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Drug Coated Balloons to Improve Femoropopliteal Artery Patency: Rationale and Design of the LEVANT 2 Trial

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Background: Atherosclerotic peripheral artery disease (PAD) is common and results in limitations in quality of life and potential progression to limb loss. Options for therapy include medical therapy, supervised exercise, surgical revascularization, and more recently, endovascular therapies to restore arterial perfusion to the limb.

Endovascular revascularization has evolved over the past two decades, from percutaneous transluminal angioplasty (PTA) to self-expanding stents, atherectomy, laser angioplasty, and drug eluting stents. Despite impressive technologic advances, PTA remains the standard of care at many institutions and is the recommended primary treatment modality for femoral-popliteal PAD according to current ACCF/AHA guidelines. However, restenosis after PTA is common. Therefore, a significant clinical need remains for a device that is able to achieve more durable patency than PTA but does not require a permanent implant.

Drug coated balloons (DCB) have the potential to address this need. Several randomized controlled clinical trials of PTA balloons coated with different formulations of paclitaxel have been conducted in Europe[1,2,3,4] and demonstrated more durable efficacy than PTA with comparable safety. These studies were limited by small sample sizes and powered solely for an angiographic primary endpoint. The pivotal LEVANT 2 trial was designed in collaboration with the United States (US) Food and Drug Administration (FDA) to demonstrate safety and efficacy in a large population and to obtain US FDA approval.

Methods: A prospective, multicenter, single blind, trial comparing the Lutonix® drug coated balloon vs. PTA for treatment of femoropopliteal PAD (LEVANT 2) is the first US based 2:1 randomized controlled trial of 476 patients with femoral-popliteal

PAD designed to demonstrate superior efficacy and non-inferior safety of a novel paclitaxel DCB compared to PTA. The primary efficacy endpoint is primary patency at 12 months. The primary safety endpoint is composite freedom at 12 months from peri-operative death, index limb amputation, re-intervention, and limb-related mortality. A series of important secondary endpoints include physical functioning, quality of life, revascularizations, and alternative measures of patency. In order to minimize bias potential for confounding variables, LEVANT 2:

(1) excluded patients stented after predilation prior to randomization;

(2) incorporated very stringent criteria for bailout stenting;

(3) did not count bailout stenting as a TLR or failure of any endpoint

(4) required a blinded clinician to perform up clinical evaluations at follow up and

(5) required clinical assessment prior to review of duplex ultrasound results.

Conclusions: LEVANT 2 represents the first US-inclusive multicenter, randomized, controlled trial to assess the safety and efficacy of a novel drug coated balloon (DCB) compared to PTA as primary therapy for symptomatic PAD on the background of standard medical therapy.

Background

PAD is a prevalent, world wide problem, affecting ~5-18% of the adult population depending on age[5] and income status[6]. Although a significant proportion of patients with PAD have no reported symptoms from the syndrome[7], many patients experience disabling inability to walk or, in advanced cases, may suffer limb loss.[8] With the global epidemic of diabetes mellitus, particularly among the elderly[9], it is anticipated that more severe manifestations of PAD will become more prevalent[10].

The cornerstone of management of PAD is medical therapy. Antiplatelet therapy is commonly offered to patients with PAD[11]. Exercise, either supervised[12] or performed independently[13] has demonstrated significant improvement in physical function, quality of life and walking distances, even when compared to revascularization[14]. Because of lack of patient compliance, revascularization remains popular. Surgical revascularization is no longer the first line treatment for most patients with PAD due to the associated morbidity and mortality associated with these procedures[11].

Technology has advanced the field of revascularization for patients with PAD over many years, allowing patients with intermittent claudication and CLI to undergo endovascular procedures as an initial therapeutic strategy. PTA was initially widely performed, but 12-month primary patency rates of 28-37%[15] reduced the enthusiasm for PTA. Stents, which initially were used when procedural complications of PTA occurred, offered superior outcomes particularly for self-expanding stents[16]. Subsequently, several studies demonstrated that primary use of stents offered improved patency than PTA alone[17,18].

As stent use continued, reports of stent fracture began to emerge, raising questions about the durability of these metallic implants[19]. Longer follow up of these devices suggested a direct causal relationship between fracture and loss of patency[20]. Newer generation stents resulted in lower fracture rates[21]. Based upon the dramatic efficacy of anti-proliferative drug coating on coronary stents, and despite initial failure of similar devices in the femoropopliteal segments[22], a randomized trial comparing a drug coated self expanding stent demonstrated superiority over PTA[23]. Finally, treatment of in-stent restenosis is particularly problematic.

PTA is still the first line standard-of-care at many institutions, and it remains the primary treatment recommendation of the American College of Cardiology and American Heart Association (ACC/AHA) guideline for management of patients with femoropopliteal PAD[24], with stent used only "as salvage therapy for a suboptimal or failed result from balloon dilatation."

DCB have the potential to improve options by delivering an anti-restenotic agent to the peripheral arteries while avoiding a permanently implanted metallic scaffold. Multiple randomized controlled clinical trials of PTA balloons coated with various formulations of paclitaxel have been conducted in Europe[25,26,27,28]. All of these studies, including this study's precursor LEVANT 1, were of limited sample size and powered only to evaluate an angiographic primary endpoint at 6 months. Each demonstrated treatment with DCB resulted in significantly less late lumen loss (the primary endpoint) with safety comparable to standard PTA.

The pivotal LEVANT 2 IDE trial was designed to demonstrate safety and efficacy of DCB in a large population including US centers and to obtain device FDA approval.

Several limitations of historic femoropopliteal studies were carefully considered during this process. For example, in devices studies it is often not possible for the interventionalist to be blinded to treatment group: both stents and DCBs look and feel different than conventional PTA. This limitation makes it difficult to avoid bias from clinical assessments performed by unblinded investigators in follow-up. Furthermore, it is a subjective decision whether or not to perform a target lesion revascularization (TLR) in cases where symptoms are worsening or restenosis is observed on imaging. The impact of this potential bias was observed in several studies; for example, of subjects with restenosis documented by angiography in the THUNDER study, the decision to reintervene (TLR) was made by the unblinded physician in only 29% of DCB cases but 95% of control PTA cases[1]. Another potential source of unintentional bias was apparent in historic studies that counted bail-out stenting as an immediate primary endpoint failure[29,30]. In RESILIENT[29] and ZILVER PTX[30] the test group had a 40 and 50% primary endpoint advantage over control immediately following the index procedure. In PTA studies, differences in bailout stenting, for example 4% vs. 22% ($p = 0.02$) in THUNDER,[1] may also confound interpretation primary outcomes. The LEVANT 2 trial was designed with these historic limitations in mind.

Methods

A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Lutonix® Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries, LEVANT 2 is a multicenter, single blind, 2:1 randomized, controlled trial comparing outcomes after treatment of symptomatic PAD with paclitaxel-coated (DCB) vs. uncoated PTA balloons. The study hypothesis is that DCB will provide superior patency and non-inferior safety compared to PTA.

The trial was conducted at 55 centers located in the United States and Europe. The first subject was enrolled on July 20, 2011 and last subject enrolled on July 10, 2012. The trial is in compliance with the International Conference on Harmonization Good Clinical Practice, ISO 14155, and Declaration of Helsinki. One-year follow-up has been completed, and study follow-up, monitoring, and adjudications are ongoing through 5 years.

Study Population

Eligible patients have symptomatic claudication or ischemic rest pain (Rutherford category 2-4) with an angiographically significant atherosclerotic lesion (>70% diameter stenosis) in the superficial femoral and/or popliteal arteries and a patent outflow artery to the foot. Total target lesion length per patient is ≤15 cm and reference vessel diameter is 4 to 6 mm. Inclusion and exclusion criteria are provided in Table 1.

Study Device

The Lutonix DCB® (Bard Lutonix, New Hope, Minnesota, USA) is an 0.035" guidewire compatable PTA catheter with a semi-compliant balloon that is coated with paclitaxel at a concentration of 2 μg/mm^2. Paclitaxel is a well-known and widely used anti-proliferative agent, with its' mechanism associated with prevention of mitosis. The Lutonix DCB coating includes excipient polysorbate and sorbitol to facilitate drug release and tissue deposition. Pre-clinical[26] and pilot randomized clinical data[25] support safety, efficacy, and feasibility of use to treat femoropopliteal arteries. Balloon sizes included in the study are 4.0-6.0 mm in diameter and 40-100 mm in length.

Study Objectives and endpoints

The primary objective of the study is to demonstrate the superior efficacy and non-inferior safety of DCB compared to uncoated PTA for treatment of stenosis or occlusion of the femoropopliteal arteries. The primary safety endpoint is the composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death. The primary efficacy endpoint is primary patency of the target lesion at 1 year. Primary patency is defined as the absence of target lesion restenosis (adjudicated by a blinded duplex ultrasosonography core laboratory based on peak systolic velocity ratio (DUS PSVR) ≥2.5) and freedom from target lesion revascularization (TLR).

Planned secondary endpoints are detailed in Table 2 and include procedural success, revascularizations, alternative thresholds for DUS patency, and change over time in clinical and quality of life measures.

Sample Size and Statistical Considerations

The pre-specified analysis population includes all evaluable randomized patients. The primary proportion-based analysis is based on events through the close of the 12 month follow-up window on day 395. Sensitivity analyses are conducted in order to assess the potential impact of missing data, including tipping point, worst case, and Kaplan-Meier time-to-event analyses.

Expected outcomes for sample size calculations were based on 6 month results observed in the LEVANT 1 trial extrapolated to 12 months (70% vs. 48% for safety and 59% vs. 42% for efficacy). The sample size is based on primary efficacy, for which 405 evaluable patients provides 90% power for superiority based on a two-sided $\alpha = 0.05$ likelihood ratio chi-square tests of binomial proportions. Randomization of 476 patients accounted for an expected 15% loss of patients from the primary, as observed in recent studies of similar populations.[29,30] This sample size provides > 95% power for the primary safety endpoint based on a one-sided $\alpha = 0.025$ Farrington-Manning test of binomial proportions with a 5% non-inferiority margin.

For analysis of demographics and secondary outcomes, continuous variables are compared using t-tests and Wilcoxon nonparametric tests for means and categorical variables are compared using $\chi 2$ for proportions.

Study Procedure

Enrollment and Randomization: Patients signed informed consent, underwent screening, ankle-brachial index determination, walking impairment questionnaire, and a six-minute hall walk test[31]. Arteriography was performed to confirm angiographic inclusion criteria are met (lesion location, length, run-off). Patients meeting entry criteria were required to have a protocol defined pre-dilatation before randomization to study treatments. The pre-dilation balloon was a standard PTA balloon inflated to a diameter approximately 1 mm less than the reference vessel diameter. Following pre-dilatation, patients that were likely to require a stent based on strict angiographic criteria (major flow-limiting dissection or > 70% residual stenosis) were treated and not randomized in order to minimize this confounding variable. Patients unlikely to require a stent based on angiographic assessment after predilation were randomized 2:1 to Lutonix DCB or control PTA. (Figure 1). Balloons were sized to target 100% of reference vessel diameter and have length sufficient to treat 5mm proximal and distal to the target lesion and the predilated segment (including overlap of multiple balloons). For patients randomized to DCB, balloons were inflated for as long as necessary to achieve a satisfactory procedural result. Since drug delivery occurs on the first inflation, two DCBs must be deployed to treat longer lesions. A minimum overlap of at least 5mm was required to ensure drug delivery to the entire segment. For subjects randomized to the control arm, treatment was performed with uncoated PTA catheter(s). Use of cutting/scoring balloons was not allowed. Control PTA balloons may be deflated and repositioned to treat longer lesions.

Bailout stenting was allowed in both treatment groups only if the following criteria were met after treatment and prolonged (≥ 2 min) post-dilatation: residual

stenosis >50% or major flow-limiting dissection AND a translesional pressure gradient >20mmHg (using ≤4F end-hole catheter) or >10mmHg (pressure wire) is measured immediately distal to the target lesion.

After angioplasty, all patients were treated with dual antiplatelet therapy for at least one month and aspirin indefinitely.

Follow-up procedures: All randomized subjects are to return at 1, 6, 12 and 24 month intervals for laboratory testing (complete blood count, metabolic panel), ankle brachial index, Rutherford class assessment, six minute walk test, walking impairment and quality of life questionnaires, and DUS. A pharmacokinetic substudy was conducted in a subset of DCB-treated patients in order to assess serum paclitaxel exposure over time. At 6, 12, and 24-months, the clinical status of the subject was assessed prior to performing (or reviewing, if technician already completed) the required DUS (for assessment of patency). A physician other than the one who performed the index procedure must conduct the clinical assessments.

Study management and AE Adjudication

Lutonix, a subsidiary of CR Bard, is the study sponsor and has overall responsibility for the conduct of the study. Two independent contract research organizations (Prairie Education and Research Cooperative, IL, and Genae associates, BE) are engaged to provide study site management and monitoring of all case report forms in the US and EU, respectively. Statistical analyses were performed by independent biostatisticians from NAMSA Medical Research. The study sponsor is responsible for ensuring that the study meets all applicable regulatory requirements

and good clinical practices, and the CROs are responsible for clinical events committee (CEC) and data monitoring committee (DMC) management. The principal investigators are actively involved in the assessment of site performance and contact sites directly to improve compliance. The steering committee has final responsibility for scientific conduct and contractual rights to publish the primary results independent of the trial outcome.

The clinical trial is designed in accordance with Good Clinical Practices (GCP), HIPAA requirements, and applicable laws of various governing bodies. Data are collected in accordance with the Guidance for Industry on the collection of race and ethnicity data in clinical trials.

The LEVANT 2 study was expected to complete enrollment within 12 months of first patient enrolled. A single roll-in case was to be performed at each clinical site in order to train site personnel in proper procedure and data collection. Roll-in subjects were required to meet all protocol requirements (including enrollment criteria and follow-up). The LEVANT 2 trial includes angiographic (Synvacor, Prairie Education and Research Cooperative, Springfield, IL) and duplex ultrasonography (Vascore, Massachusetts General Hospital, Boston, MA) core laboratories. Vascular technologists who performed the required DUS were provided with hands-on duplex ultrasound training by the core laboratory.

A data monitoring committee, composed of physician experts in peripheral vascular disease or cardiovascular medicine, and biostatisticians who were not participating in the trial and had no affiliation with Lutonix, regularly reviewed and evaluated aggregate subject data to ensure continued safety, validity and scientific merit

of the trial. All adverse events, including non-serious events, are reviewed and adjudicated by an independent CEC composed of 3 clinicians who are experts in the field of vascular intervention or cardiovascular medicine and were not participants or investigators in the study. The CEC members are blinded to subject treatment.

No extramural funding was used to support this work. Employees of Bard/Lutonix did provide statistical support for the trial and those segments of this manuscript, however the authors are solely responsible for the drafting and editing of this manuscript and it's final contents.

Discussion

LEVANT 2 is the first femoropopliteal device trial that (1) excluded patients stented after predilation prior to randomization, (2) incorporated very stringent criteria for bailout stenting, (3) does not count bailout stenting as a TLR or failure of any endpoint, (4) required a blinded clinician to perform up clinical evaluations at follow up, and (5) required clinical assessment prior to review of DUS images. These design elements were intended to minimize potential sources of unintentional bias that may confound interpretation of historic stent and drug coated balloons trials.

Another source of potential bias occurs with unblinded clinical follow-up assessment. It is a subjective decision whether or not to reintervene in cases of worsening symptoms or in cases where restenosis is observed on imaging. The LEVANT 2 protocol therefore requires that both the subject and the investigator conducting the follow-up visit be blinded to treatment until the completion of the 12 month visit. Furthermore, since reinterventions may be driven by imaging data rather than worsening of clinical symptoms, the clinical status of the subject is to be assessed prior to reviewing the

imaging data. These LEVANT 2 design elements remove the potential for subjective bias at follow-up to affect one year outcomes.

Funding

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Disclosures

Michael R Jaff, DO is a Board Member of VIVA Physicians, a 501(c)3 not-for-profit education and research organization and is the Medical Director of VasCore. Dr. Jaff receives no personal compensation for his work on this trial from the sponsor. Kenneth Rosenfield MD: Abbott Vascular, Vortex/Angiodynamics, Shockwave Medical, Endospan, Primacea - scientific advisory board/consultant Institution Receives Research funding - Lutonix/Bard, Abbott vascular, Atrium, IDEV, Cordis; Equity - Primacea, Vortex; Board of Directors - VIVA, a 501c3 not for profit organization Christopher J. White M.D. is a member of the Levant 2 Steering Committee, and the International Steering Committee for the EUCLID trial. Mark Nehler, MD is on the steering committee for Astra Zeneca and provides consulting services for the Colorado Prevention Center.

James Benenati, MD has no disclosures. Dierk Scheinert, MD is a paid consultant and member of the scientific advisory board to Bard/Lutonix. Krishna Rocha-Singh, MD is a paid consultant to Bard/Lutonix.

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Table 1- Subject Inclusion/Exclusion Criteria

INCLUSION	EXCLUSION
Clinical Criteria 1. Male or non-pregnant female ≥18 years of age; 2. Rutherford Clinical Category 2-4; 3. Patient is willing to provide informed consent, is geographically stable and comply with the required follow up visits, testing schedule and medication regimen; **Angiographic Criteria** Lesion Criteria 4. Length ≤15 cm; 5. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm); 6. ≥70% stenosis by visual estimate; 7. Lesion location starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk; 8. de novo lesion(s) or non-stented restenotic lesion(s) >90 days from prior angioplasty procedure; 9. Lesion is located at least 3 cm from any stent, if target vessel was previously stented; 10. Target vessel diameter between ≥4 and ≤6 mm and able to be treated with available device size matrix; 11. Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion; 12. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions); 13. NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication. 14. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure); 15. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications; 16. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment.	**Patients will be excluded if ANY of the following conditions apply:** 1. Pregnant or planning on becoming pregnant or men intending to father children; 2. Life expectancy of <5 years; 3. Patient is currently participating in an investigational drug or other device study or previously enrolled in this study; NOTE: Enrollment in another clinical trial during the follow up period is not allowed. 4. History of hemorrhagic stroke within 3 months; 5. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure; 6. History of MI, thrombolysis or angina within 2 weeks of enrollment; 7. Rutherford Class 0, 1, 5 or 6; 8. Renal failure or chronic kidney disease with MDRD GFR ≤30 ml/min per 1.73 m^2 (or serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis); 9. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion; 10. Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication; 11. Anticipated use of IIb/IIIa inhibitor prior to randomization; 12. Ipsilateral retrograde access; 13. Composite lesion length is >15 cm or there is no normal proximal arterial segment in which duplex flow velocity can be measured; 14. Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment; 15. Known inadequate distal outflow (>50 % stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion; 16. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel; 17. Severe calcification that renders the lesion un-dilatable; 18. Use of adjunctive treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

Table 2- Secondary Endpoints

Safety	Efficacy
• Freedom at 30 days from all-cause death, index limb amputation above the ankle and target vessel revascularization (TVR) (VIVA Safety Endpoint) • Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 1, 6, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and index-limb-related death. The following endpoints will be assessed at 1, 6, 12, 24, 36, 48 and 60 months: • All-cause death • Amputation (above the ankle)-Free Survival (AFS) • Target Vessel Revascularization (TVR) • Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature • Major vascular complications • Readmission for cardiovascular events	• Acute Device, Technical and Procedural success The following endpoints will be assessed at 6, 12 and 24 Months: • Primary and Secondary Patency (DUS PSVR <2.5) • Alternative Primary and Secondary Patency based on alternative definitions of DUS PSVR <2.0 and <3.0 • DUS Clinical Patency (DUS PSVR <2.5 without prior Clinically Driven TLR) • Target Lesion Revascularization (TLR) o Clinically-driven o Total *(clinical and DUS/angiography-driven)* • Change of Rutherford classification from baseline • Change of resting Ankle Brachial Index (ABI) from baseline • Change in Walking Impairment Questionnaire from baseline • Change in Six Minute Walk Test from baseline in a subset of patients • Change in quality of life from baseline, as measured by EQ-5D and SF36-v2 surveys

Figure 1-Study Overview