As men age, the prostate gland can enlarge to benign hyperplasia. Enlargement of the prostate can constrict the urethra, which can reduce urinary flow rates and cause urinary hesitancy, urgency, increased frequency, dysuria, and urinary tract infection. In addition to the mechanical component caused by the physically...
enlarged prostate, a dynamic component caused by variations in the tone of the prostate smooth muscle contributes to the obstruction. This tone is controlled by the $\alpha$-1 adrenergic receptors of the sympathetic nervous system. Selective $\alpha$-1 inhibitors, such as doxazosin, have been shown in several clinical trials to improve urinary function and clinical symptoms of subjects with benign prostate hyperplasia (BPH) [1,2].

The doxazosin Gastrointestinal Therapeutic System (GITS) is a controlled release formulation. It has been developed to produce a peak plasma concentration with no higher than the 1-mg dose of immediate-release doxazosin, while achieving greater overall systemic exposure. Moreover, curative levels can be achieved more rapidly with this formulation without the addition of excessive titration steps [3]. Doxazosin GITS has demonstrated efficacy, particularly for improvement of symptom scores and increase in maximum urinary flow (Qmax), as well as demonstrating benefits on quality of life (QoL) [4,5]. The efficacy and tolerability of 4-mg and 8-mg single doses of doxazosin GITS have been compared with a single dose of 1 mg immediate release doxazosin in subjects with mild-to-moderate hypertension, which results in similar outcomes [2].

The prevalence of BPH is difficult to determine because a standardized definition is lacking; however, the manifestation of lower urinary tract symptoms is widely accepted [6,7]. Some clinical estimates of BPH prevalence range from 80% in subjects aged >80 years in the United States [8] to 63% in those aged >70 years in an Asian population [9]. Surgical therapy has been associated with higher treatment failure rates, coupled with greater costs over the long term, therefore, effective and tolerable medical treatment is highly sought after [10,11].

Although data are available on doxazosin GITS for the treatment of BPH in many western populations, there remain limited data in Asian populations, particularly in Taiwan. This study was designed to evaluate the safety and efficacy of doxazosin GITS in Taiwanese subjects with BPH.

**Methods**

**Study design**

This was a post-marketing open-label study conducted at five centers in Taiwan. Subjects were required to attend the center on three occasions: baseline, week 4, and week 8. All subjects were initiated on doxazosin GITS 4 mg once daily to be taken at breakfast. At week 4, an efficacy response-based dose titration occurred: subjects who achieved an increase in Qmax of $\geq 3$ mL/s and a $\geq 30\%$ reduction in the total International Prostate Symptom Score (IPSS) from baseline continued on doxazosin GITS 4 mg for the remainder of the study; all other subjects were up-titrated to doxazosin GITS 8 mg once daily for the remainder of the study. The 8-week duration was chosen because previous studies have shown that most changes in total IPSS and Qmax are rapid and occur within the initial 8 weeks of doxazosin GITS treatment [12].

**Inclusion and exclusion criteria**

This study was conducted in accordance with the latest version of the Declaration of Helsinki in 2008. The protocol (study code: A0351063) was approved by the Institutional Review Board at each center and written informed consent was obtained from each subject as a condition of entry.

We enrolled Taiwanese male subjects aged 50–80 years with a primary diagnosis of BPH, which was defined an enlarged prostate (confirmed by digital rectal examination and/or B-mode ultrasound), a baseline IPSS score $\geq 12$, and a baseline Qmax of 5–15 mL/s in a total voided volume $\geq 150$ mL. Subjects who had previous prostate surgery or those who had a stent, microwave thermotherapy, and/or balloon dilation within the previous 6 months were excluded. Individuals who presented with known or suspected prostate malignancy, or prostate specific antigen (PSA) levels $>10$ ng/mL, were also excluded.

**Measurements**

Efficacy was assessed using a subject-completed IPSS questionnaire and Qmax at baseline, week 4, and week 8 (primary evaluations). The IPSS questionnaire comprised of two components: symptom score and QoL. At each visit, Qmax was determined using a urinary flow meter. Other efficacy assessments included post-void residual urine volume, as determined by B-mode ultrasound at each visit. The efficacy response was classified as the proportion of subjects who achieved an increase in Qmax of $\geq 3$ mL/s and a $\geq 30\%$ reduction in total IPSS score. Safety assessment included adverse events, treatment discontinuation, clinical laboratory tests, and physical examination at baseline and week 8.
Vital signs (sitting blood pressure and heart rate) were measured at each visit.

**Statistical analysis**

Sample size calculations were based on a significance level of 2.5% to ensure that the overall type I error did not exceed 5% for both of the primary endpoints. Assuming a 20% attrition rate, a sample size of 80 subjects would provide 95% power to detect a difference from baseline of four units in the total IPSS (standard deviation (SD): 8 units), and 85% power to detect a difference from baseline of 3 mL/s (SD: 7 mL/s) in Qmax.

The intent-to-treat (ITT) population (subjects who took at least one dose of study medication and provided at least one post-baseline efficacy measure) and the per-protocol population (ITT subjects without major protocol violations who were compliant with taking study medication, and had both primary endpoints measured at day 26 or thereafter) were used to test the primary efficacy endpoints. Evaluation of the mean change from baseline to the end of the study (week 8) was conducted on total IPSS and Qmax using two-sided paired t tests at the 2.5% significance level. Secondary efficacy endpoints were analyzed using paired t tests for the ITT population. If a subject withdrew, the last available post-baseline observation was carried forward and used in the analyses at weeks 4 and 8. Mean change, ±SD or p values and 95% confidence intervals (CIs) are presented.

Standard summaries of safety parameters as defined by the sponsor’s worldwide safety standards were generated for the safety population (i.e. all subjects who took at least one dose of study medication). Compliance was assessed at each visit by calculating the ratio between the total dosage taken and the total dosage that should have been taken during follow-up. Non-compliance was defined as taking <80% or >120% of study treatment.

**RESULTS**

**Participants**

A total of 90 male Asian subjects from five centers were screened: 80 (100%) were treated with doxazosin GITS, and 53 (66.3%) completed the study. Subject disposition is presented in the Figure. The mean age was 64 years (range, 49–84 years), and the mean duration of BPH at baseline was 2.2 years (range, 0–11.9 years). The mean baseline PSA level was 2.3 ± 2.5 ng/mL. Hypertension (n = 16, 20.0%), diabetes (n = 9, 11.3%), and urethra and urinary tract disorders (n = 8, 10.0%) were the most common disorders present at baseline. Concomitant medications were taken by 47 (58.8%) subjects; the most common of which were antacids.

**Figure.** Study flow chart. GITS = gastrointestinal therapeutic system; AE = adverse event; ITT = intent to treat; PP = per protocol; Inc/exc = inclusion/exclusion.
(16%), anti-inflammatory analgesics (15%), calcium channel blockers (11%), and oral antidiabetic drugs (11%).

**Study treatment**
The median duration of treatment was 53 days (range, 1–62 days). Thirty (38%) subjects were uptitrated to doxazosin GITS 8 mg at week 4, and 24 (30%) remained on doxazosin GITS 4 mg. The compliance (80–120%) to study treatment at each visit was high (94–98%), and the overall mean compliance was 95±15.3%.

**IPSS**
The absolute mean baseline total IPSS for the ITT population was 20.6±5.4. Doxazosin GITS significantly improved (decreased) the total IPSS from baseline to week 8 by −8.9±7.0 (p < 0.001, 95% CI = 10.5 to −7.3). Furthermore, this improvement was evident as early as week 4 (Table 1). A similar improvement was observed for the per protocol analysis population at week 8: change from baseline to −10.6±6.4 (p < 0.001; 95% CI = −12.4 to −8.8).

**Qmax**
Statistically significant mean increases from baseline in Qmax were observed at week 8 following treatment with doxazosin GITS for the ITT and per protocol populations. Table 2 presents the baseline absolute mean and week 4 and 8 changes from baseline for both population groups. The majority of increases in Qmax occurred by week 4: change from baseline was 3.2±4.7 mL/s (p < 0.001).

**Urine volume**
The change in post-void residual volume did not reach statistical significance at any time point, although it decreased (improved) from a mean baseline value of 40.3±53.3 mL at week 4 by 9.4±51.7 mL and at week 8 by 9.3±49.5 mL.

**QoL**
Doxazosin GITS produced a significant decrease (improvement) in QoL score at weeks 4 and 8. The mean baseline QoL index score was 4.1±1.1. A mean change from baseline to week 4 of −1.1±1.4 (p < 0.001; 95% CI = −1.4 to −0.8) was observed. This improvement

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**Table 1. International Prostate Symptom Scores in different groups**

<table>
<thead>
<tr>
<th>IPSS</th>
<th>Absolute values</th>
<th>Relative value†</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population (n=75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.6±5.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4/LOCF</td>
<td>12.4±6.4</td>
<td>−8.2±7.6</td>
<td>&lt;0.001</td>
<td>−9.9 to −6.5</td>
</tr>
<tr>
<td>Week 8/LOCF</td>
<td>11.7±6.3</td>
<td>−8.9±7.0</td>
<td>&lt;0.001</td>
<td>−10.5 to −7.3</td>
</tr>
<tr>
<td>PP population (n=51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.7±5.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>11.4±5.4</td>
<td>−10.3±6.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8/LOCF</td>
<td>11.1±5.6</td>
<td>−10.6±6.4</td>
<td>&lt;0.001</td>
<td>−12.4 to −8.8</td>
</tr>
</tbody>
</table>

*Data presented as mean±standard deviation or confidence intervals; †changes from the baseline. IPSS = International Prostate Symptom Scores; CI = confidence interval; ITT = intent to treat; PP = per protocol; LOCF = last post baseline observation carried forward.

**Table 2. Maximum urinary flow rates in different groups**

<table>
<thead>
<tr>
<th>Qmax (mL/s)</th>
<th>Absolute values</th>
<th>Relative values†</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (n=75)</td>
<td>10.7±3.4</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 4/LOCF (n=68)</td>
<td>13.7±4.3</td>
<td>3.2±4.7</td>
<td>&lt;0.001</td>
<td>2.1–4.4</td>
</tr>
<tr>
<td>Week 8/LOCF (n=68)</td>
<td>13.8±4.6</td>
<td>3.3±4.6</td>
<td>&lt;0.001</td>
<td>2.2–4.4</td>
</tr>
<tr>
<td>PP population (n=51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.5±2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>13.9±4.4</td>
<td>3.4±4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8/LOCF</td>
<td>14.1±4.6</td>
<td>3.7±4.7</td>
<td>&lt;0.001</td>
<td>2.3–5.0</td>
</tr>
</tbody>
</table>

*Data presented as mean±standard deviation or confidence intervals; †changes from the baseline. Qmax = maximum urinary flow; CI = confidence interval; ITT = intent to treat; PP = per protocol; LOCF = last post baseline observation carried forward.
advanced at week 8 to \(-1.3 \pm 1.5\) (\(p<0.001\); 95% CI = \(-1.7\) to \(-1.0\))

**Responders**

The proportion of subjects who achieved a \(\geq 3\) mL/s increase in Qmax and a \(\geq 30\%\) reduction in total IPSS from baseline at weeks 4 and 8 was 34% and 43%, respectively. A greater proportion of subjects on doxazosin GITS achieved a \(\geq 30\%\) reduction in total IPSS from baseline at weeks 4 (64%) and 8 (67%) than subjects who achieved a \(\geq 3\) mL/s increase in Qmax at weeks 4 (41%) and 8 (51%).

**Safety**

A total of 49 adverse events were reported in 33 (41.3%) subjects, and 35 adverse events reported in 23 (28.8%) subjects were considered to be treatment-related. The most commonly reported treatment-related adverse event was dizziness (\(n=12\), 15.0%). Other treatment-related events had a frequency of \(\leq 5\%\); the most frequent of which were chest pain, pruritus, dry mouth, and peripheral edema (all of which had a frequency of \(\geq 2\%\)). Ten (12.5%) subjects permanently discontinued treatment due to related adverse events; all subjects were on doxazosin GITS 4 mg at the time of discontinuation. Eight (10.0%) subjects discontinued due to dizziness, which might have been experienced alone or in combination with other adverse events. Only two treatment-related adverse events were reported as severe: dizziness and sexual dysfunction. One (1.3%) subject experienced acute pancreatitis and exacerbation of gouty arthritis, both of which were reported as serious adverse events that were not related to study treatment; the subject recovered and remained in the study.

**DISCUSSION**

The aim of this study was to evaluate the efficacy and safety of doxazosin GITS 4 mg per day (with an 8 mg/day titration step) in a Taiwanese population with BPH. The results showed significantly marked improvements from baseline for the primary efficacy endpoints and a number of the secondary efficacy endpoints. In addition, benefits in QoL and a favorable safety profile were observed.

The total IPSS was significantly improved from baseline by \(-8.9\) with doxazosin GITS at week 8. IPSS is a validated tool for assessing symptom frequency and severity, and is widely recognized as the international standard [7]. Doxazosin GITS decreased the mean baseline total IPSS from a classification of severe (20.6; severe 20–35) to moderate (11.7; moderate 8–19), as determined by the American Urological Association [13], within 8 weeks. Furthermore, this result was observed as early as week 4. The results of this study are comparable to those published from other studies of doxazosin GITS in western populations in which total IPSS improvements of \(-8.1\) [1] and \(-8.0\) [14] have been reported. It is worth noting that the IPSS improvements shown in these western populations were observed after 13 weeks of treatment. However, a comparable improvement was observed after only 4 weeks in our Taiwanese population.

The proportion of subjects who achieved a \(\geq 3\) mL/s increase in Qmax and a \(\geq 30\%\) reduction in total IPSS (responders) from baseline at weeks 4 and 8 was 34% and 43%, respectively. These results are similar to those observed by Kirby et al, who documented that 32% of subjects achieved both of these endpoints at week 13 [2]. A greater proportion of subjects achieved a \(\geq 30\%\) reduction in total IPSS from baseline at weeks 4 (64%) and 8 (67%) than subjects who achieved a \(\geq 3\) mL/s increase in Qmax at weeks 4 (41%) and 8 (51%). Chung et al reported that 84% of subjects achieved a \(\geq 30\%\) reduction in IPSS from baseline at week 12 with doxazosin 2, 4 or 8 mg per day [15]. The higher figure is probably explained by the longer duration of treatment compared with the present study. Doxazosin GITS has demonstrated efficacy for up to 13 weeks, and further investigation is required to establish its efficacy in the longer term.

Further to the improvements in efficacy measures, doxazosin GITS also demonstrated benefits in QoL as measured by the IPSS questionnaire. The change from baseline in QoL after 2 months of treatment with doxazosin GITS was \(-1.3\), which is comparable with the 3–9-month QoL results (change from baseline, \(-1.25\)) presented for doxazosin in a recent review of all α-blockers [16]. As prevalence of BPH is increasing as a result of an aging population, agents that improve symptoms as well as QoL are increasingly important.

Individuals with BPH commonly report higher levels of PSA, possibly due to the disruption and change in volume of the prostate. The Medical Therapy of the Prostatic Symptoms (MTOPS) trial observed that baseline PSA level in the doxazosin treatment group (mean baseline PSA = 2.4 ng/mL) was a predictor of
risk of clinical progression of BPH and invasive therapy [17]. Subjects in this study had a mean baseline PSA level of 2.3 ng/mL, which is similar to that in previous studies.

In the current study, we observed a favorable safety profile with doxazosin 4 and 8 mg per day. The most common adverse event was dizziness, which was also the most frequent reason for treatment discontinuation. Dizziness is known to occur with α-blockers, although differences in frequency have been shown with different agents [16]. Dizziness has been reported previously with doxazosin use [18,19], therefore, this finding was not unexpected.

A few limitations must be noted for the present study. The study was designed as an open-label, non-comparative trial; however, the treatment effect observed was similar to findings reported for placebo-controlled studies. The present study had a relatively short duration of 8 weeks, and longer-term studies in this population are needed to establish a sustained benefit over time.

In summary, this multicenter, open-label study demonstrated that doxazosin GITS 4 mg per day (with an 8 mg/day titration step) effectively improved urinary flow and other symptoms of BPH in a Taiwanese population. Statistically significant improvements were observed in the majority of efficacy measures, as early as week 4, and maintained at week 8. Additionally, significant benefits were demonstrated in QoL, and doxazosin GITS was found to be safe and well-tolerated in this study population. These data will provide further information for clinicians on the use of doxazosin GITS for the treatment of BPH, particularly in Taiwanese patients.

ACKNOWLEDGMENTS

This study was funded by Pfizer. Manjula Schou is an employee of Pfizer. Many thanks to all study team members from Pfizer Taiwan and the Phase 3b/4 Unit Asia, Pfizer Global Research and Development, Sydney, Australia for their invaluable contributions to the study design, conduct, and reporting. Andrea Malcolm and Ruth O’Halloran of the Phase 3b/4 Unit Asia provided medical writing assistance during the production of this manuscript. The authors and study team extend their gratitude to the subjects who participated in this study.

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評估 Doxazosin GITS 對於前列腺肥大
病患的療效和安全性

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執行本試驗是為了收集 doxazosin GITS（經由控制緩慢釋放的劑型）在良性前列腺肥大之台灣受試者的療效與安全性資料。Doxazosin 在亞洲族群的試驗缺少台灣單獨的資料。此試驗為期 8 週、開放性、非對照研究。80 位有良性前列腺肥大（BPH）男性受試者（平均年齡 64 歲）接受 4 mg doxazosin GITS 一天一次。在第 4 週達到最大尿流率（Qmax）增加 3mL/s 以上，且國際前列腺症狀評分（IPSS）減少 30% 以上的受試者，接下來 4 週會繼續服用 4 mg doxazosin GITS。其他所有受試者則會調整劑量至 8 mg doxazosin GITS 一天一次。對意圖治療（intent-to-treat）族群是使用雙尾配對樣本之 t 檢驗（two-sided paired t tests），評估自基準點至第 4 週與第 8 週（主要終點）的 IPSS 與 Qmax 的變化。試驗期間全程做安全性評估，共有 53 位受試者（66.3%）完成試驗。基準點的 Qmax 與 IPSS 的總分，分別為 10.7 ± 3.4 mL/s 與 20.6 ± 5.4。在第 8 週觀察到之 Qmax 比基準點時顯著增加 3.3 ± 4.6mL/s（95% CI = 2.2–4.4；p < 0.001）；而且 IPSS 總分顯著降低 –9.9 ± 7.0（95% CI = –10.5 to –7.3；p < 0.001）。最常出現與治療相關的作用是眩暈。Doxazosin GITS 4 mg/day（與調整劑量至 8 mg）能有效改善 BPH 的症狀。由本試驗獲得的結果將能提供臨床醫師更多使用 doxazosin GITS 治療 BPH 的資料，特別是對於台灣患者。

關鍵詞：前列腺肥大，可迅（doxazosin），腸胃治療系統，國際前列腺症狀評分，前列腺
（高雄醫誌 2010;26:532–9）