividing the tablet in half and administering half of the tablet. These two cases reported the strength of Cialis was 20 mg. The cases reported patient outcome of blurred vision and temporary amnesia.

One case from 2006 (ISR #4900020-4) reported dividing a 20 mg tablet in several pieces containing approximately 5 mg and administering one piece of the tablet at a time. The case reported patient outcome of progressively blurred vision.

Chewing Tablets (n=1)

One case from 2007 (ISR #5427102-5) reported chewing tablets prior to intercourse. The case reported that the reason for chewing the tablets was for the tablets "to act fast". The patient did not experience any adverse events except a bitter taste.

3.1.2 Overdose (n=1)

One case from 2004 (ISR #4535588-3) reported that the patient administered one and a half tablet of Cialis 20 mg. No additional information was provided.

3.1.3 Wrong Drug (n=1)

One case from 2005 (ISR #4747252-6) reported that Levitra was dispensed to the patient instead of Cialis during the refill of Cialis prescription. No additional details were reported. We suspect the error could have occurred during product selection, because it occurred on a refill and the prescription would already be saved in a pharmacy computer system and would only need to be filled and dispensed to the patient eliminating the computer entry of the original prescription. The confusion might have occurred because Cialis and Levitra share the same strengths (i.e., 2.5 mg, 5 mg, 10 mg, and 20 mg), indication (i.e. erectile dysfunction), and may be stored next to each other on a shelf (i.e., fast rack shelf or restricted access shelf). The container labels for Cialis is different from Levitra (see Appendix B for Levitra container labels). Since the labels of these two products are well-differentiated and the wrong drug error involving Cialis and Levitra was identified only once, additional action is not warranted at this time. However, DMEPA will continue to monitor this issue.

3.2 Labels Labeling, and Packaging Risk Assessment

Our evaluation of the bottle container closure system determined that it is adequate because the container closure is child resistant. However, for the blister packs, the Applicant listed several components of the container closure system (i.e., blister laminate and aluminum foil lid) and stated that one particular type of aluminum foil lid (b) (4) is child-resistant. From the submission, we are unable to determine whether this is the type of aluminum foil lid used for the current Cialis's blister packs.

Our evaluation of the container label, carton, and prescribing labeling notes that NDC numbers are appropriately differentiated because the middle numbers are different among different strengths of the product. However, our evaluation of the container label, carton, prescribing labeling identified the following deficiencies:

- The professional labeling uses error-prone symbols such as slash marks (i.e.,'/') and less than or grater than signs (i.e.,'<' and '>').
- The prfessional labeling uses abbreviations to express the indications such as ED for Erectile Dysfunction and BPH for Benign Prostatic Hyperplasia.
- (b) (4)
- The prescribing information does not contain a warning against dividing, chewing, or crushing tablets. However, the tablets should not be divided, chewed, or crushed.
- (b) (4)
- (b) (4)
- The expression of days of the week and the statement "last tablet" above the tablets on the blister label is confusing and unnecessary.

- The company logo appears very prominently on the container label and carton labeling, and thus, competes for prominence with the most important information on the principle display panel such as proprietary and established names, dosage form, and strength.
- The abstract graphic of yellow and greens shape combination is prominently located on the principle display panel of the container labels and carton labeling; and thus, competes for prominence with the most important information on the principle display panel such as proprietary and established names, dosage form, and strength.

4 DISCUSSION

We evaluated six cases of postmarketing medication errors. Five of the six cases involve the splitting or chewing of Cialis tablets. Although the patient outcomes involved blurred vision, it may not be due to the wrong administration technique error, but due to the use of Cialis itself, because visual field defects are a known adverse reaction which has a temporal association with phosphodiesterase type 5 inhibitors. However, it is unknown whether administering divided tablets increases the risk of this adverse reaction. Additionally, Cialis tablets should not be divided, chewed, or crushed because they are film-coated. Furthermore, the tablets are not scored, which increases the risk of dividing a tablet unequally and administering a wrong dose. As a result, changes to the labels and labeling regarding dividing, chewing, or crushing tablets should be made to help decrease the incidence of tablet division or chewing.

Additionally, as we stated in OSE Review #2007-2565, our labels and labeling risk assessment finding indicates that blister labels and carton labeling have an error-prone design. The 2.5 mg and 5 mg blister cards contain days of the week, a statement 'last tablet', and a clockwise arrow above the tablets organized in a circular manner and a tablet in the middle. The product should be administered once daily without respect to any cyclical pattern. Thus, having the product labeled by days of the week is confusing and may lead to dosing errors. Additionally, the phrase "last tablet" may lead to confusion in that patients may misinterpret this phrase to stop taking medication after administering the dose labeled "last tablet". As a result, we believe that the blister cards should be revised to delete the days of the week, the statement "last tablet", and the clockwise arrows. Ideally, the blister pack should also be revised to eliminate the circular pattern and a tablet in the middle and to expand the blister pack to contain 30 tablets in a linear manner to avoid confusion and to provide an adequate day supply (i.e., 30 days) in one blister pack.

Furthermore, although the container bottle closure system is child-resistant, we are unable to determine whether blister pack packaging configuration is child-resistant as well. Thus, it is important to ensure the all of the container closure systems for Cialis are child-resistant in order to prevent accidental child exposure and possible serious adverse reactions associated with it.

5 CONCLUSSIONS AND RECOMMENDATIONS

Our evaluation of the container and blister labels as well as carton and professional labeling noted deficiencies that can be improved upon to minimize the potential of medication errors. Thus, DMEPA recommends labels and labeling revisions outlined below be implemented prior to approval of the Efficacy Supplements-020 and 021. Section 5.1 *Comments to the Division* contains our recommendations regarding the prescribing information labeling and Section 5.2 *Comments to the Applicant* contains our recommendations regarding container and blister labels as well as carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior the approval of the Supplements.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

5.1 COMMENTS TO THE DIVISION

Prescribing Information Labeling

1. General

   Revise all instances of the of the abbreviation 'ED' and 'BPH' in the *Indications and Usage* as well as *Dosage and Administration* Sections to state "Erectile Dysfunction" and "Benign Prostatic Hyperplasia" because abbreviations can often be misinterpreted.

2. *Dosage and Administration* Section in Highlights of Prescribing Information

   [redacted] (b) (4) Please separate the dosing for these two separate indications under different bullet points to increase comprehension of this information. The information may appear as follows:

   - Benign Prostatic Hyperplasia: 5 mg, administered at approximately same time every day
   - Erectile Dysfunction and Benign Prostatic Hyperplasia: 5 mg, administered at approximately same time every day

3. *Dosage and Administration* Section in Highlights and Full Prescribing Information

   a. As a part of the campaign to reduce medication errors related to error-prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that included the use of error-prone abbreviations, symbols, and dose designations. Thus, we recommend the following revisions be implemented in support of this campaign.

      - The slash mark '/' is a dangerous abbreviation that appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations[2] because this symbol has been mistaken as number '1'. Additionally, this symbol may be misinterpreted as 'or' when 'and' is implied and vice versa. Therefore, we request you revise '/' to read "and". As a result, please revise statements "efficacy/tolerability" to read " efficacy and tolerability" and "ED/BPH" to read "Erectile Dysfunction and Benign Prostatic Hyperplasia".

      - Revise all instances of the symbol '<' and '>' to read "less than" and "greater than." The symbols '<' and '>' are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended.

   b. Add a statement to appear immediately below the heading *Dosage and Administration* that reads. "Do not divide, crush, or chew Cialis tablets" to warn patients not to break or chew the tablets. DMEPA identified several medication error cases which reported that Cialis tablets were either divided or chewed and several patients developed adverse reactions such as blurred vision.

[2] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

5.2 COMMENTS TO THE APPLICANT

A. Blister Labels and Carton Labeling (2.5 mg and 5 mg)

1. Ensure the size of the established name is at least ½ size the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
2. Increase the prominence of the dosage form by increasing the font size on the principle display panel. As currently presented, the dosage form appears in a very small font and is hard to read.
3. Delete or relocate the phrase "for once daily use" (b) (4) This statement is unnecessary and occupies space since the Usual Dosage statement already instructs the consumers to administer Cialis once daily. (b) (4) Furthermore, 5 mg tablets used for Erectile Dysfunction may also be administered on "as needed" basis and the statement "for once daily use" may be misinterpreted that the product should be administered every day.
4. Add the statement to blister label and carton labeling that reads "Swallow whole. Do not divide, chew, or crush tablets". We recommend this change because we identified several cases reporting patients dividing or chewing Cialis tablets.

B. Blister Card Labels (2.5 mg and 5 mg)

1. Revise the blister card so that days of the week, the statement "last tablet", and clockwise arrows are removed. The product should be administered once daily without respect to any cyclical pattern. Thus, having the product labeled by days of the week is confusing and may lead to dosing errors. Additionally, the phrase "last tablet" may lead to confusion in that patients may misinterpret this phrase to stop taking medication after administering the dose labeled "last tablet".
2. Increase the differentiation between the blister cards containing 2.5 mg of Cialis and 5 mg of Cialis by using contrasting background color font, proprietary name color font, or some other means. (b) (4)
3. (b) (4)
4. Delete the web address (i.e., www.cialis.com) from both blister label and carton labeling as this information is unnecessary, clutters the label, and distracts from the other important text appearing on the principle display panel.
5. Decrease the prominence of the 'Rx Only' statement (b) (4)

B. Carton Labeling (2.5 mg and 5 mg)

1. Delete the graphic containing the name 'Cialis' with green and yellow abstract drawing next to it as well as the Applicant's logo in an oval graphic. These items are prominently displayed on the principle display panel and compete for prominence with the most

important information on the principle display panel such as proprietary name and established name, dosage form and strength.

2. Once the blister labels are revised to delete unnecessary and confusing information such as days of the week, the statement "last tablet", and clockwise arrows, we request you also delete the administration instructions under the heading "How to take CIALIS for once daily use" from the back panel. These directions will no longer be necessary because the arrows and days of the week will be removed.

C. Container Labels (5 mg, 10 mg, and 20 mg)

1. Delete the abstract graphic of yellow and green shape combination from the principle display panel as this graphic is the most prominent item on the principle display panel. The most important information on the label should be the proprietary name and established name, dosage form and strength.
2. (b) (4)
3. Increase the prominence of the dosage form by increase the font size on the principle display panel. As currently presented, the dosage form appears in a very small font and is hard to read.
4. Decrease the prominence of the 'Rx Only' statement by unbolding it and decreasing the font size as this statement appear almost as prominent as the established name of the product.
5. If space permits, revise the side panel containing Usual Dosage, storage, contents, and warning information to appear in horizontal manner to improve readability of this information. As currently presented in a vertical manner, the information is hard to read.
6. Add the statement "Swallow whole. Do not divide, chew, or crush tablets" to appear prominently on the principle display panel. We recommend this change because we identified several cases reporting patients dividing or chewing Cialis tablets.

REFERENCES

Holquist, Carol. OSE Review #2007-2565, Cialis Labeling Supplement Review, 12/21/2007

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YELENA L MASLOV
06/27/2011

ZACHARY A OLESZCZUK
07/05/2011

CAROL A HOLQUIST
07/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See list attached.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
James McGill	GBD-Leader-Sr Dir-Medical-Urology
FIRM / ORGANIZATION Eli Lilly & Company	
SIGNATURE	**DATE** 17 Sep 2010

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06)

PSC Graphics (301) [illegible]

Site Name & Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)
Feldman, Robert, MD #100	29	(b) (6)
Gaylis, Franklin, MD #101	84	
Kriteman, Lewis, MD #102	14	
Wurzel, Rafael, MD #104	19	
Greengold, Richard, MD #105	13	
Aliotta, Phillip, MD #106	18	
Dula, Eugene, MD #107	70	
Hudnall, Clayton, MD #108	31	
Auerbach, Stephen, MD #109	28	

[1]See attached FDA form 3455.

		(b) (6)
McMurray, James, MD #110	56	
Rollins, Raleigh, MD #112	32	
Roberts, Brian, MD #113	16	
Bar-Chama, Natan, MD #114	19	
Broderick, Gregory, MD #115	1	
Kaufman, Joel, MD #116	43	
Beccia, David, MD #117	35	
Efros, Mitchell, MD #118	45	
McCullough, Andrew, MD #119	20	
Bailen, James, MD #120	24	
Barada, James, MD	31	

[1]See attached FDA form 3455.

		(b) (6)
#121		
Baum, Neil, MD #122	12	
Cowan, Barrett, MD #123	31	
Fitch, William, MD #125	23	
Kaminetsky, Jed, MD #126	38	
Karlin, Gary, MD #127	19	
Klimberg, Ira, MD #128	3	
Knoll, Dean, MD #129	8	
McVary, Kevin, MD #130	1	
Roy, Johnny, MD #133	18	
Sweet, Robert, MD #134	17	
Steidle, Christopher, MD #135	12	
Gambla, Michael, MD #138	40	

[1]See attached FDA form 3455.

		(b) (6)
Goldfischer, Evan, MD #139	31	
Jones, William, MD #140	15	
Kim, Edward, MD #141	13	
Morgentaler, Abraham, MD #142	6	
Donatucci, Craig, MD #143	25	
Costabile, Raymond, MD #145	3	
Rosenberg, Steven, MD #146	26	
Cochran, James, MD #147	5	

[1]See attached FDA form 3455.

		(b) (6)
Gerald Brock, MD[1] #201	15	
Bryniak, Steven, MD #202	12	
Carrier, Serge, MD #203	17	
Pommerville, Peter, MD #204	18	
Andreou, Charalambos, MD #205	16	
Chevallier, Daniel, MD #300	33	
Cuzin, Beatrice, MD #302	10	
Ibrahim, Hussien, MD #303	20	
Lan, Oliver, MD #304	15	
Rischmann, Pascal, MD #306	5	
Costa, Pierre, MD #308	13	
Giuliano, Francois, MD #309	2	
Melekos, Michalis, MD #314	14	
Perimenis, Petros, MD #315	16	
Hatzichristou, Dimitrios, MD #316	30	
Sofras, Frank, MD #317	3	
Mirone, Vincenzo, MD[1] #322	14	
Montorsi, Francesco, MD #323	30	
Carone, Roberto, MD #324	1	
Canclini, Luca, MD	18	

[1]See attached FDA form 3455.

		(b) (6)
#326		
Hernandez, Carlos, MD #329	5	
Pineiro, Luiz, MD #330	5	
Segarra, Jose, MD #331	10	
Gutierrez, Carlos, MD #332	3	
Franco, Eladio, MD #334	2	
Wiklund, Peter, MD #343	12	
Oldbring, Jorgen, MD #344	13	
Pileblad, Erik, MD #345	9	
Mansour, Essum, MD #346	8	
Binder, Manfred, MD #400	13	
Fluehr, Wolfram, MD #401	3	
Stoeckle, Michael, MD #402	4	
Heicappell, Ruediger, MD #403	3	
Helder, Thomas, MD #405	38	
Liebald, Timo, MD #406	11	
Mueller, Detlef, MD #407	10	
Porst, Hartmut, MD[1] #409	31	
Quast, Detlef, MD #410	22	
Richter, Arndt, MD #411	9	
Stief, Christian, MD #412	4	

[1]See attached FDA form 3455.

von Keitz, Alexander, MD #413	26	(b) (6)
Warnack, Wolfgang, MD #414	12	
Willgerodt, Joerg, MD #415	30	
Andrade, Rene, MD #520	17	
Rueda, Alejandro, MD #522	14	
Feria, Guillermo, MD #523	7	
Martinez, Rafael, MD #524	54	
Zepeda, Sebastian, MD #525	50	
Mendoza, Arturo, MD #526	25	
Sutherland, Peter, MD #600	27	
Gardiner, Robert, MD #601	4	
Kovac, Paul, MD #603	2	

[1]See attached FDA form 3455.

Tadalafil FDA Form 3455 Attachment

Financial Disclosure Form 3455 Supplemental

13-Oct-2009

H6D-MC-LVHG

Re: Accrued Equity above suggested Limits

(b) (6)

(b) (6), the Investigator, reported to Lilly that he received payments in the amount of $40,475.70 during 2006 thru 2008. (b) (6) was one of 98 Investigators who participated in LVHG, A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia. His site enrolled (b) (6) pts; this was (b) (6) of the total patients enrolled in the study (b) (6)

Tadalafil FDA Form 3455 Attachment

Financial Disclosure Form 3455 Supplemental

13-Oct-2009

H6D-MC-LVHG

Re: Accrued Equity above suggested Limits

(b) (6)

(b) (6), the Investigator, reported to Lilly that he received payments in the amount of $67,000 during 2006 and 2007. (b) (6) was one of 98 Investigators who participated in LVHG, A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia. His site enrolled (b) (6) pts; this was (b) (6) of the total patients enrolled in the study (b) (6)

Tadalafil FDA Form 3455 Attachment

Financial Disclosure Form 3455 Supplemental

13-Oct-2009

H6D-MC-LVHG

Re: Accrued Equity above suggested Limits

(b) (6)

(b) (6) the Investigator, reported to Lilly that he received payments in the amount of $43,365.85 during 2006 and 2007. (b) (6) was one of 98 Investigators who participated in LVHG, A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia. His site enrolled (b) (6) pts; this was (b) (6) of the total patients enrolled in the study (b) (6)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) , who participated
Name of clinical investigator

as a clinical investigator in the submitted study Study to Evaluate Efficacy & Safety of Daily Tadalafil for 12 wk in Men with Signs and Symptoms of BPH - LVHJ is submitted in accordance with 21 CFR part 54. The
Name of clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
James McGill	GBD Leader-Sr Director-Medical-Urology
FIRM/ORGANIZATION: Eli Lilly & Company	
SIGNATURE: [signature]	Date *(mm/dd/yyyy)*: 06/25/2010

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attachment	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
James McGill	GBD Leader-Sr Director-Medical-Urology
FIRM/ORGANIZATION Eli Lilly & Company	
SIGNATURE	DATE *(mm/dd/yyyy)*
	06/25/2010

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study Study to Evaluate Efficacy & Safety of Daily Tadalafil for 12 wk
Name of

in Men with Signs and Symptoms of BPH - LVHJ is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
James McGill	GBD Leader-Sr Director-Medical-Urology
FIRM/ORGANIZATION Eli Lilly & Company	
SIGNATURE	Date *(mm/dd/yyyy)* 06/25/2010

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

Financial Query Form

Date 09 Dec 2009

Request Submitted by: Beverly Braun

Please provide information on payments of other sorts[1] that Lilly has made to the investigators listed below during the specified time period. **Please provide this information within 30 days of receipt of this form.**

Protocol Number H6D-MC-**LVHJ**

Protocol Title **A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia**

Investigator Name (Last name first)	Institution Name and City and State, Province, etc.	OUS Lilly Affiliate	Start Date	Stop Date
(b) (6)	Instituto Medico Especializado Hidalgo 568 Buenos Aires Buenos Aires, 1405, Argentina	Argentina	22May09	09Nov09
	Praxis Dr. Med. Thomas Helder Hindenburgstrasse Muhlacker, D-75417, Germany	Germany	18Feb09	09Nov09
	Praxis Dr Bloemers Ludolfingerweg 5 Berlin, 13465, Germany	Germany	19Mar09	09Nov09
	Praxis Prof Porst Neuer Jungfernstieg 6a Hamburg, 20354, Germany	Germany	10Feb09	09Nov09
	Praxis Dr. Med. Detlev Quast Bernauer Strasse 100 Oranienburg, D-16515, Germany	Germany	02Feb09	09Nov09
	Arztpraxis Dr. Alexander Von Keitz Krummbogen 15 Marburg, 35039, Germany	Germany	25Feb09	09Nov09
	San Raffaele Hospital Via Olgettina 60 Milan, 20132, Italy	Italy	30Jan09	09Nov09

[1] Payments **NOT** including grants to fund clinical trials. Payments including, but not limited to: grants to fund **ongoing** research, honoraria, and consulting fees.

(b) (6)

Ospedali Riuniti Di Bergamo Largo Barozzi, 1 Bergamo, 24128, Italy	Italy	23Jan09	09Nov09
Policlinico Umberto I Viale Del Policlinico 155 Roma Roma, 00161, Italy	Italy	28Jan09	09Nov09
Universita Di Napoli Federico Ii Via Pansini, 5 Napoli, 80131, Italy	Italy	17Feb09	09Nov09
Azienda Sanitaria Ospedaliera S. Luigi Di Orbassano Regione Gonzole 10 Orbassano, Torino, 10043, Italy	Italy	24Feb09	09Nov09
Hospital Universitario De Monterrey Av Gonzalitos 235 Nte Monterrey, 64040, Mexico	Mexico	04Feb09	09Nov09
Office Of Dr Sebastian Zepeda Av Adrian Muguerza 1115 Cons 206 Col Las Brisas Saltillo, Coahuila, 25210, Mexico	Mexico	19Feb09	09Nov09
Hospital Angeles Interlomas Av. Vialidad De La Barranca S/n Cons. 545 Mexico City, Distrito Federal, 52763, Mexico	Mexico	24Feb09	09Nov09
Hospital Angeles Del Pedregal Camino A Sta Teresa #1055 Col Heroes De Padierna Mexico City, 10700, Mexico	Mexico	13May09	09Nov09
Office Of Dr Arturo Rodriguez Nino Obrero 850 Zapopan, Jalisco, 45040, Mexico	Mexico	06Apr09	09Nov09
Northwestern University 675 N St Clair St Chicago, Il, 60611, United States	United States	16Feb09	09Nov09
Duke University Medical Center 1112-C Duke South Green Zone Dumc Box 3274 Durham, NC 27710, United States	United States	23Apr09	09Nov09
Medical Affiliated Research Center 303 Williams Ave Huntsville, AL 35801, United States	United States	23Jan09	09Nov09

(b) (6)

University Urology Associates 215 Lexington Avenue New York, NY 10016, United States	United States	04Mar09	09Nov09
Urology Of Virginia PC 1200 First Colonial Road Virginia Beach, VA 23454, United States	United States	16Feb09	09Nov09
Urologic Research Of Western New York, LLC 6645 Main Street Williamsville, NY 14221, United States	United States	11Feb09	09Nov09
Medical And Clinical Research Associates, LLC 332 East Main Street Bayshore, NY 11706, United States	United States	17Feb09	09Nov09
Connecticut Clinical Research Center 1579 Straits Turnpike Middlebury, CT 06762, United States	United States	26Feb09	09Nov09
Columbus Urology Inc 1707 Bethel Rd Columbus, OH 43220, United States	United States	20Feb09	09Nov09
Volunteer Research Group 1928 Alcoa Highway Knoxville, TN 37920, United States	United States	27Jan09	09Nov09

(b) (6)				
	North Fulton Urology 1357 Hembree Road Roswell, GA 30076, United States	United States	01Apr09	09Nov09
	The Florida Urology Center PA 1 S School Ave Sarasota, FL 34237, United States	United States	17Feb09	09Nov09

Tadalafil FDA Form 3455 Attachment

Financial Disclosure Form 3455 Supplemental

25-Jun-2010

H6D-MC-LVHJ

Re: Accrued Equity above suggested Limits

(b) (6)

(b) (6) the Investigator, reported to Lilly that he received payments in the amount of $41,000 during the year of 2009. (b) (6) was one of 28 Investigators who participated in LVHJ, A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia. His site enrolled (b) (6) pts; this was (b) (6) of the total patients enrolled in the study (b) (6)

Tadalafil FDA Form 3455 Attachment

Financial Disclosure Form 3455 Supplemental

25-Jun-2010

H6D-MC-LVHJ

Re: Accrued Equity above suggested Limits

(b) (6)

(b) (6) the Investigator, reported to Lilly that he received payments in the amount of $ 41,131.30 during the year of 2009. (b) (6) was one of 28 Investigators who participated in LVHJ, A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia. His site enrolled (b) (6) pts; this was (b) (6) of the total patients enrolled in the study (b) (6)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

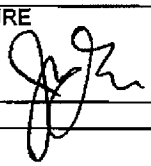
Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attachment	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
James McGill, MD	Sr. Medical Director
FIRM/ORGANIZATION	
Eli Lilly and Company	
SIGNATURE	**DATE** *(mm/dd/yyyy)*
	10/20/2010

Paperwork Reduction Act Statement

Site Name & Number	Number of Subjects Screened (V1)	Names of Investigators (Principal and Sub-Investigators)
#100 – California Professional Research	17	(b) (6)
#101 – West Coast Clinical Research	74	
#102 – MedResearch	62	
#103 – Integrity Medical Research, LLC	6	
#104 – Urology San Antonio Research	20	
#105 – Urology Associates	40	
#106 – University of Minnesota Hospital	5	
#107 – The Iowa Clinic	17	

		(b) (6)
#108 – Urology Clinics of North Texas PA	36	
#109 – Rockwood Clinic Research Center	32	
#111 – Carle Clinic Association	31	
#112 – Johnny Roy, MD	41	
#114 – Hope Research Institute	35	
#115 – San Diego Clinical Trials	58	
#116 – Urology Group of Southern California	24	

		(b) (6)
#117 – Alaska Clinical Research	6	
#118 – Five Valley Urology	5	
#205 – Charalambos Andreou, MD	19	
#206 – Steven Bryniak, MD	20	
#207 – Urology Associates	23	
#208 – Can-Med Clinical Research Inc.	22	
#209 – Dr. G. Steinhoff Clinical Research	23	
#210 – The Male/Female Health & Research Center	28	
#300 – CIF-Biotec	14	
#301 – Clinica Galeno	9	
#302 – Orio de Especialidad en Urologica Privado	18	
#303 – Unidad de Diagnostico Integral	21	
#304 – Asociacion Mexicana pra La Salud Sexual	81	

		(b) (6)
#400 – Universita de Sassari	20	
#401 – Ospedale Cattinara	9	
#402 – Ospedale San Martino Universita Genova	4	
#404 – San Raffaele Hospital	14	
#500 – Hospital Sao Joao	7	
#501 – Hospital Geral de Santo Antonio	1	
#502 – Hospitals da Universidade de Coimbra	6	
#503 – Hospital Fernando Fonseca	1	
#505 – Hospital Militar do Porto	16	
#600 – Gesundheitszentrum Holzminden	23	
#601 – Wolfram Fluehr, MD	10	
#602 – Arzt fuer Urologie	8	
#603 – Urologische Gemeinschaftspraxis Dr. Marin	10	
#604 – Praxis fuer Urologie Dr. Schorn	1	
#700 – Hospital Caremau Chu	13	

		(b) (6)
#701 – Hopital Edouard Herriot	15	
#702 – CHU – Hopital de Nice Hopital Pasteur	27	
#703 – CHR D'Orleans Hopital de La Source	23	
#704 – Synergia Polyclinique	9	
#705 – CHU Toulouse Hopital de Rangueil	8	
#800 – University General Hospital of Patras	11	
#801 – University General Hospital of Heraklion	8	
#802 – Regional Generaly University Hospital of Larissa	9	
#803 – Papageorgiou Regional General Hospital of Thessaloniki	1	

		(b) (6)
#804 – Laiko General Hospital of Athens	2	
#900 – Clinical Diagnostic Center Zdorovie	24	
#901 – Moscow Medical Academy	11	
#902 – Russian University Friendship of People Hospital N29	20	
#904 – National Medico-Surgical Center named after N.I. Pirogov	11	
#905 – Scientific & Research Institute of Urology	18	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attachment	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

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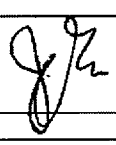
NAME	TITLE
James McGill, MD	Medical Director
FIRM/ORGANIZATION: Eli Lilly and Company	
SIGNATURE: 	DATE *(mm/dd/yyyy)*: 09/27/2010

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

Site Name & Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)
Sociedad de Urologia Especializada #101	7	(b) (6)
Rivera-Herrera, Jorge, MD #102	4	
Guzman-Virella, Jose, MD #103	2	
VA Caribbean Healthcare System Urology Section #104	6	
The Conrad Pearson Lab #105	11	
Medical & Clinical Research Associates, LLC #106	9	
University Urology Associates #107	12	
AcuMed Research Associates a Division of Integrated Medical Professionals #108	38	
Hudson Valley Urology, PC #109	9	
Northeast Urology Research #110	15	
Roy, Johnny, MD #112	25	
Bidair, Mohamed, MD #113	41	
Medical Affiliated Research Center, Inc. #114	16	

Site Name & Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)
Winter Park Urology Associates, PA #115	10	(b) (6)
Bashein, Hal, MD #116	10	
Urology San Antonio Research, PA #117	7	
Pinellas Urology, Inc. #118	9	
Piedmont Medical Research #119	12	
Crescent Medical Research #120	13	
Urology Clinics of North Texas #121	29	
Urology Group of New Mexico #122	5	
Sutter Institutes for Medical Research #123	14	
American Institute of Research #124	28	

Site Name & Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)
Advanced Urology Medical Center Clinical Trials #125	13	(b) (6)
Bayview Research Group, LLC #126	12	
Salt Lake Research, PLLC #127	9	
Alaska Clinical Research Center, LLC #128	12	
Medical Associates, Inc. #129	8	
Melbourne Internal Medicine Associates #131	10	
University Clinical Research, Inc. #132	13	
Michigan Institute of Urology, P.C. #133	18	
Five Valleys Urology #134	14	
Urology of Indiana #135	4	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021368/S-020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021368 SUPPL # 020 HFD # 580

Trade Name Cialis

Generic Name tadalafil

Applicant Name Eli Lilly and Company

Approval Date, If Known October 6, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021368 Cialis (tadalafil)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

LVHG
LVHJ

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study LVHG
Study LVHJ

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !

IND # 073502 YES ☒ ! NO ☐
 ! Explain:

Investigation #2 !
 !

IND # 073502 YES ☒ ! NO ☐
 ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 !

YES ☐ ! NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: George Lyght
Title: Sr. Regulatory Health Project Manager
Date: October 6, 2011

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE A LYGHT
10/06/2011

SCOTT E MONROE
10/06/2011

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 021368 Supplement Number: 020 NDA Supplement Type (e.g. SE5): SE-1

Division Name:DRUP PDUFA Goal Date: 10-06-11 Stamp Date: 12/6/2010

Proprietary Name: Cialis

Established/Generic Name: tadalafil

Dosage Form: tablets

Applicant/Sponsor: Eli Lilly and Co.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Treatment of erectile dysfunction
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of signs and symptoms of benign prostatic hyperplasia (BPH)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☒ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE A LYGHT
10/03/2011

DEBARMENT CERTIFICATION

NDA application No: 21-368

Prior Approval Supplements for the following Proposed Indications:

CIALIS (tadalafil) once-daily use for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

CIALIS (tadalafil) once-daily use for the treatment of erectile dysfunction and the signs and symptoms of BPH, (ED/BPH).

Drug Name: CIALIS® (tadalafil)

Pursuant to the provisions of 21 U.S.C. 335a (k)(1), Eli Lilly and Company, through Gregory Brophy, hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a (a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By _____

Gregory T. Brophy, PhD.
Senior Director, Global Regulatory Affairs-US

7 December 2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 021368 BLA #	NDA Supplement # 020 BLA STN #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Cialis Established/Proper Name: tadalafil Dosage Form: tablets		Applicant: Eli Lilly and Company Agent for Applicant (if applicable):
RPM: George Lyght		Division: Division of Reproductive and Urologic Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 6, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 8/29/11

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Yes
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	Yes
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA ☒ DRISK ☒ DDMAC ☒ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	8-12-11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 9-14-11 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Yes
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 4-13-10
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 9-25-08
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 10-06-11
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 10-04-11
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	09-14-11
• Clinical review(s) *(indicate date for each review)*	09-13-11
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Yes
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 07-22-11

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 09-15-11
Statistical Review(s) *(indicate date for each review)*	☐ None 09-15-11
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None 09-16-11 & 09-27-11
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 09-16-11 & 09-27-11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 08-08-11
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 08-08-11
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 07-15-11 & 09-28-11
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 07-15-11 & 09-28-11
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	09-28-11
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	09-28-11
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE A LYGHT
10/11/2011

Lyght, George

From: Greeley, George
Sent: Tuesday, September 20, 2011 1:46 PM
To: Lyght, George
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Monroe, Scott
Subject: NDA 21-368/020 & 021 Cialis

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi George,

The email serves as confirmation of the review for Cialis (tadalalafil) conducted by the PeRC PREA Subcommittee on September 14, 2011.

The Division presented a full waiver for the indications of treatment of erectile dysfunction and signs and symptoms of benign prostatic hyperplasia (ED/BPH) and treatment of signs and symptoms of benign prostatic hyperplasia (BPH).

The PeRC agreed with the Division to grant a full waiver for this product because the disease/condition does not exist in children.

The pediatric record is attached for Cialis.

1_Pediatric_Rec
ord.pdf (65 KB)...

Thanks,

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: ge[illegible]e.greeley@fda.hhs.gov

Orga	Product I	Appl Typ	Subm Ty	Applic	Subm	FDA Rec	Dosage	Orph	Subm S	Goal Du	Submi	Su	Pe	PREA S	Pediat	Min Va	Max V	Waive	Waive	Study
DR	CIALIS	NDA	SUPPL	ELI	PEN	12/6/20	TABL	N	12/6/	10/6/2	INDI	T	1	WAIV	FUL	0	16	DISE	THE	
DR	CIALIS	NDA	SUPPL	ELI	PEN	12/6/20	TABL	N	12/6/	10/6/2	INDI	T	1	WAIV	FUL	0	16	DISE	THE	

Organization:	**DRUP**	**Product Name: CIALIS (TADALAFIL) TABLET**	
Appl Type No:	**NDA 21368**	**Applicant: ELI LILLY AND CO**	
Submission Type #:	**SUPPL - 20**	**Submission Status: PENDING**	

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
12/6/2010	TABLET	N	12/6/2010	10/6/2011	INDICATION	TREATMENT OF SIGNS AND SYMPTOMS OF BENING PROSTATIC HYPERPLASIA (BPH)

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
1,443	WAIVED	FULL	0	16	DISEASE/CONDITION DOES NOT EXIST IN CHILDREN	THE DISEASE IS OF ADULT MEN. NECESSARY STUDIES WOULD BE IMPRACTICAL	

APPEARS THIS WAY ON
ORIGINAL

Organization: DRUP **Product Name: CIALIS (TADALAFIL) TABLET**

Appl Type No: NDA 21368 **Applicant: ELI LILLY AND CO**

Submission Type #: SUPPL - 21 **Submission Status: PENDING**

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
12/6/2010	TABLET	N	12/6/2010	10/6/2011	INDICATION	TREATMENT OF ERECTILE DYSFUNCTION (ED) AND SIGNS AND SYMPTOMS OF BENIGN PROSTATIC HYPERPLASIA(BPH)

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
1,443	WAIVED	FULL	0	16	DISEASE/CONDITION DOES NOT EXIST IN CHILDREN	THE DISEASE IS OF ADULT MEN. NECESSARY STUDIES WOULD BE IMPRACTICAL	

Lyght, George

From: Lyght, George
Sent: Friday, August 26, 2011 1:25 PM
To: 'Sofia Khan'
Subject: CIALIS Labeling

Attachments: Picture (Metafile); CIALISLabel(Aug26).doc

Hi Sofia,

Included below is the proposed labeling for the Cialis S-020 and S-021 supplements. There is also an additional proposed change.

We would like you to re-edit the label to reflect the recent (2010) change in the FDA Guidance on renal insufficiency. Specifically, the Creatinine Clearance cut-points for normal, mild, moderate, etc, have been changed (see table below)

Stage	Description[b]	eGFR[c] (mL/min/1.73m^2)	CLcr[d] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

Also we would like you to change the wording in the label to reflect this change in CrCl.so as to be consistent going forward. Please e-mail me that you have received this e-mail.

Thanks,

George Lyght. PRM
FDA/CDER/DRUP

CIALISLabel(Aug 26).doc (3 MB)

34 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE A LYGHT
08/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021368/S-020
NDA 021368/S-021

INFORMATION REQUEST

Eli Lilly and Company
Attention: Sofia S. Khan, Pharm.D.
Manager, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, Indiana, 46285

Dear Dr. Khan:

Please refer to your supplemental new drug applications submitted December 3 and 6, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cialis® (tadalafil) tablets.

The Division of Medication Error Prevention and Analysis has reviewed the carton and container labeling sections of your submission and have the following *preliminary* comments and information requests. We recognize that this labeling may already be in use. We therefore request your commitment, in written response to this letter, that you will incorporate these comments at the next printing.

A. Blister Labels and Carton Labeling (2.5 mg and 5 mg)

1. Ensure the size of the established name is at least ½ size the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
2. Increase the prominence of the dosage form by increasing the font size on the principle display panel. As currently presented, the dosage form appears in a very small font and is difficult to read.
3. Delete or relocate the phrase "for once daily use" (b) (4) This statement is unnecessary because the Usual Dosage statement already instructs patients to administer Cialis once daily. Additionally, this statement should not appear between the established name and strength because it is considered intervening material. Furthermore, 5 mg tablets used for Erectile Dysfunction may also be administered on "as needed" basis and the statement "for once daily use" may be misinterpreted that the product should be administered every day.
4. Add the statement to blister label and carton labeling that reads "Swallow whole. Do not divide, chew, or crush tablets." We recommend this revision because we have identified several cases that report patients dividing or chewing Cialis tablets.

B. Blister Card Labels (2.5 mg and 5 mg)

1. Revise the blister card so that days of the week, the statement "last tablet," and clockwise arrows are removed. The product should be administered once daily without respect to any cyclical pattern. Thus, having the product labeled by days of the week is confusing and may lead to dosing errors. Additionally, the phrase "last tablet" may lead to confusion in that patients may misinterpret this phrase to stop taking medication after administering the dose labeled "last tablet."
2. Increase the differentiation between the blister cards containing 2.5 mg of Cialis and 5 mg of Cialis by using contrasting background color font, proprietary name color font, or some other means. (b) (4) .
3. (b) (4)
4. Delete the web address (i.e., www.cialis.com) from both blister label and carton labeling as this information is unnecessary, clutters the label, and distracts from the other important text appearing on the principle display panel.
5. Decrease the prominence of the 'Rx Only' statement (b) (4)

B. Carton Labeling (2.5 mg and 5 mg)

1. Delete the graphic containing the name 'Cialis' with green and yellow abstract drawing next to it as well as the Lilly logo in the oval graphic. These items are prominently displayed on the principle display panel and compete for prominence with the most important information on the principle display panel such as proprietary name and established name, dosage form and strength.
2. Once the blister labels are revised to delete unnecessary and confusing information such as days of the week, the statement "last tablet," and clockwise arrows, we request you also delete the administration instructions under the heading "How to take CIALIS for once daily use" from the back panel. These directions will no longer be necessary because the arrows and days of the week will be removed.

C. Container Labels (5 mg, 10 mg, and 20 mg)

1. Delete the abstract graphic of yellow and green shape combination from the principle display panel as this graphic is the most prominent item on the principle display panel. The most important information on the label is the proprietary name and established names, dosage form, and strength.

2. Your company's logo appears prominently on the principle display panel in two locations: 1) as the brown-red graphic and 2) in the red-color font. We request as it competes for prominence with most important information such as proprietary and established names, dosage form, and strength.
3. Increase the prominence of the dosage form by increase the font size on the principle display panel. As currently presented, the dosage form appears in a very small font and is hard to read.
4. Decrease the prominence of the 'Rx Only' statement by unbolding it and decreasing the font size.
5. If space permits, revise the side panel containing Usual Dosage, storage, contents, and warning information to appear in horizontal manner to improve readability of this information. As currently presented in a vertical manner, the information is hard to read.
6. Add the statement "Swallow whole. Do not divide, chew, or crush tablets" to appear prominently on the principle display panel. We recommend this change because we identified several cases that report patients dividing or chewing Cialis tablets.

If you have questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARET M KOBER
08/15/2011
Chief, Project Management Staff

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073502

MEETING MINUTES

Eli Lilly and Company
Attention: Sofia Khan, Pharm.D.
Associate Manager, Global Regulatory Affairs, US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Khan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cialis® (tadalafil).

We also refer to the meeting between representatives of your firm and the FDA on April 13, 2010. The purpose of the meeting was to discuss and gain agreement on the format and content of anticipated supplemental New Drug Applications (sNDAs) for the following indications:

- Cialis® (tadalafil) once daily use for the treatment of men with signs and symptoms of benign prostatic hyperplasia (BPH).
- Cialis® (tadalafil) once daily use for the treatment of men with signs and symptoms of benign prostatic hyperplasia (BPH) and erectile dysfunction (ED).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Olga Salis at (301) 796-0837.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes and handouts

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-sNDA

Meeting Date and Time: April 13, 2010, 10:00am-11:30am
Meeting Location: White Oak Building 22, Room 1313

Application Number: 073502
Product Name: Cialis® (tadalafil)
Indications: (1) benign prostatic hyperplasia (BPH), and
(2) BPH and erectile dysfunction (ED)

Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Mark Hirsch, M.D.
Meeting Recorder: Olga Salis

FDA ATTENDEES:

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D., Medical Team Leader Officer, (DRUP)
Roger Wiederhorn, M.D., Medical Officer, (DRUP)
Jonathan Jarow, M.D., Medical Officer, (DRUP)
LaiMing Lee, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology
Mahboob Sobhan, Ph.D., Lead Statistician, Division of Biometrics, (DB III)
Xin Fang, Ph.D., Statistician, Division of Biometrics, (DB III)
Yangmee Shin, Ph.D., Pharmacologist, (DRUP)
Margaret Kober, R.P.h., M.P.A., Chief, Project Management Staff, (DRUP)
Olga Salis, Regulatory Health Project Manager, (DRUP)

SPONSOR ATTENDEES:

Gregory Brophy, Ph.D., Senior Director, Global Regulatory Affairs-US
James McGill, M.D., Leader GBD, Senior Director Medical-Men's Health
Suzanne Klise, B.S., Senior Research Scientist-Clinical
Sofia Khan, Pharm.D., Regulatory Scientist, Global Regulatory Affairs-US
Nina Barchha, Pharm.D., Regulatory Scientist, Global Regulatory Affairs-US
Lars Viktrup, M.D., Ph.D., Medical Fellow-Men's Health
Roberta Secrest, Pharm.D., PhD., Senior Research Scientist-Clinical
Mayra Ballina, M.D., Medical Fellow-Global Product Safety
Todd Sanger, Ph.D., Senior Research Advisor-Statistics
Steven Watts, M.S., Research Scientist-Statistics
Lei Xu, Ph.D., Research Scientist-Statistics

Jay Kissel, Ph.D., Associate Consultant-Scientific Communications
Malcolm Mitchell, M.D., Senior Director-Medical Exploratory Medicine
Rebecca Wrishko, Ph.D., Research Advisor-PK/PD

1.0 BACKGROUND

Tadalafil is approved under NDA 021368 as Cialis for the treatment of men with ED, and as Adcirca under NDA 022232 for the treatment of patients with pulmonary arterial hypertension (WHO Group I) to improve exercise ability. For the treatment of men with ED, Cialis may be dosed as needed or once daily.

On January 17, 2006, a Pre-IND meeting was held to discuss the development of tadalafil for the treatment of men with the signs and symptoms of BPH. On April 25, 2006, IND 073502 was opened in DRUP for tadalafil for the treatment of men with the signs and symptoms of BPH. An End-of-Phase 2 meeting was held on September 25, 2008. On November 23, 2009, Lilly requested a Type B meeting to discuss the format and content for their upcoming supplemental new drug application submissions for the following indications: tadalafil once daily use for the treatment of men with signs and symptoms of BPH and Cialis® (tadalafil) once daily use for the treatment of men with signs and BPH and ED. The sponsor's meeting package was submitted on March 9, 2010. On April 9, 2010, the Division sent preliminary comments to the sponsor.

The sponsor's questions are represented below in **bolded text**. The Division's preliminary responses are represented below in normal text. Additional discussion items from the meeting are represented below in *italics*.

2. DISCUSSION

Question 1: **Does FDA agree with the proposal to provide a clinical study report for Study LVHN and to summarize Study LVHN data in relevant sections of the CTD, and cross- reference previous applications for the other clinical pharmacology data?**

Response: We request that you also provide references to Phase 1 studies from the original Cialis NDA that support dosing recommendations for use in specific populations such as geriatric, hepatic impairment, renal impairment, and race/ethnicity.

We further request that the adverse event data from the elderly subjects ($\geq$ 65 years, and $\geq$ 75 years of age) in Study LVHN be integrated with the adverse event data from elderly patients in Studies LVHJ, LVHS, LVHR, LVHK, and LVHG as a separate, combined, safety analysis within the Integrated Summary Safety (ISS). This will create a larger group of elderly for more powerful subgroup analysis.

Discussion*: The sponsor agreed to provide references to Phase 1 studies from the approved Cialis NDA that support dosing recommendations for use in specific populations.*

The Division requested clarification from the sponsor regarding dosing recommendations for specific populations for the BPH indication, which will be dosed at 5 mg daily.

The daily use ED indication, as well as the BPH/ED indication, may be dosed as low as 2.5 mg daily. The sponsor stated that the dosing recommendations in specific populations will likely be the same as that in the 2.5 mg daily use ED indication. The sponsor proposed to provide a summary of results from studies conducted to support the ED indication along with justification for labeling in specific populations sections based on once daily use.

The Division re-reiterated the need to see an integrated summary in the elderly population as stated in the preliminary comment. The sponsor proposed that a threshold of >65 years be utilized for analyses rather than ≥65; while ≥75 years cut-off would remain the same. The Division agreed with this proposal.

The Division requested clarification regarding the designs of the following studies; LVHK, LVHN, and LVHS. After the sponsor's explanation, the Division agreed that the LVHS could be excluded from this and all other integrated analyses of safety and efficacy due to confounding study design (co-administration of alpha blockers). Additionally, for LVHK the data could be presented separately as well.

The sponsor proposed to present the analyses using crude incidences of adverse events at individual doses (e.g., 2.5 mg, 5 mg, 10 mg, 20 mg). The Division agreed.

Question 2: **Does FDA agree that the submission of data from Studies LVHG, LVHJ, LVHR, LVHS, LVHK, and LVHN is acceptable to support a filing of a sNDA for the proposed indications?**

Response: In addition to Studies LVHG, LVHJ, LVHR, LVHS, LVHK and LVHN, a complete study report for the 12-week, placebo-controlled phase of Study LVIA, as well as an abbreviated study report for the open-label extension of Study LVIA containing at least 6 months of safety data, should be submitted.

Discussion: *The sponsor agreed with the Division's request.*

Question 3: **Does FDA agree with Lilly's plan to submit a descriptive summary of Study H6D-JE-LVIA (LVIA) pharmacokinetic results in Module 2 and the study report of clinical efficacy and safety results in Module 5 of the CTD?**

Response: No. In addition to the stand-alone report of Study LVIA in Module 5, the adverse event data from the Japanese subjects in Study LVIA should be integrated with the adverse event data from Asian subjects in Studies LVHJ, LVHS, LVHR, LVHK, and LVHG as a separate, combined, safety analysis within the ISS. In addition, the Integrated Summary of Efficacy (ISE) should include a separate discussion of efficacy in Asians, across the aforementioned studies. The efficacy results from Study LVIA do not appear to show statistically significant differences between tadalafil and placebo, and this will be a review issue. See our response to Question 4 in regard to our preference for an ISE and ISS.

Also, results of Protocol LVIA should be included in all appropriate sections, including pharmacokinetics, clinical safety, and clinical efficacy.

Discussion: *The Division restated that the adverse event data from the Japanese subjects in Study LVIA should be integrated with the adverse events data from Asian subjects in LVHJ, LVHS, LVHR, LVHK, and LVHG as a separate, combined, safety analysis within the ISS. After additional discussion, the Division agreed that the LVHS could be excluded from this and all other integrated analyses of safety and efficacy due to confounding study design (co-administration of alpha blockers). The Division also stated it is important that the sponsor provide the efficacy results in Asians, across the aforementioned studies because those results, specifically from study LVIA, do not appear to show statistical significance between tadalafil and placebo. The sponsor agreed to include results of Protocol LVIA.*

The Division inquired about the availability of PK data in the Japanese population in studies LVHT and LVHB; the sponsor stated no PK sampling was done because those studies were ongoing before differences in PK between Asians and non-Asians were noted in study LVIA.

In addition to LVIA, the Division inquired about clinical study report for LVHB, a study being conducted in Japan, Taiwan, and Korea. The timing of submission of this study was discussed, and the Division expressed a preference for this study to be submitted with the original submission. However, if it was not submitted in the original submission, this would not appear to be a reason to refuse to file the applications.

Question 4: **Does FDA agree with the proposal to include the required contents of the Integrated Summaries of Efficacy and Safety within the Summaries of Clinical Efficacy and Safety?**

Response: No. An ISE and ISS are requested. An ISE and ISS are needed because we seek additional presentations of the efficacy and safety data, as follows.

Efficacy and safety data should be presented separately for each of the following 3 groups:

1. All patients, whether or not they have erectile dysfunction ("All patients")
2. Patients without erectile dysfunction ["Benign Prostatic Hyperplasia (BPH) only"]
3. Patients with erectile dysfunction ["co-morbid BPH and Erectile Dysfunction (ED)"]

The ISS and ISE should include a discussion of any major safety or efficacy differences noted in these three groups. The safety data from Studies LVHS and LVHK should be integrated into the safety analyses for each of these three groups, in addition to being presented separately.

Discussion: *The sponsor agreed with the Division and will include the ISE, ISS, CSS and CSE for both indications. An agreement was reached that within analyses in the ISS, Study LVHS (co-administration of alpha blocker) and Study LVHK (urodynamic study using 20 mg daily) would be excluded from the integrated analyses, and displayed separately due to the differences in design of these studies and the other studies.*

Question 5: **Does FDA agree that the data to support each indication can be presented within 2 separate Summary of Clinical Efficacy sections (that is, 2.7.3a BPH and 2.7.3b BPH/ED) and a single summary of clinical safety?**

Response: No. Refer to our response to Question 4.

Discussion: *The sponsor agreed with the Division and will include within one document the ISE, ISS, CSS and CSE for both indications.*

Question 6: **Does FDA agree that the draft, high-level Table of Contents for this NDA is appropriately structured and indicates appropriate content to support filing of this application?**

Response: In regard to structure, we request an ISS and ISE. We further request that the Clinical Summaries of Efficacy and Safety and the ISS/ISE contain the analyses requested in our response to Question 4. In addition, a complete study report for the 12-week, placebo-controlled phase of Study LVIA, as well as an abbreviated study report for the open-label extension of Study LVIA containing at least 6 months of safety data should be submitted. The efficacy results from Study LVIA will be a review issue. The safety data from Study LVIA should be integrated with safety data from the other studies in the ISS. In regard to appropriateness of the content, this will be determined at the time of the filing review.

Discussion: *As discussed in question 1, the Division agrees that the sponsor can exclude LVHS and LVHK and display the data from those studies separately.*

Question 7: **Does FDA agree with the studies/data supporting each of the sections noted in the TPP (Sections 1, 2, 4-7, 11, 12, and 14)?**

Response: It appears that the data from the studies conducted could support the sections of the TPP. However, whether the data from these studies supports specific labeling is subject to satisfactory review.

In regard to the content of the TPP, we remind you of your previous agreement to discourage concomitant use of tadalafil with alpha blockers for the treatment of BPH. In addition, the results of LVIA appear to be a potential labeling issue.

Discussion: *The sponsor agreed to the comment from the Division.*

Question 8: **Does the Division agree with submission of the proposed datasets?**

Response: We recommend you submit SAS programs creating analysis datasets from SDTM datasets. Analysis datasets must be consistent to SDTM datasets and reproducible from SDTM datasets.

In addition, we request SAS transport files for Study LVIA.

Discussion: *The Division clarified that we would like PC-SAS programs.*

Post-Meeting Note: *The sponsor provided clarification for this question in their April 23, 2010, submission. In response, the Office of Biometrics has the following comment:*

> *We need to know how the efficacy variables (primary and secondary) were derived from the observed/raw variables. The related SAS programs that will be provided should read SDTM datasets and should create analysis datasets that are identical to the submitted analysis datasets.*

Question 9: **Does FDA agree that submission of datasets from only Studies LVHG, LVHJ, LVHR, and LVHS in SDTM format is acceptable?**

Response: In addition to datasets in SDTM format from the studies listed, we request datasets from Study LVIA in SDTM format.

Discussion: *The sponsor agreed to the request from the Division.*

Question 10: **Does FDA agree with the proposed integration plan and presentation of data for clinical efficacy analyses?**

Response: In addition to the proposed integration plan, we request a separate section in the ISE in which efficacy data from Study LVIA is integrated with data from Studies LVHJ and LVHG. The ISE should also comment upon whether efficacy persists in the open-label extension periods of LVHG and LVIA.

In addition to your proposal to present the data from LVHR ("co-morbid BPH and ED") separately from LVHG and LVHJ, we also refer to our response to Question 4 regarding the structure and content of the ISE.

We remind you that we will also consider the efficacy of tadalafil for treatment of BPH in the subgroup of patients with ED in Studies LVHJ and LVHG.

Discussion: *The Division and sponsor repeated the agreement items in question 1 and 4.*

Question 11: **Does FDA agree with Lilly's proposal for efficacy subgroup analyses for the 2 indications?**

Response: In addition to your proposed subgroups, add analysis by prior alpha blocker therapy (yes/no), by prior PDE inhibitor therapy (yes/no), and by Asian versus non-Asian. Also, we request the same subgroup analyses as you plan for LVHG and LVHJ for the integrated Studies LVHG, LVHJ, and LVIA.

In regard to efficacy in Asians, are you actively conducting or planning any additional studies in follow-up to Study LVIA?

Discussion: *The sponsor acknowledged that the Division requested additional subgroups for the efficacy subgroup analyses. In regard to any studies being conducted in follow-up to LVIA, the sponsor confirmed that study LVHB is ongoing in Taiwan, Japan, and Korea.*

Question 12: **Does FDA agree with the proposed integration plan and presentation of data for clinical safety analyses?**

Response: In addition to your proposal for integration of safety data, we request that the safety data be organized in the ISS using the 3 groups stated in our response to Question 4.

Further, in addition to the proposed safety integration plan, we request a separate section in the ISE in which safety data from Study LVIA is integrated with data from Studies LVHJ, LVHG.

We do not agree that the safety data from the once-daily ED studies LVFP, LVCV and LVFZ should be integrated with the safety data from the BPH studies LVHG, LVHJ and LVHR.

The ISS should include a discussion of whether safety was different in Study LVHR ("co-morbid BPH and ED") compared to Studies LVHJ and LVHG, and the integrated safety database of these three studies should be explored to determine if safety was different in the co-morbid BPH and ED population.

Discussion: *The Division clarified that this response concerned the ISS, not the ISE. The sponsor agreed to the comment from the Division.*

Question 13: **Does FDA agree with Lilly's proposal for safety subgroup analysis for the 2 indications?**

Response: In addition to your proposed subgroups, add analysis by prior alpha blocker therapy (yes/no), by prior PDE inhibitor therapy (yes/no), and by Asian versus non-Asian.

Discussion: *The sponsor agreed to add analysis by prior use of alpha blocker therapy and by prior use of PDE5 inhibitor therapy for studies LVHG, LVHJ, and LVHR. In regard to the Asian/non-Asian subgroups, the sponsor will provide such an analysis using data from studies LVIA and LVHT. Timing of submission of data from ongoing study LVHB is under consideration.*

Question 14: **Do the proposed analyses of data collected during the washout period address the agency's request regarding symptomatic worsening/urinary retention during the washout of alpha blockers?**

Response: Yes. The number of patients contributing to this analysis will be a review issue.

Discussion: *No additional discussion.*

Question 15: **Does the FDA agree that the proposed list of special safety topics is acceptable?**

Response: No. We request that you add cardiovascular events to your proposed list of special safety topics. In addition, the Special Safety Topics section should include a brief discussion of myalgias/back pain, seizures, and transient global amnesia.

Discussion: *The sponsor agreed with the comment.*

Question 16a: **Does FDA agree with the proposal for providing individual subject data for this submission and the proposed data cut-of dates?**

Response: Individual patient data should also be submitted for studies LVHN and LVIA.

In regard to the open-label safety extension studies, we have the following comments:

1. We remind you of your previous agreement to submit a final study report for the completed 1-year of Study LVHG with the application.
2. We request an abbreviated study report for the open-label extension of Study LVIA containing at least 6 months of safety data.

Finally, are any additional safety studies ongoing, and if so, what are your plans for submitting results from those studies?

Discussion: *The sponsor concurred with items 1 and 2 regarding the open label extension studies. The sponsor will submit individual patient data for LVHN. There are no SAEs, deaths, or discontinuations due to AEs to report from that study. The Division informed the sponsor that narratives for patients who experienced TEAEs that can be related to hypotension should also be submitted. The sponsor stated that there are no other ongoing safety studies.*

The Division also requested that individual subject data should be provided for study LVIA, as proposed for studies LVHG, LVHJ, LVHR, LVHK, LVHS, and LVIA.

Question 16b: **Does FDA agree with the format of the patient narrative reports?**

Response: Yes.

Discussion*: No additional discussion.*

Question 17: **Does FDA agree with Lilly's proposal for the 4-Month Safety Update?**

Response: No. See our response to question 16a regarding the open-label safety Studies LVHG and LVIA. In addition to listings of SAEs and CIOMS reports from ongoing studies, and summaries of trial design and objectives, we request that the 4-Month Safety Update include a text summary and analysis of new safety findings and an update on special safety topics.

Discussion: *The sponsor informed the Division that it would not be useful to provide information beyond SAEs and CIOMS reports given that the ongoing clinical trials were blinded. The Division concurred with the sponsor's explanation.*

Question 18: **Does FDA agree with Lilly's approach in response to comments 1, 2, and 3?**

Response: We agree with your response to our comments 1, 2, and 3 regarding the statistical analysis plan.

Discussion: *No additional discussion.*

Question 19: **Does FDA agree that the Sponsor needs to submit one user fee?**

Response: No. You are seeking two indications, one for the treatment of men with signs and symptoms of benign prostatic hypertrophy (BPH), and the other for the treatment of men with signs and symptoms of BPH and erectile dysfunction (ED), for which you have conducted separate trials. Therefore, two supplements and two user fees will have to be submitted.

Discussion: *The sponsor acknowledged that they will be submitting two separate supplements and paying two fees. The sponsor requested clarification regarding acceptability to cross-reference. The Division clarified that the sponsor may pay for two supplements, but cross-reference the data to one as long as they submit a cover letter and 356h for each.*

Question 20: **Does FDA agree that it is acceptable to submit financial disclosure information for only these studies?**

Response: Yes.

Discussion: *No additional discussion.*

Question 21: **Does the FDA agree, that at this time, there are no apparent issues or deficiencies that would result in a "Refusal to File?"**

Response: The package you propose appears adequate to support the filing of two supplements (with two user fees). However, the decision to file is made after submission and following initial review of the application contents.

Discussion: *The sponsor acknowledged the comment from the Division.*

Additional Clinical Comments

1. Overall, the meeting package provided very limited information:
   a. No data from Studies LVHR and LVHS.
   b. Minimal efficacy and safety data from Study LVHJ.
   c. No safety information in the elderly (≥ 75 years) subpopulation.
   d. No information regarding the wash-out of alpha-blockers.

   The overall lack of information, especially the general lack of study results, serves to limit the extent of the comments that can be provided at this meeting.

   Assuming the supplements are filed, review issues based on these results will be conveyed at the time of the 74-Day letter.

2. The observed improvement for tadalafil 5mg over placebo for change-from baseline in total IPSS was approximately 2 points in Study LVHJ and 2.5 points in Study LVHG. The improvement in IPSS observed in Study LVIA (Japan) was smaller. We recommend that the supplements contain justification for the clinical benefit of these observed placebo-subtracted changes-from-baseline in total IPSS.

3. (b) (4)

4. It appears that approximately 130 patients (approximately 30% of those enrolled) discontinued treatment before 1 year in the open-label extension of Study LVHG. The supplements should describe the reasons for these drop-outs.

5. The meeting package describes unexpected variability in the systemic exposures to tadalafil in Japanese men in Study LVIA. The results were concluded to be "atypical". The supplements should contain information to explain these atypical results.

6. (b) (4)

3. ACTION ITEMS

- On April 23, 2010, the sponsor submitted additional comments in follow-up to the April 13, 2010, Pre-sNDA meeting discussions. The April 23, 2010, submission will be reviewed by the Division and comments will be provided to the sponsor as deemed necessary by the Division.

4. ATTACHMENTS AND HANDOUTS

Handouts provided by the sponsor are attached.

Summary of Requested Integrated Summaries

(FDA Questions 1, 3, 4, 6, 10, 11, 12, and 13)

Listed below are FDA additional requested integrated analyses received in preliminary draft comments Friday. Lilly understands FDA's requests as shown below in bold font.

FDA Response to Question 1:

"We further request that the AE data from elderly subjects (≥65 years and ≥75 years of age) in Study LVHN be integrated with the AE data from elderly patients in Studies LVHJ, LVHS, LVHR, LVHK, and LVHG..."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Safety includes the following:

LVHJ (PLA, 5mg) + LVHS (PLA, 5mg) + LVHR (PLA, 5mg) + LVHK (PLA, 20mg) + LVHG (PLA, 5mg) + LVHN (20mg) - All subjects who are >65 years and ≥75 years of age

- Treatment-emergent adverse events
- This analysis is supportive of the BPH indication

FDA Response to Question 3

".....the adverse event data from the Japanese subjects in Study LVIA should be integrated with the adverse event data from Asian subjects in Studies LVHJ, LVHS, LVHR, LVHK, and LVHG as a separate, combined, safety analysis within the ISS."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Safety includes the following:

LVIA (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHS (PLA, 5mg)+LVHR (PLA, 5mg)+ LVHK (PLA, 20 mg) + LVHG (PLA, 5mg)- Data in Asian subjects only

- Treatment-emergent adverse events
- This analysis is supportive of the BPH indication

FDA Response to Question 3 (cont..)

"...In addition, the ISE should include a separate discussion of efficacy across the aforementioned studies."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Efficacy includes the following:

LVIA (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHS (PLA, 5mg)+LVHR (PLA, 5mg)+ LVHK (PLA, 20 mg), +LVHG (PLA, 5mg)- Data in Asian subjects only

- IPSS total
- This analysis is supportive of the BPH indication

FDA Response to Question 4

Efficacy and safety data should be presented separately for each of the following 3 groups:

1) *All patients, whether or not they have ED ("All patients")*
2) *Patients without ED ("BPH only")*
3) *Patients with ED ("co-morbid BPH and ED")*

...The safety data from Studies LVHS and LVHK should be integrated into the safety analyses for each of these three groups...

Lilly's Response:

Lilly's interpretation for Integrated Summary of Efficacy includes the following:

- **Point #1:**
  - **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHR (PLA,5mg) – *All subjects***
    - IPSS total and BII
    - This analysis is supportive of the BPH indication
- **Point #2:**
  - **LVHG (PLA, 5mg) + LVHJ (PLA,5mg) – *Subjects who did not report ED***
    - IPSS total and BII
    - This analysis is supportive of the BPH indication
- **Point #3:**
  - **LVHG (PLA, 2.5, 5mg) + LVHJ (PLA, 5mg) + LVHR (PLA, 2.5, 5mg) – *Subjects who reported ED***
    - IPSS total and BII; and IIEF-EF
    - This analysis is supportive of the BPH/ED indication

FDA Response to Question 4 (cont...)

Lilly's interpretation for Integrated Summary of Safety includes the following:

- Point #1:
  - **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHR (PLA, 5 mg) + LVHS (PLA, 5mg) + LVHK (PLA, 20 mg) – *All subjects***
    - Safety parameters
    - This analysis is supportive of the BPH indication

- Point #2:
    - **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHS (PLA, 5mg) + LVHK (PLA, 20 mg) – *Subjects who did not report ED***
        - Safety parameters
        - This analysis is supportive of the BPH indication
- Point #3:
    - **LVHG (PLA, 2.5, 5mg) + LVHJ (PLA, 5mg) + LVHR (PLA, 2.5, 5mg) + LVHS (PLA, 5mg) + LVHK (PLA, 20 mg) – *Subjects who reported ED***
        - Safety parameters
        - This analysis is supportive of the BPH/ED indication

FDA Response to Question 6:

"The safety data from Study LVIA should be integrated with safety data from the other studies in the ISS"

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Safety includes the following:

- **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHR (PLA, 5 mg) + LVHS (PLA, 5mg) + LVHK (PLA, 20 mg) + LVIA (PLA, 5mg) – *All subjects***
    - Safety parameters
    - This analysis is supportive of the BPH indication

FDA Response to Question 10:

"In addition to the proposed integration plan, we request a separate section in the ISE in which efficacy data from Study LVIA is integrated with data from Studies LVHJ and LVHG"

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Efficacy includes the following:

- **LVHG (PLA, 5mg) +LVHJ (PLA, 5mg) + LVIA (PLA, 5mg)**
    - IPSS total
    - This analysis is supportive of the BPH indication

FDA's response to Question 11:

"...In addition to the originally proposed subgroups, add analysis by prior alpha blocker therapy (yes/no), by prior PDE5i (yes/no), and by Asian versus non-Asian."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Efficacy includes the following:

> **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg)**- prior alpha blocker, prior PDE 5 inhibitor, Asian/non-Asian to support BPH indication
>
> **LVHR (PLA, 2.5, 5 mg)**- prior alpha blocker, prior PDE 5 inhibitor, Asian/non-Asian to support BPH/ED indication

"...Also , we request the same subgroup analyses as you plan for LVHG and LVHJ for the integrated studies LVHG, LVHJ, and LVIA."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Efficacy includes the following:

> **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) + LVIA (PLA, 5mg)**- prior alpha blocker, prior PDE 5 inhibitor, Asian/non-Asian to support BPH indication

FDA Response to Question 12:

*"Further, in addition to the proposed safety integration plan, we request a separate section in the **ISE** in which safety data from LVIA is integrated with data from Studies LVHJ, LVHG."*

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Safety includes the following:

- **LVHG (PLA, 5mg) +LVHJ (PLA, 5mg) + LVIA (PLA, 5mg)**
  - Safety parameters
  - This analysis is supportive of the BPH indication

Comment: In the above comment, we believe FDA is discussing the ISS and not the ISE; can you please confirm?

FDA Response to Question 12: (cont...)

"The ISS should include a discussion of whether safety was different in Study LVHR compared to Studies LVHJ and LVHG, and the integrated safety database of these three studies should be explored to determine if safety was different in the co-morbid BPH and ED population."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Safety includes the following:

- **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) + LVHR (PLA, 5mg) – *Subjects who reported ED***
  - Safety parameters
- **LVHG (PLA, 5mg) + LVHJ (PLA, 5mg) – *Subjects who did not report ED***
  - Safety parameters
  - These will be supportive of the BPH indication and the BPH/ED indication

FDA's response to Question 13:

"...In addition to the originally proposed subgroups, add analysis by prior alpha blocker therapy (yes/no), by prior PDE5i (yes/no), and by Asian versus non-Asian."

Lilly's Response:

Lilly's interpretation for the Integrated Summary of Safety includes the following:

LVHG (PLA, 5mg) + LVHJ (PLA, 5mg)- prior alpha blocker, prior PDE 5 inhibitor, Asian/non-Asian to support BPH indication

LVHR (PLA, 2.5, 5 mg)- prior alpha blocker, prior PDE 5 inhibitor, Asian/non-Asian to support BPH/ED indication

61 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73502	GI-1	LILLY ICOS LLC	CIALIS (TADALAFIL) IC351/LY450190

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/s/

MARK S HIRSCH
05/12/2010

Lyght, George

From: Lyght, George
Sent: Friday, April 29, 2011 10:45 AM
To: 'Sofia Khan'
Subject: Clinical information request/NDA 021368/ S020 and S-021

Hi Sofia,

The following is an information request requiring your response:

> We are currently reviewing your Cialis sNDA submission of December 6, 2010. We have noted in the Open-Label Extension of Study LVHG 60 subjects (14%) discontinued on the basis of subject decision. This was a greater percentage than discontinued for the same reason from the Open-Label extension for Study LVIA. We request additional clarifying information concerning these patient's reasons for discontinuation, site locations, and any analysis that you could provide.

Thanks,

George Lyght, RPM
FDA/CDER/DRUP

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/s/

GEORGE A LYGHT
04/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021368/S-020
NDA 021368/S-021

FILING COMMUNICATION

Eli Lilly and Company
Attention: Sofia S. Khan, PharmD
Manager
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Khan:

Please refer to your Supplemental New Drug Applications (sNDAs) received December 6, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cialis® (tadalafil) tablets, 5mg.

We also refer to your submission dated December 10, 2010.

These supplemental applications propose the following changes:

> Supplement 20 - a new indication for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
>
> Supplement 21 - a new indication for the treatment of erectile dysfunction (ED) and the signs and symptoms of benign prostatic hyperplasia (BPH).

We have completed our filing review and have determined that your supplemental applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), these supplemental applications are considered filed 60 days after the date we received your supplemental applications. The review classification for these supplemental applications is **Standard**. Therefore, the user fee goal date is October 6, 2011.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate

proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 18, 2011.

During our filing review of your supplemental application, we identified the following potential review issues:

1. The Study Endpoints and Labeling Development (SEALD) Team in the Office of New Drugs has completed its review of the BPH Impact Index (BII), a questionnaire used in the Phase 3 studies, (b) (4) SEALD finds the BII to be not well defined nor reliable (not "validated"). The Division agrees. (b) (4)
   A separate regulatory letter will be conveyed to you containing detailed regulatory review comments for the BII.

2. Tadalafil-related adverse events related to hypotension may be more common in geriatric patients ≥ 75 years of age compared to patients < 65 years of age:

   a. An increased incidence of hypotension-related adverse events was observed in tadalafil-treated elderly patients (≥ 75 years of age) compared to placebo-treated elderly patients in Study LVHS. The independent effect of tadalafil on hypotension-related adverse events appeared greater in the elderly (≥75 years of age) compared to the young (< 65 years of age) in that study, both in patients taking alpha blockers and those not taking alpha blockers.

   b. In the BPH/ED analysis set encompassing all patients with ED from Studies LVHG, LVHJ, and LVHR, for subjects ≥75 years of age there was a significantly greater percentage of subjects in the tadalafil 5 mg group versus placebo reporting at least 1 adverse event possibly related to hypotension (6 subjects [8.5%] versus 1 subject [1.4%]). This finding appears to be driven by adverse event reports of headache (3 [4.2%] versus 1 [1.4%]), and dizziness (3 [4.2%] versus 0).

3. Safety data have been provided in geriatric patients >65 years of age with BPH (n=586), and in geriatric patients ≥75 years of age (n=160). A total of 120 subjects and 102 subjects > 65 years of age were exposed for at least 6 months and 1 year, respectively. However, the extent of 6 month and 1 year exposure in geriatric patients ≥75 years of age is not as great (34 and 28 subjects ≥ 75 years of age, for 6 months and 1 year, respectively). You may wish to submit summaries of safety data in patients ≥75 years of age treated in previous as-needed and daily-dosing ED studies in order to better support long-term safety in this age group.

4. In the pooled double-blind periods from the Studies LVHG, LVHJ, and LVHR, there were reports of three patients who experienced myocardial infarctions resulting in study discontinuation in the tadalafil 2.5 and 5.0 mg dose groups (N=797) versus 0 myocardial infarctions (N=786) resulting in study discontinuation in the placebo group. In addition,

there are other cardiovascular adverse events reported, some resulting in serious outcomes or discontinuation, and others of clinical significance. These cases will be reviewed individually.

5. In the pivotal BPH/ED analysis set, encompassing all patients with ED from Studies LVHG, LVHJ and LVHR, an increased incidence of "hypertension" reported as an adverse event was observed in the tadalafil 5 mg group (2.4%, 11/464) compared to the tadalafil 2.5 mg group (0%, 0/333), and the placebo groups (2.5 mg placebo group 0.6% [2/342], 5 mg placebo group 0.7% [3/454]). This will be a review issue. Detailed narratives for each of these "hypertension" AE cases should be submitted. A rationale/explanation for the observed differences between groups should be provided. In addition, detailed narratives should be provided for each and every adverse event report of "hypertension" in these supplemental efficacy applications.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GEORGE S BENSON
02/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE-

FROM: George Lyght RPM
Division of Reproductive and Urologic Products (DRUP) 301-796-0948

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/15/11		NDA 021368 S-020 and S-021	NDA	12/6/10 (DARRTS and EDR)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cialis (tadalafil)	Standard	ED and BPH	July 21, 2011

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
This is an electronic submission in DARRTS/EDR
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NDA 021368/S-020 Submission date: December 6, 2010
NDA 021368/S-021 Submission date December 6, 2010
Please review labeling for completeness.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☑ e- MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

GEORGE A LYGHT
02/15/2011

DSI CONSULT: Request for Clinical Inspections

Date: February 9, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Roy Blay, Ph.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Roger Wiederhorn, M.D., Medical Officer
Division of Reproductive & Urologic Products (DRUP)
Mark Hirsch, M.D., Medical Team Leader, DRUP

From: George Lyght, R.Ph., Sr. Regulatory Health Project Manager/DRUP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-368/SE1-020 and SE1-021
Applicant/ Applicant contact information (to include phone/email):
Drug Proprietary Name: Tadalafil
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

- The treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
- The treatment of ED and the signs and symptoms of BPH (ED/BPH)

PDUFA: October 6, 2011
Action Goal Date: October 6, 2011
Inspection Summary Goal Date:

II. Protocol/Site Identification

There are three Phase 3 studies for which we are requesting DSI clinical site inspections:

For Study H6D-MC-LVHR: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Tadalafil 2.5 and 5 mg Once-Daily Dosing for 12 Weeks for the Treatment of Erectile Dysfunction and Signs and Symptoms of Benign Prostatic Hyperplasia in Men With Both Erectile Dysfunction and Benign Prostatic Hyperplasia."

Site # (Name,Address, Phone number, email, fax#)	Protocol ID Site Number	Number of Subjects	Indication
Site 115 Dr. Mohamed Bidair 6699 Alvarado Rd, Suite 2207 San Diego, CA 92120	LVHR Site #115	30	BPH/ED
Site 101 Dr. Eugene Dula* West Coast Clinical Research 5525 Etiwanda Ave., Suite 202 Tarzana, CA. 91356	LVHR Site #101	29	BPH/ED

∗Eugene Dula also participated as an investigator in Study H6D-MC-LVHG (LVHG, Site #107).

For Study H6D-MC-LVHG: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia."

Site # (Name,Address, Phone number, email, fax#)	Protocol ID Site Number	Number of Subjects	Indication
Site 101 Dr. Franklin Gaylis* Franklin D. Gaylis MedResearch 8851 Center Drive, Suite 501 La Mesa, CA 91942	LVHG Site #101	50	BPH

*Franklin Gaylis also participated as an investigator in Study H6D-MC-LVHR (LVHR, Site #102).

For Study H6D-MC-LVHJ: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia."

Site # (Name,Address, Phone number, email, fax#)	Protocol ID Site Number	Number of Subjects	Indication
Site 102 Dr. James McMurray 303 Williams Ave. S.W., Suite 411 Huntsville, AL 35801	LVHJ Site #102	21	BPH

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply): N/A

___ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

We request that all efficacy and safety data collected at the requested sites be verified

Should you require any additional information, please contact George Lyght (Regulatory Project Manager) at 301-796-0948 or Roger Wiederhorn (Medical Officer) at 301-796-2146.

Concurrence:
Roger Wiederhorn, M.D., Medical Officer
Mark Hirsch, M.D., Medical Team Leader

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/s/

GEORGE A LYGHT
02/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021368/S-020

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Eli Lilly and Company
Attention: Sofia S. Khan, PharmD
Manager
Lilly Corporate Center
Indianapolis, Indiana, 46285

Dear Dr. Khan:

We have received your December 3, 2010, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021368

SUPPLEMENT NUMBER: 020

PRODUCT NAME: Cialis® (tadalafil) tablets

DATE OF SUBMISSION: December 3, 2010

DATE OF RECEIPT: December 6, 2010

This supplemental application proposes the following change: a new indication for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 4, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be October 6, 2011.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call George Lyght, Senior Regulatory Health Project Manager at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MARGARET M KOBER
12/21/2010
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 73,502

Attention: Lori de los Reyes, M.S.N., J.D.
Eli Lilly
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Reyes:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cialis® (tadalafil).

We also refer to the meeting between representatives of your firm and the FDA on September 25, 2008. The purpose of the meeting was to discuss your clinical development plan for tadalafil for once daily use for the signs and symptoms of benign prostatic hyperplasia (BPH) and for the treatment of men with erectile dysfunction (ED) and signs and symptoms of BPH.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 25, 2008
TIME: 10:00-11:30 AM
LOCATION: WO BLD 22 Room 1418
APPLICATION: IND 73,502
DRUG NAME: Cialis® (tadalafil)
TYPE OF MEETING: End-of-Phase 2 (Type B)

MEETING CHAIR: Mark Hirsch, M.D.
MEETING RECORDER: Olga Salis

FDA ATTENDEES:

George Benson, M.D., Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D., Medical Team Leader Officer (DRUP)
Roger Wiederhorn, M.D., Medical Officer
Hae Young Ahn, Ph.D., Deputy Director, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)
Sandhya Apparaju, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology
Mahboob Sobhan, Ph.D., Lead Statistician, Division of Biometrics (DB III)
Xin Fang, Ph.D., Statistician, Division of Biometrics (DB III)
Yangmee Shin, Ph.D., Pharmacologist, (DRUP)
Olga Salis, Regulatory Health Project Manager
Eufrecina DeGuia, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Gregory Brophy, Ph.D., Director U.S. Regulatory Affairs
Malcolm Mitchell, M.D., Director Clinical Pharmacology
Steven Watts, M.S., Research Scientist, Statistics
Chris Miskel, M.B.A, Cialis Global Development Leader
James McGill, M.D., Medical Director
Suzanne Klise, B.S., Associate Clinical Research Scientist
Lori de los Reyes, M.S.N., J.D., Associate Regulatory Consultant
Mallik Angalakuditi, Ph.D., Research Scientist, Health Outcomes
Nina Barchha, Pharm.D., Regulatory Scientist
Lars Viktrup, M.D., Ph.D., Medical Advisor

BACKGROUND:

On July 11, 2008, Lilly submitted a (Type B) End-of-Phase 2 meeting request to discuss clinical development plans for tadalafil for once daily use for the signs and symptoms of benign prostatic hyperplasia (BPH) and for the treatment of men with erectile dysfunction (ED) and signs and symptoms of BPH. On September 23, 2008, preliminary responses were faxed to the sponsor and these are shown below. Additional discussion items are outlined below in bold italicized font.

MEETING OBJECTIVES:

To reach agreement with the Division on the design of the Phase 3 clinical studies for the following new indications:

- Cialis® (tadalafil) is indicated for once-daily use for the treatment of men with signs and symptoms of benign prostatic hyperplasia (BPH)
- Cialis® (tadalafil) is indicated for once-daily use for the treatment of men with erectile dysfunction (ED) and signs and symptoms of BPH.

QUESTIONS, DIVISION RESPONSES AND DISCUSSION ITEMS

Question 1: Does Study LVHN address DRUP's concern regarding the adequacy of pharmacokinetic and pharmacodynamic information in elderly BPH patients?

Response: No. While Study LVHN adequately addresses the pharmacokinetics (pK) of tadalafil in elderly patients, the pharmacodynamic data do not allay our concern.

Results from Study LVHN demonstrate additional blood pressure (BP) lowering in the elderly compared to the young for the 20 mg daily dose that was tested. For example, the mean additional drop in supine systolic and diastolic BP for the elderly compared to the young was 8 mmHg and 4 mmHg, respectively. These differences were similar on Days 1 and 10. The blood pressure reductions broadly reflect the pK profile of tadalafil, with maximum reductions in blood pressure observed at C_{max}, and systolic BP reductions from baseline continuing for 4 days after the last dose in the elderly.

In order to address this continuing clinical safety concern, you will need to provide relevant *clinical* safety data from elderly subjects in your Phase 3 BPH program. To this end, we request data from at least 100 men aged 75 years and older in the Phase 3 study. This safety data should include baseline and repeated supine and standing BP and heart rate measurements and collection of adverse events, with specific attention paid to those adverse events reflective of potential hemodynamic adverse effects.

Discussion: Lilly acknowledged the Division's concern and will comply with the Division's request for additional information. There was no further discussion.

Question 2: Does DRUP agree that the pharmacokinetic and hemodynamic aspects of tadalafil are independent of the age of subjects with BPH?

Response: No. While it does not appear that the pharmacokinetics of tadalafil are markedly altered with age (pending a thorough review of Study LVHN), elderly patients had a larger drop in BP compared to younger patients. See our response to Question 1.

Discussion: See additional discussion for Question 1. There was no further discussion.

Question 3: Does DRUP agree that additional pharmacokinetic and clinical pharmacology (including drug-drug interaction) studies are not required for the proposed indications?

Response: Yes. We agree that no additional pharmacokinetic and clinical pharmacology are required for the BPH indication.

Discussion: Lilly asked whether this response applied to both indications and not just the BPH indication. The Division confirmed the response applied to both the "general BPH" indication and the co-morbid indication (concomitant ED and BPH).

Question 4: Does DRUP agree that the urodynamic results from Study LVHK, along with the lack of effect on postvoid urine residual volume and on urinary tract adverse events in Studies LVGC, LVHG, and LVHK, appropriately establish the bladder safety of tadalafil up to 20 mg daily?

Response: Yes

Discussion: There was no further discussion.

Question 5: Based on the balance of efficacy and safety demonstrated in Study LVHG, Lilly proposes to study only 5 mg versus placebo in the subsequent Phase 3 study. Does DRUP agree with this proposal?

Response: For the general BPH population, as reflected in indication #1 ("....*treatment of men with signs and symptoms of BPH*"), we agree with your proposal to study only 5mg versus placebo in the subsequent Phase 3 study.

However, should you continue to seek approval of indication #2 ("....treatment of men with *erectile dysfunction and signs and symptoms of BPH*"), then we do not agree with your proposal to study only 5mg versus placebo in the subsequent Phase 3 study. In the specific subgroup of patients with ED and BPH, 5mg was no more effective than 2.5mg in Study LVHG. Therefore, you should study both those doses versus placebo, in a separate Phase 3 study.

Discussion: ***Lilly reiterated that they are seeking two separate indications (general BPH and co-morbid ED+BPH) and agreed to study 5mg only in LVHJ and 2.5mg and 5mg in a separate co-morbid study per the Division's recommendation. The Division commented that they would consider a label that has a lower starting dose in the co-morbid population versus the general BPH population. The sponsor confirmed they wanted to communicate to both the HCP and the patient that tadalfil for once daily use is an option for patients with ED only, for those with BPH only, and for those with both ED and BPH.***

Question 6: Does DRUP agree that the inclusion and exclusion criteria for Study LVHJ are appropriate for the proposed indication?

Response: No. For Study LVHJ: we request the following revisions:

1. For exclusion criteria [10], for patients with PSA $\geq$ 4.0 to $\leq$ 10.0 ng/mL at Visit 1, prostate cancer should be ruled out to the satisfaction of *a urologist*.

2. Patients with clinically significant microscopic hematuria should be excluded.

In addition, Study LVHJ should include at least 100 subjects 75 years of age and older and it would be optimal to have this subgroup evenly distributed between active drug and placebo.

For comments related to the LVHJ Substudy (in patients taking alpha-blockers), see Question 11

Discussion: Lilly indicated that all investigators for the BPH program would be urologists, thus ensuring that prostate cancer would be ruled out to the satisfaction of a urologist. Lilly further agreed that clinically significant microscopic hematuria should be excluded, but asked for clarification on the definition of "clinically significant." The Division commented and concluded that it can be defined by the discretion of the urologist with wording similar to that described for PSA.

(b) (4)

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Question 9: Does DRUP agree with the proposed safety evaluation/lab collection for Study LVHJ?

Response: No. For Study LVHJ, we request uroflowmetry, with measurement of Qmax at screening, baseline and endpoint.

For comments related to the LVHJ Substudy (in patients taking alpha-blockers), see Question 11.

Discussion: Lilly agreed with the recommendation for LVHJ, but proposed to conduct uroflowmetry at screening only in the co-morbid study. The Division disagreed and stated that this request applied to both studies.

Question 10: Does DRUP agree that the integrated safety database of tadalafil in men with BPH-LUTS from the proposed Phase 3 clinical study, the completed Phase 2 studies and pivotal Study LVHG (including the 1 year open-label extension), and the referenced ED safety databases constitute an adequate safety database (including long-term safety) for the proposed indication?

Response: No. We request additional safety information and changes to the proposed Phase 3 studies, including:

- Safety information from at least 100 BPH patients aged 75 years or older in Study LVHJ.
- Measurement of Qmax in Study LVHJ.
- Revisions to the Study LVHJ Substudy, as delineated in response to Question 11.
- Safety information, perhaps from new clinical investigations, relevant to discontinuing alpha blockers prior to initiating Cialis monotherapy for BPH.

Discussion:

- ***Lilly agreed to collect the requested safety information in at least 100 BPH patients aged 75 years and older (see question 1).***
- ***Lilly agreed to collect Qmax as requested in LVHJ. The Division requested the same Qmax collection in the co-morbid study (see question 9).***
- ***Lilly's responses for the LVHJ substudy revisions appear under question 11.***
- ***Lilly asked the Division to clarify bullet number four above. The Division commented that one concern is symptomatic worsening/urinary retention in patients discontinuing alpha blockers and initiating monotherapy with Cialis. The Division requested information to address this concern. Lilly mentioned that safety data to address this concern might be available from studies LVGC/LVHG/LVHK, where approximately 25% of patients had taken alpha-blockers in the last year and 10% washed out of alpha-blocker therapy at enrollment. Discussion continued regarding the number of patients needed, the duration of the washout period for alpha-blockers, and the specific safety information needed (e.g., collection of IPSS and AE's before and after washout). Lilly will provide the Division with a plan to address this concern using data from already completed studies. The Division agreed to review the plan.***

Question 11: Is Study LVHJ appropriately designed to assess the efficacy and safety of tadalafil dosed once daily for the proposed indications? Is the clinical plan as proposed by Lilly acceptable for the proposed indications?

Response: *For Study LVHJ*
Study LVHJ is generally acceptable for the broad BPH population (indication #1), setting aside the issue of alpha blocker use. At least 100 patients aged 75 years and older should participate. We also refer to previous requests related to exclusion criteria, secondary efficacy, and safety endpoints. We have the following additional statistical comments:

1. We remind you that the sample size of 151/arm for testing the IPSS may not be adequate, because the assumed SD of 6.00 is lower than what you have seen in your other studies (LVGC, LVHG, and LVHK). We recommend that you recalculate the sample size.

2. In the statistical analysis plan, the use of ANOVA model is acceptable, however, we also suggest you include a treatment-by-region interaction term (test at alpha=0.10) in the model.

Discussion: ***The rationale for the sample size was further discussed. The Division reiterated its concern regarding underestimation of sample size. Lilly agreed to include a treatment-by-region interaction term (test at alpha=0.10) in the model.***

Response (continued):
Study LVHJ is not appropriately designed for patients with co-morbid BPH and ED (indication #2), because it lacks the 2.5mg dose. For indication #2, we recommend a separate Phase 3 study, employing both 2.5mg and 5mg doses, and using the IPSS and the EF domain of the IIEF as co-primary endpoints.

Discussion: ***Lilly agreed to conduct a separate co-morbid study using the 2.5mg and 5mg doses and the IIEF and IPSS as co-primary endpoints. Additional discussion ensued regarding the statistical plan for that study. Lilly proposed a hierarchichal approach with statistical testing being initiated with 5mg versus placebo, followed by 2.5mg versus placebo. The Division agreed with the approach.***

Response (continued): *For Study LVHJ Substudy*
The LVHJ Substudy (the "Addendum") requires revision to address our main concerns related to alpha blockers. We recommend the following:

- *At least 20% of patients should be 75 years of age and older.*
- *Increase the sample size to at least 300 (from 150).*
- *Recalculate the sample size needed for testing the difference in proportions of treatment-emergent dizziness in patients on concomitant alpha-blocker therapy. A sample size of 75/arm is too small to test the null hypothesis of no difference in proportions.*
- *Allow alpha-blocker titration during the treatment period (not mandatorily fixed).*
- *Selective and non-selective alpha blockers should be represented.*
- *Patients should be stable on alpha blocker therapy for 4 weeks (not 12 weeks).*
- *Hemodynamic adverse events should be targeted, and a means of grouping and analyzing these adverse events, should be proposed.*

Discussion:

- ***Lilly agreed with 20% of patients >75 years in the Substudy but sought clarification regarding whether the 20% requested in the Substudy was in addition to or was included in the 100 elderly patients requested in total. The Division stated that the Sponsor should propose a means of distributing the requested number of elderly patients in their Phase 3 protocols and the Division would provide comment at the time of special protocol assessment.***
- ***Lilly agreed to recalculate and increase the sample size.***
- ***Lilly agreed to allow alpha-blocker titration during the treatment period. It was agreed by both parties to preclude upward titration during both the four weeks***

of single-blind study medication and the first four weeks following initiation of the double blinded phase with active study medication.

- ***Lilly agreed to allow both selective and non-selective alpha blockers (all "US marketed" alpha blockers).***
- ***Lilly agreed that patients should be stable on alpha blocker therapy for four weeks, not 12 weeks.***
- ***Lilly agreed that hemodynamic adverse events should be targeted. They also proposed to group and analyze these adverse events as previously done for the "once daily" ED submission. The Division agreed, but requested that this exploratory analysis be expanded to include additional hemodynamic adverse event terms The Division agreed to provide additional terms to Lilly.***

Response (continued): *For the remainder of the clinical plan*
Our concern related to discontinuing alpha blockers and starting Cialis monotherapy is not addressed by Study LVHJ. An additional clinical investigation may be necessary.

We remind you that even if Study LVHJ Addendum (Substudy) shows no significant hemodynamic clinical adverse events, labeling should still discourage the use of alpha blockers with Cialis for BPH. The purpose of this Substudy is not to support combined use, but rather to provide some safety data for combined use, in the event that your proposed labeling recommendations are not followed.

The off-label combined use of alpha blockers and Cialis for BPH would likely warrant plans to manage safety risks associated with such use, including efforts to discourage such use, to increase awareness of the potential risks, and to assess compliance with labeling.

Discussion:

- ***The Division's concern regarding symptomatic worsening/urinary retention upon discontinuation of alpha blockers was addressed in question 10.***
- ***Lilly agreed that the purpose of the Substudy is not to support combined use, but rather to provide safety data for combined use in the event of inadvertent or off-label combined use, and that labeling would discourage the use of alpha blockers with Cialis for BPH. Lilly clarified that this would be consistent with the current WARNING and PRECAUTIONS language in section 5.6 of the label. The Division also commented that even if the alpha blocker study is "clean," labeling would still discourage combined use. Lilly agreed and confirmed that they are only pursuing monotherapy.***
- ***Regarding plans for management of safety risks, Lilly asked if there were anything additional beyond the label and Risk Management Plan that the Division was contemplating regarding "discouraging use". The Division stated no, that there was nothing additional being contemplated, however, it is expected that OSE would also be reviewing the submission.***

Question 12: Does DRUP agree that tadalafil 5 mg will be the recommended starting dose for the BPH patient and the comorbid BPH-LUTS and ED patient?

Response: No. While we agree that tadalafil 5mg will be the recommended starting dose for the broad BPH population, we do not agree for the comorbid BPH and ED patient population. For that population (indication #2), the 2.5mg dose should be evaluated in Phase 3.

Discussion: Lilly agreed with FDA's recommendation to evaluate 2.5mg and 5mg dosing in the co-morbid study (see question 5).

Question 13: …FDA also acknowledged that the results of the pharmacoepidemiology study would ideally be available prior to the timing of BPH approval; however, this was not a requirement. FDA stated they would like this topic to be discussed at the EOP2 meeting….Would the FDA please clarify this comment and how this may affect the Phase 3 clinical plan?

Action Items:

- ***Lilly will submit validation information to the FDA on the BII.***
- ***Lilly will submit a plan to a plan to address the Division's concern regarding symptomatic worsening/urinary retention in patients discontinuing alpha blockers and initiating monotherapy with Cialis.***
- ***Lilly will submit special protocol assessments for LVHJ (confirmatory study in general BPH population), LVHS (alpha blocker co-administration study) and the co-morbid study. These protocols will include plans for statistical analysis of multiple endpoints and multiple doses, as appropriate.***
- ***The Division will provide Lilly with a list of hemodynamic adverse event terms for exploratory analyses (see question 11).***

Post EOP2 Meeting Follow-up:

- ***On October 1, 2008 Lilly proposed to the Division to conduct the alpha-blocker co-administration substudy not as an addendum to LVHJ but rather as a separate stand-alone study (to be coded LVHS). Lilly stated that the rationale for this change was internal administrative and logistical issues encountered when preparing the LVHJ Substudy as an addendum. Thus LVHJ would be a stand alone pivotal study and LVHS would be a separate co-administration study. The***

Division responded on October 2, 2008, stating agreement with the proposal to separate the two studies.

Linked Applications	Sponsor Name	Drug Name
IND 73502	LILLY ICOS LLC	CIALIS (TADALAFIL) IC351/LY450190

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/s/

MARK S HIRSCH
10/23/2008