Tadalafil for the Treatment of Lower Urinary Tract Symptoms in Japanese Men with Benign Prostatic Hyperplasia: Results from a 12-week Placebo-controlled Dose-finding Study with a 42-week Open-label Extension

Masayuki TAKEDA,1 Osamu NISHIZAWA,2 Takeshi IMAOKA,3 Yoji MORISAKI,3 and Lars VIKTRUP4∗

1Department of Urology, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Chuo, Japan, 2Department of Urology, Shinshu University School of Medicine, Matsumoto, Japan, 3Lilly Research Laboratories Japan, Eli Lilly Japan K.K., Kobe, Japan, and 4Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, USA

Objectives: To examine the efficacy, safety, and dose response of tadalafil once daily in Japanese men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH-LUTS).

Methods: Men ≥45 years with moderate-to-severe BPH-LUTS were randomized to once-daily placebo (N = 140), tadalafil 2.5 mg (N = 142), or tadalafil 5.0 mg (N = 140), in a 12-week double-blind phase, followed by a 42-week, tadalafil 5.0 mg open-label extension (OLE) phase (N = 394). The primary outcome was total International Prostate Symptom Score (IPSS) change from baseline to last available observation in the double-blind phase.

Results: The least squares (LS) mean difference between placebo and tadalafil in total IPSS change from baseline was −0.7 (P = 0.201) and −1.1 (P = 0.062) for tadalafil 2.5 and 5 mg, respectively (ANCOVA; a dose-dependent improvement in placebo-adjusted total IPSS for tadalafil 5 mg versus 2.5 mg of 57%). Repeated-measures analyses identified a significant total IPSS change for tadalafil 5 mg (LS mean difference between placebo and tadalafil 5 mg: −1.2; P = 0.035), but not tadalafil 2.5 mg, at week 12. Significant improvements for tadalafil 5 mg were demonstrated (ANCOVA) for IPSS obstructive subscore (P = 0.033) and IPSS quality of life index (P = 0.022). Numerical improvements in IPSS scores were maintained over the OLE phase. Tadalafil was well tolerated with no unexpected adverse events.

Conclusion: Tadalafil (5.0 mg) had a favorable benefit-to-risk profile, supporting further investigation of tadalafil (5.0 mg) in Japanese men with BPH-LUTS.

Key words benign prostatic hyperplasia, Japanese, lower urinary tract symptoms, phosphodiesterase type 5 inhibitors, tadalafil

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis characterized by the proliferation of stromal and epithelial cells leading to prostate enlargement.1 The condition may be associated with storage, voiding, and postmicturition lower urinary tract symptoms (LUTS), including urinary frequency, urgency, nocturia, urinary hesitancy and intermittency, straining, weak urinary stream, incomplete bladder emptying, and postmicturition dribbles.2 The term “LUTS suggestive of BPH” (or BPH-LUTS), even without the histological diagnosis of BPH, is recognized and continues to be used among clinicians3 and as an indication for pharmacological treatment of LUTS associated with benign prostatic obstruction.

Population-based studies conducted in Australia, Canada, France, the USA, and parts of Asia have shown that LUTS in men with BPH is common over the age of 50 years, and the prevalence significantly increases with increasing age.4 In a Japanese community-based study, the prevalence of moderate-to-severe BPH-LUTS (defined as an International Prostate Symptom Score [IPSS] > 7) was 44, 52, and 63% for men aged 50–59, 60–69, and 70–79 years, respectively.5 Although BPH-LUTS is not life-threatening, the condition may have a significant impact on quality of life (QoL).6,7

Pharmacotherapy is the first-line treatment for BPH-LUTS. In Japan, treatments approved for moderate-to-severe BPH-LUTS include α1-adrenoceptor blockers

∗Correspondence: Lars Viktrup, MD, PhD, Lilly Research Laboratories, DC 1548, Lilly Corporate Center, Indianapolis, IN 46285, USA. Tel: +1-317-651-6219; Fax: +1-317-433-4901. Email: viktrulp@lilly.com

Trials registration: ClinicalTrials.gov NCT00783094.

Received 9 October 2011; revised 8 December 2011; accepted 15 January 2012.

DOI: 10.1111/j.1757-5672.2012.00144.x
Tadalafil for BPH-LUTS in Japanese men

(α-blockers; e.g. tamsulosin, prazosin, silodosin, naftopidil, and terazosin), antiandrogens (e.g. oxandrolone, chloramadinone acetate, and allylestrenol), and the 5-α reductase inhibitor, dutasteride. Although these treatments are effective in reducing symptoms caused by BPH, they have been associated with side-effects such as dizziness and hypotension (α-blockers), or sexual dysfunction (tamsulosin, silodosin, dutasteride, and antiandrogens), which may impact treatment adherence. In a retrospective assessment of Japanese men treated with silodosin, a low 1-year continuation rate (12.0%) was attributed in part to the occurrence of adverse events (AEs; 28.7%).

In the human prostate, nitric oxide (NO) plays a role in mediating contractile function, and lower urinary tract dysfunction in BPH might be associated with the lack of NO-related relaxation of prostate smooth muscle. The effect of NO on prostate smooth muscle occurs via cyclic guanosine monophosphate production and phosphodiesterases (degrading enzyme of cyclic nucleotides) including phosphodiesterase type 5 (PDE5), which is present in the human prostate and other tissues of the urogenital tract. Hence, PDE5 inhibitors may be effective in treating BPH-LUTS. Tadalafil, a selective PDE5 inhibitor, is currently approved in over 90 countries, including Japan, for the treatment of erectile dysfunction (ED). In a 24-month multinational extension study enrolling 1173 men with ED, tadalafil (up to 20 mg, as needed) treatment for up to 24 months was reported to be safe and well tolerated; most treatment-emergent AEs (TEAEs), such as headache, dyspepsia, flushing, back pain, myalgia, and nasal congestion, were mild or moderate in severity. A similar safety profile for tadalafil (5–20 mg, as needed) has been reported in a 12-week randomized, double-blind, placebo-controlled study in Japanese men with ED.

We report the results of a randomized, placebo-controlled, dose-finding study examining the efficacy and safety of tadalafil once daily in Japanese men with BPH-LUTS. The study consisted of a 12-week, double-blind, placebo-controlled phase followed by a 42-week, open-label extension (OLE) phase.

2. METHODS

2.1. Study design

The study was a prospective, multicenter, double-blind, randomized, parallel-group, placebo-controlled, dose-finding study, which included a 4-week, single-blind, placebo run-in period, and a 12-week double-blind phase. The double-blind phase was followed by a 42-week OLE phase. The study was conducted at 19 sites in Japan. Eligible patients were randomized (1:1:1), using a computer-generated random sequence and an interactive voice response system, to receive once-daily placebo or tadalafil (2.5 mg or 5.0 mg) for 12 weeks. Randomization was stratified by baseline BPH-LUTS severity (moderate: IPSS < 20; severe: IPSS ≥ 20) and previous α-blocker therapy within 12 months of the first visit.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by the participating institutional review boards. All patients provided written informed consent before participating in the study.

2.2. Participant population

The study enrolled Japanese men, aged ≥45 years, with moderate-to-severe BPH-LUTS (total IPSS ≥ 13) at the beginning of the 4-week placebo run-in period. At screening, physical examination included digital rectal examination. Histological verification of BPH was not required. Inclusion criteria included bladder outlet obstruction of intermediate severity, defined by a urinary peak flow rate (Qmax) of 4–15 mL/s (from a previod bladder volume of 150–550 mL and a minimum voided volume ≥125 mL) and a prostate volume >20 mL. Major exclusion criteria were prostate-specific antigen (PSA) levels >10.0 ng/mL or between 4.0 and 10.0 ng/mL without clinical judgment of “negative prostate cancer”, postvoid residual volume (PVR) ≥300 mL, pelvic surgical procedures on the urinary tract including minimally invasive BPH therapies, clinical evidence of prostate cancer or any bladder or urinary tract conditions that may have affected LUTS, history of significant renal insufficiency, or received dutasteride within the previous 6 months. All participants agreed not to use any other treatments for BPH, ED, or overactive bladder (OAB), including α-blockers, 5-α reductase inhibitors, PDE5 inhibitors, or herbal preparations during the study.

2.3. Treatment protocol

The first part of the study comprised a 2-week screening/wash-out period (if on BPH, OAB, or ED therapy), a 4-week placebo run-in period, and a 12-week double-blind phase (Fig. 1). Participants entering the double-blind phase were randomized to receive oral placebo, tadalafil 2.5 mg, or tadalafil 5.0 mg once daily. All participants who completed the double-blind phase entered the 42-week OLE phase and received tadalafil 5.0 mg once daily. The timing of all assessments is displayed in Figure 1.

2.4. Outcome measures

The primary outcome measure was the total IPSS change from baseline (week 0) to the double-blind phase endpoint (week 12) or last available observation. The IPSS is a seven-item, self-administered questionnaire internationally validated to assess the severity of BPH-LUTS. Each question is scored from 0 to 5 to give a total IPSS of 0 to 35 points; higher total scores represent greater symptom severity.

Secondary efficacy outcome measures included: (i) IPSS obstructive subscore (IPSS questions 1, 3, 5, and 6); (ii) IPSS irritative subscore (IPSS questions 2, 4, and 7); (iii) IPSS QoL index; and (iv) Qmax. Values obtained for Qmax were considered valid only if the previod bladder volume (assessed by ultrasound) was ≥150 mL and ≤550 mL, and the voided volume was ≥125 mL. Safety outcome measures included frequency and severity of
AEs, vital signs, clinical laboratory tests, PSA level, and PVR. Adverse events were summarized using the Medical Dictionary for Regulatory Activities (double-blind phase: version 12.0; OLE phase: version 13.0) preferred term. During the double-blind phase, TEAEs were defined as events that first occurred or worsened on or after the day of randomization (week 0) to the end of the double-blind phase. During the OLE phase, TEAEs were defined as events that first occurred or worsened on or after the day of enrollment (week 12) in the OLE phase to the end of the OLE phase.

2.5. Statistical analyses

A sample size of 140 participants was planned for each treatment group based on outcomes from a previous similarly designed study. This sample size was estimated to provide 90% power to detect an expected difference between the tadalafil 5 mg and placebo groups of 2.36 in total IPSS change from baseline to endpoint (week 12 or last available observation; based on a two-sided t-test at a significance level of 0.05).

For the double-blind phase, efficacy and safety analyses included all participants who were randomized and started study medication, grouped by allocated treatment. For efficacy analyses only, participants were excluded if no postbaseline data were available. For the primary analysis, the change from baseline (week 0) to endpoint (week 12) was based on the last observation carried forward (LOCF). Treatment differences were assessed using analysis of covariance (ANCOVA) models, with treatment group and previous α-blocker therapy as fixed effects, and baseline total IPSS as a covariate. Changes in total IPSS were compared using least squares (LS) means and the corresponding 95% confidence intervals (CI). Prespecified mixed-effects models repeated measures (MMRM) analyses, with unstructured covariance matrices, were performed to evaluate the total IPSS change over time (weeks 2, 4, 8, and 12) from baseline. This model included treatment group, previous α-blocker use, time, and treatment-by-time interaction as fixed effects, and baseline total IPSS as a covariate. All data were analysed with a two-sided significance level of 0.05. For the OLE phase, efficacy analyses were primarily descriptive and included the change in efficacy variables from baseline (week 0) and from the beginning of the OLE phase (week 12) to week 54, based on LOCF. Safety and efficacy analyses included all randomized participants who received at least one dose of tadalafil (5.0 mg) during the OLE phase.

Statistical analyses were performed using SAS® Drug Development (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

3.1. Participant disposition

A total of 422 participants were enrolled in the double-blind phase (Fig. 2). Efficacy analyses included 421 participants; one participant was excluded from the analyses because no postbaseline data were available. Safety analyses included all 422 participants. Of the randomized participants, 394 (93.4%) completed the double-blind phase. During the double-blind phase, the number of participants who discontinued because of AEs was similar for all treatment groups (placebo: 5/140, 3.6%; tadalafil 2.5 mg: 4/142, 2.8%; tadalafil 5 mg: 5/140, 3.6%; Fig. 2).

All 394 participants who completed the double-blind phase entered the OLE phase and received at least one dose of tadalafil. A total of 323 (82.0%) participants completed the OLE phase; AEs were the most common reason for discontinuation (n = 35, 8.9%; Fig. 2).

3.2. Baseline characteristics

The demographic and other baseline characteristics were similar among all treatment groups (Table 1). The median age of participants was 67.4 years (range: 45.4–87.4 years) and the majority (n = 274; 64.9%) of participants were older than 65 years. At baseline, 302 (71.6%) participants had mild-to-moderate BPH-LUTS (IPSS < 20) with BPH-symptom duration of 4.2 ± 3.1 years (mean ± standard deviation [SD]). Most participants had received previous BPH therapy (α-blocker: 77.0%; other BPH therapy: 19.7%). Overall, the demographic and baseline characteristics of the participants enrolled in the OLE phase were similar to those in the double-blind phase (Table 1).
Fig. 2  Study flow diagram and participant disposition. DB, double-blind; OLE, open-label extension.
3.3. Efficacy: double-blind phase

The LS mean difference between the placebo and tadalafil groups (placebo-adjusted LS mean) in total IPSS change from baseline was −0.7 (CI: −1.8, 0.4; P = 0.201; ANCOVA) for the tadalafil 2.5 mg group and −1.1 (CI: −2.2, 0.1; P = 0.062; ANCOVA) for the tadalafil 5 mg group. Although, there were no statistically significant differences in the total IPSS change between the placebo group and either tadalafil group, the placebo-adjusted total IPSS improvement was 57% greater in the tadalafil 5 mg group than the tadalafil 2.5 mg group (Table 2).

Analyses using MMRM identified a statistically significant change in total IPSS for the tadalafil 5 mg group compared with the placebo group at week 12 (placebo-adjusted LS mean change: −1.2; CI: −2.4, −0.1; P = 0.035), but not at weeks 2, 4, and 8 (Table 3). There were no statistically significant differences in the change in total IPSS at weeks 2, 4, 8, and 12, between the tadalafil 2.5 mg and the placebo groups (Table 3).

There was a statistically significant difference between the tadalafil 5 mg and placebo groups in the change in IPSS obstructive subscore and IPSS QoL index from baseline to last available observation, but not for the IPSS irritative subscore (Table 2). There were no statistically significant differences between the tadalafil 2.5 mg and the placebo groups for any of the symptom scores (Table 2). A small improvement in Qmax was observed for all treatment groups during the double-blind phase, but there was no statistically significant difference in Qmax from baseline to last available observation in either tadalafil group compared with the placebo group (Table 2).

3.4. Efficacy: open-label extension phase

During the OLE phase, all participants showed numerical improvements in symptom scores, with the largest improvements in those who switched from placebo to tadalafil 5 mg (Table 4 and Fig. 3a). From the start of the
Tadalafil for BPH-LUTS in Japanese men

3.5. Safety and tolerability

Tadalafil (2.5 mg or 5.0 mg) treatment once daily was well tolerated, with few treatment-related AEs reported (Table 5). Generally, during the 12-week double-blind phase, the frequency and type of AEs were similar across all treatment groups, as was the percentage of participants discontinuing because of AEs (Table 5). The most frequent TEAEs were nasopharyngitis, diarrhea, back pain, and headache. In all treatment groups, most TEAEs (150/166; 90.4%) were mild in severity. Dyspepsia, reflux esophagitis, cataract, and hot flush were reported by at least four participants treated with tadalafil (2.5 mg or 5.0 mg), but were not reported for participants treated with placebo (Table 5). Nasopharyngitis was the most frequently occurring TEAE in the placebo group and occurred at a higher frequency than in either of the tadalafil groups. There was no apparent relationship between tadalafil dose and the frequency or type of AEs. Similar percentages of participants in each group experienced at least one treatment-related AE (placebo: 7.9%, 11/140; tadalafil 2.5 mg: 4.9%, 7/142; tadalafil 5 mg: 6.4%, 9/140). During the double-blind phase, five serious AEs (SAEs) were experienced by five participants (placebo: one participant; tadalafil 2.5 mg: two participants; tadalafil 5 mg: two participants). None of these SAEs were considered to be related to tadalafil treatment.

Adverse events reported during the OLE phase were similar to those reported during the double-blind phase. During the 42-week OLE phase, 232/394 (58.9%) participants experienced at least one TEAE. The most frequent TEAEs were the same as those reported during the double-blind phase (Table 5). During the OLE phase, 12
SAEs were experienced by 11 participants. The percentage of participants experiencing an SAE was similar irrespective of the treatment received during the double-blind phase (placebo: 3.1%, four participants; tadalafil 2.5 mg: 2.2%, three participants; tadalafil 5 mg: 3.1%, four participants). One SAE (urinary retention) was possibly related to tadalafil treatment; this 74-year-old participant was catheterized because of prostatitis and urinary retention approximately 4.5 months after randomization and initiation of tadalafil (5.0 mg). Subsequent biopsy revealed prostate cancer and the participant underwent radical prostatectomy. One participant died of subarachnoid hemorrhage approximately 5 months into the OLE phase; this 69-year-old participant, initially randomized to the placebo group, had preexisting hypertension and his death was considered unrelated to tadalafil treatment.

There were 128 participants who received tadalafil (5.0 mg, once daily) during both the double-blind and OLE phases (54 weeks). Of these participants, 66.4% (85/128) reported one or more TEAEs during the double-blind and OLE phases, and 57.0% (73/128) reported one or more TEAEs during the OLE phase only. For those participants who received tadalafil 5.0 mg during the double-blind and OLE phases, dyspepsia (five events; 3.9%) was the only AE with an incidence ≥2% that was considered to be possibly related to tadalafil treatment.

During the double-blind and OLE phases, there were no clinically adverse changes in vital signs, laboratory values, or PVR (Fig. 4). There were two participants (placebo and tadalafil 2.5 mg group) in the double-blind phase and eight participants (previous treatment placebo: four participants; tadalafil 2.5 mg: two participants; tadalafil 5 mg: two participants) in the OLE phase who had PSA values ≥10 μg/L at either study discontinuation or endpoint. After further examination, all 10 participants had prostate malignancy ruled out by the investigators. The rise in PSA, which was transient in most participants, was not considered related to tadalafil treatment.

4. DISCUSSION

Tadalafil resulted in numeric, but insignificant, improvements in total IPSS with placebo-adjusted LS mean changes from baseline to last available observation of −0.7 and −1.1 in the tadalafil 2.5 and 5 mg groups, respectively. The magnitude of improvement was greater at the 5.0 mg dose compared with the 2.5 mg dose of tadalafil. Treatment with tadalafil 5.0 mg once daily during the OLE phase was associated with a further numeric reduction in total IPSS in participants who changed from placebo or tadalafil 2.5 mg. The improvement in total IPSS in participants who had previously received tadalafil 5.0 mg was maintained during the OLE phase. Over the 54-week treatment period, tadalafil (5.0 mg) was well tolerated and there were no unexpected TEAEs.

Although there was no statistically significant difference between tadalafil treatment and placebo in the primary analysis (ANCOVA) with respect to the primary outcome (total IPSS change from baseline to last available observation), MMRM analyses showed that at week 12 there was a statistically significant change in total IPSS for the tadalafil 5 mg group compared with the placebo group. There was also a statistically significant difference between the tadalafil 5 mg and placebo groups in the change in the secondary outcome variables, IPSS obstructive subscore and IPSS QoL, from baseline to last available observation. The changes in other efficacy variables (IPSS irritative subscore and Qmax) were not statistically significant for tadalafil 5 mg versus placebo; however, the changes observed were maintained or numerically increased during the 42-week OLE phase. In addition, participants switching from placebo or tadalafil 2.5 mg to tadalafil 5.0 mg in the OLE phase experienced improvements in total IPSS and other efficacy variables, which
TABLE 5. Treatment emergent adverse events in the double-blind and open-label extension (OLE) phases of the study†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 140)</th>
<th>Tadalafil 2.5 mg (n = 142)</th>
<th>Tadalafil 5 mg (n = 140)</th>
<th>Tadalafil 5 mg (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more TEAE, n (%)</td>
<td>53 (37.9)</td>
<td>56 (39.4)</td>
<td>57 (40.7)</td>
<td>232 (58.9)</td>
</tr>
<tr>
<td>TEAEs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18 (12.9)</td>
<td>12 (8.5)</td>
<td>14 (10.0)</td>
<td>42 (10.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (3.6)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>24 (6.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
<td>12 (3.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
<td>4 (2.9)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Eczema</td>
<td>3 (2.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>9 (2.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td>Cataract</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>3 (2.1)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
<td>0 (0.0)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Discontinuation as a result of an AE, n (%)</td>
<td>5 (3.6)</td>
<td>4 (2.8)</td>
<td>5 (3.6)</td>
<td>36 (9.1)</td>
</tr>
<tr>
<td>One or more SAE, n (%)</td>
<td>1 (0.7)</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>11 (2.8)</td>
</tr>
<tr>
<td>Treatment-related AE, n (%)‡</td>
<td>11 (7.9)</td>
<td>7 (4.9)</td>
<td>9 (6.4)</td>
<td>57 (14.5)</td>
</tr>
</tbody>
</table>

†Reported by ≥ 2% of participants in any treatment group. For the double-blind phase, TEAEs were defined as events that first occurred or worsened from the day of randomization (Visit 3) to the end of the double-blind phase; for the OLE phase, TEAEs were defined as events that first occurred or worsened from the day of enrollment (Visit 7) in the OLE phase to the end of the OLE phase; ‡Assessed by the investigator as possibly related to the study drug. AE, adverse event; n, number of participants who were randomized and started study medication; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Fig. 4 Change in mean postvoid residual volume (PVR) during the placebo run-in, double-blind, and open-label extension (OLE) phases. The figure legend refers to treatment group and dose of tadalafil administered during the double-blind phase (closed symbols) and the OLE phase (open symbols). Mean data were calculated from participants who entered the OLE phase (placebo, n = 131; tadalafil 2.5 mg, n = 135; tadalafil 5 mg, n = 128).

were similar to the improvements observed with the tadalafil 5 mg group in the double-blind phase.

The observed safety and efficacy trends are similar to those from a previous phase-2/3 study conducted in 10 non-Asian countries to examine the safety and efficacy of tadalafil in the treatment of BPH-LUTS.25 This study by Roehrborn et al.25 had a similar design to the current study, except that there was a longer wash-out period (4 weeks) and the inclusion criteria did not specify a minimum prostate volume. Roehrborn et al.25 reported that during a 12-week double-blind phase, tadalafil (5.0 mg) was associated with a statistically significant improvement in total IPSS (LS mean ± SE) from baseline (−4.9 ± 0.5) compared with placebo (−2.3 ± 0.5). Although in the current study tadalafil (5.0 mg) was associated with a similar change in total IPSS from baseline (−4.9 ± 0.4), this change was not statistically different from placebo. This may reflect the large placebo effect observed in the current study. In the placebo group, the total IPSS change from baseline (LS mean ± SE) was −3.8 ± 0.4 compared with −2.3 ± 0.5 reported by Roehrborn et al.25 The apparent differences in efficacy may reflect differences in baseline characteristics of participants enrolled in the two studies. For example, the current study enrolled older participants (≥65 years: 274/422, 64.9% versus 394/1056, 37.3%) and fewer participants had severe BPH-LUTS (120/422, 28.4% versus 354/1056, 33.5%). In addition, a higher percentage of men had received previous α-blocker therapy (325/422, 77.0% versus 304/1056, 28.8%). Nevertheless, in the current study, the total IPSS change (mean ± SD) of −5.4 ± 6.3 during the 54-week treatment period (tadalafil 5.0 mg, once daily) was similar to changes observed in a 1-year tadalafil multinational study enrolling predominantly Caucasian participants (total IPSS change over 64 weeks: −5.0 ± 7.2).26

In all treatment groups, there was a numeric improvement in Qmax that started at the beginning of the placebo run-in period and was maintained for the duration of the OLE phase. The changes in Qmax observed in the tadalafil groups were not significantly different from placebo. Improvements in Qmax that are not statistically different from placebo have previously been reported for
tadalafil.25,27 Treatment with α-blockers, such as tamsulosin and silodosin, in Japanese men with BPH-LUTS, have also been associated with changes in Qmax that were insignificant compared with placebo.28

The safety and tolerability profile of tadalafil observed in this study was similar to that previously reported for treatment with tadalafil (up to 20 mg, as needed) in Japanese men with ED.21 In the current study, there was a higher incidence of nasopharyngitis in both the placebo and tadalafil groups, which may be associated with the study being conducted during winter. During the double-blind phase, the percentage of participants who discontinued because of AEs was low and similar among all treatment groups (2.8–3.6%). Of the participants treated with tadalafil (5.0 mg) during the double-blind and OLE phases, 57.0% (73/128 participants) reported one or more TEAEs during the OLE phase. This is similar to the percentage of participants (56.6%) reporting TEAEs during the double-blind phase, the percentage of participants who discontinued because of AEs was low and similar among all treatment groups (2.8–3.6%). Of the participants treated with tadalafil (5.0 mg) during the double-blind and OLE phases, 57.0% (73/128 participants) reported one or more TEAEs during the OLE phase. This is similar to the percentage of participants (56.6%) reporting TEAEs during the OLE phase in the 1-year tadalafil multinational study enrolling predominantly Caucasian participants.26 Over the 54-week treatment period, dyspepsia was the only AE with an incidence ≥ 2% that was considered to be possibly related to treatment. There were no clinically significant changes observed in vital signs, clinical laboratory tests, or PVR.

In conclusion, this dose-finding study demonstrated that although there was no statistically significant difference between tadalafil treatment (2.5 or 5.0 mg) and placebo in the primary outcome (total IPSS change from baseline to last available observation), there was a dose-dependent improvement in all efficacy variables over the 12-week double-blind placebo-controlled phase. These improvements were maintained over a 1-year treatment period with tadalafil 5.0 mg. Tadalafil, once daily, was generally well tolerated during both the 12-week, double-blind phase (2.5 or 5.0 mg) and the 42-week, OLE phase (5.0 mg). These results support further investigation of tadalafil (5.0 mg, once daily) in Japanese men with moderate-to-severe BPH-LUTS.

Acknowledgments

The study was funded by Eli Lilly and Company, the manufacturer of tadalafil. Medical writing services were provided by Narelle Bramich, PhD, and Serina Streton, PhD, of ProScribe Medical Communications and were funded by Eli Lilly Japan K.K.

Disclosure

This study was sponsored by Eli Lilly and Company. The sponsor was involved in the study design, and in the collection, analysis and interpretation of data. T. Imaoka, Y. Morisaki, and L. Viktrup were involved in the study design. Y. Morisaki also completed the statistical analyses. All authors participated in the interpretation of the study results and in the drafting, critical revision, and approval of the final version of the manuscript. M. Takeda and O. Nishizawa have been advisory board members for Eli Lilly Japan K.K. T. Imaoka, and Y. Morisaki are employees of Eli Lilly Japan K.K., and L. Viktrup is an employee of Eli Lilly and Company.

REFERENCES