Tadalafil administered once daily for treatment of Korean men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: Results from a placebo-controlled pilot study using tamsulosin as an active control

Proposed Authors
Sae Chul Kim¹, Jong Kwan Park², Sae Woong Kim³, Sung Won Lee⁴, Tai Young Ahn⁵, Je Jong Kim⁶, Jae Seung Paick⁷, Nam Cheol Park⁸, Kwangsung Park⁹, Kweon Sik Min¹⁰, Stephen R Kraus¹¹, Roberta J Secrest¹², Albert Elion-Mboussa¹², Lars Viktrup¹²

Affiliations
¹ Chung-Ang University Hospital, Dept. of Urology, Seoul, Korea, South,
² Chonbuk National University Hospital, Dept. of Urology, Jeonju, Korea, South,
³ Seoul St. Mary’s Hospital, Dept. of Urology, Seoul, Korea, South,
⁴ Samsung Medical Center, Sungkyunkwan University School of Medicine, Dept. of Urology, Seoul, Korea, South,
⁵ Asan Medical Center, Dept. of Urology, Seoul, Korea, South,
⁶ Korea University Hospital, Dept. of Urology, Seoul, Korea, South,
⁷ Seoul National University Hospital, Dept. of Urology, Seoul, Korea, South,
⁸ Pusan National University Hospital, Dept. of Urology, Busan, Korea, South,
⁹ Chonnam National University, Dept. of Urology, Sexual Medicine Research Center, Gwangju, Korea, South,
¹⁰ Busan Paik Hospital, Dept. of Urology, Seoul, Korea, South,
¹¹ University of Texas Health Science Center, Department of Urology, San Antonio, TX, USA,
¹² Eli Lilly and Co., Lilly Research Laboratories, Indianapolis, USA

Corresponding Author
Roberta J. Secrest, Ph.D, Pharm.D.
Senior Research Scientist - Clinical
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, IN 46285
Phone: 317-433-0032
Fax: 317-433-4901
E-mail: rsecrest@lilly.com
ABSTRACT

Background: This pilot study assessed the efficacy and safety of once-daily tadalafil or tamsulosin versus placebo during 12 weeks in Korean men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Methods: Following a 4-week placebo run-in period, 151 Korean men were randomly assigned to receive once-daily tadalafil 5 mg, tamsulosin 0.2 mg, or placebo for a 12-week treatment period. An analysis of covariance (ANCOVA) model was used to analyze the primary endpoint (International Prostate Symptom Score, IPSS) and secondary continuous efficacy variables. Safety parameters were tested with Fisher’s exact test, ANCOVA and analysis of variance (ANOVA) models.

Results: The IPSS least squares mean changes from baseline to endpoint were numerically but not significantly improved in the tadalafil (-5.8) and tamsulosin (-5.4) groups compared with placebo (-4.2, P>0.05). Decreases in IPSS obstructive and irritative subscores, IPSS Quality of Life score, and BPH Impact Index (BII) from baseline to endpoint were largest in the tadalafil treatment group followed by tamsulosin, though none separated significantly from placebo. Increases in maximum urinary flow rate ($Q_{max}$) were small and not significantly different than placebo; the increase was largest in the tadalafil group (2.5 mL/s), followed by the placebo (2.3 mL/s) and tamsulosin (2.1 mL/s) groups. Subjects reporting at least 1 treatment-emergent adverse event (TEAE) were 26.5% in the tamsulosin group, 13.7% in the tadalafil group and 3.9% in the placebo group. The incidence of TEAEs was statistically significant for tamsulosin (p=.002) but not for tadalafil (p=0.16), compared with placebo.

Conclusions: In this pilot study, men with BPH-LUTS treated with tadalafil 5 mg or tamsulosin 0.2 mg once daily experienced a reduction in BPH-LUTS, which was numerically, but not statistically significantly, better than placebo. Tadalafil was well tolerated, and very few subjects discontinued the study due to TEAEs. Larger studies in Asian men with BPH-LUTS treated with phosphodiesterase type 5 (PDE5) inhibitors are needed.
**Trial registration:** ClinicalTrials.gov NCT00540124.
Men with benign prostatic hyperplasia (BPH) commonly experience lower urinary tract symptoms (LUTS) such as increased urinary frequency, urgency, intermittency, nocturia, straining, incomplete emptying, and weak urinary stream. The disorder is common in aging men, with estimates of men with BPH resulting in LUTS ranging from 30 to 35 million in the United States (US), Western Europe, and Japan [1]. One study in Korean and other Asian men found that the prevalence of symptomatic BPH (defined as International Prostate Symptom Score [IPSS] ≥8) ranged from 18% in men ages 40-49 years to 56% in men ages 70-79 years, suggesting that the prevalence in Asia is similar to that in Europe or the United States [2]. In 2 Korean studies conducted in community-dwelling men ≥50 years of age with a combined IPSS ≥8, maximum urinary flow rate (Q_{max}) ≤15 mL/second, and prostate enlargement (per digital rectal exploration or transrectal ultrasound), the prevalence of BPH-LUTS prevalence was 11.1% and 20.2% [3,4]. The current standard-of-care medical therapy, globally as well as in Korea, for the treatment of bothersome moderate to severe BPH-LUTS is the use of alpha-1 adrenergic blockers (alpha blockers) [5], while 5-alpha reductase inhibitors (5-ARIs) are an acceptable alternative for men who also have an enlarged prostate. Although potentially effective at reducing urinary symptoms as monotherapy or in combination, both alpha blockers and 5-ARIs may produce unwanted side effects, including sexual dysfunction, which prompt some patients to avoid or discontinue therapy and which may be exacerbated with combination therapy. Additionally, alpha blockers may be associated with dizziness and hypotension [5,6].

Tamsulosin, a selective alpha blocker, is the most commonly prescribed treatment in men with BPH-LUTS, both globally and in Korea [7]. In Korea, Japan, and many other Asian countries, the dose of tamsulosin approved for the treatment of men with urination disorder associated with prostatic hyperplasia is 0.2 mg, in contrast to 0.4 mg, which is the approved dose in the US and Europe [8].

Tadalafil (Cialis®), a phosphodiesterase type 5 (PDE5) inhibitor, is currently approved in a number of Asian countries for on-demand treatment of erectile dysfunction (ED) and in the US and Europe for both
on-demand and once-daily dosing for the treatment of ED. Because PDE5 is expressed and biologically active in the human bladder, urethra, prostatic tissue, and corpus cavernosum [9,10], it is postulated that a long-acting PDE5 inhibitor such as tadalafil may be efficacious not only in the treatment of men with ED, but also in the once-daily treatment of men with BPH-LUTS. In a recent 12-week global dose-finding study conducted in 1058 men with BPH-LUTS, tadalafil was associated with statistically significant and clinically meaningful improvements in multiple measures of LUTS, including quality of life, as well as ED improvement, compared to placebo [11].

The effects of tadalafil in the treatment of Korean men with BPH-LUTS have not been studied previously, and available data in Korean men treated with tamsulosin in double-blind placebo-controlled studies are limited. Furthermore, tadalafil and tamsulosin have not been assessed as medical therapies for BPH-LUTS in the same placebo-controlled clinical trial utilizing the same criteria and study design. The aim of this pilot study was to assess the safety and efficacy of once-daily tadalafil 5 mg and tamsulosin 0.2 mg versus placebo during 12 weeks in Korean men with BPH-LUTS.
METHODS

Study Design

This study was a randomized, double-blind, placebo-controlled, active-control, 12-week pilot clinical trial performed at 10 centers in Korea. Figure 1 shows the study design and schedule of events. Men ≥45 years of age with a >6 month history of BPH-LUTS at Visit 1, bladder outlet obstruction of intermediate severity (Q_{max} ≥4 to ≤15 mL/second at Visit 2), and total IPSS of ≥13 at Visit 2 were eligible for randomization. Men were excluded from the study if, at Visit 1, they had a prostate-specific antigen (PSA) >10 ng/mL, postvoid residual volume (PVR) >300 ml, or if they had a history of symptomatic orthostatic hypotension, dizziness, vertigo, loss of consciousness or syncope (Warnings from tamsulosin US product label) [12]. Men who had PSA values from 4 to 10 ng/ml must have had a prostate biopsy negative for malignancy within 12 months of Visit 1. Men who had used finasteride within 3 months or dutasteride within 6 months prior to Visit 2 were excluded. Men were prohibited from using any BPH or ED treatments during the study. Men reporting the use of BPH or ED treatments upon study entry underwent a 4-week, treatment-free screening/washout period before beginning a 4-week placebo run-in period; all others began a 4-week placebo run-in period immediately after screening results were reviewed. After the placebo run-in period, subjects were randomly assigned to receive once-daily tadalafil 5mg, tamsulosin 0.2mg, or placebo for a 12-week treatment period. Randomization was stratified by prior alpha-blocker use (yes/no) and BPH-LUTS severity at baseline (as assessed by IPSS, moderate: IPSS <20 or severe: IPSS ≥20). The clinical study was performed in accordance with the Declaration of Helsinki and all applicable regulations. The institutional review boards for each site approved the study, and all men provided written informed consent before undergoing any trial procedure or receiving any trial therapy.

Study Measures

The primary objective of this study was to compare the change from baseline to endpoint in total IPSS score in Korean men treated once daily with tadalafil 5 mg versus placebo. Secondary assessments
included IPSS obstructive and irritative subscores, IPSS nocturia subscore, IPSS Quality of Life (QoL) Index, BPH Impact Index (BII), Patient Global Impression of Improvement (PGI-I), Clinician Global Impression of Improvement (CGI-I), uroflowmetry, and safety measures, as well as a comparison of tamsulosin and placebo for all assessments (Figure 1).

Benign prostatic hyperplasia (BPH)-LUTS severity and impact was assessed with the IPSS, a 7-item validated, self-administered questionnaire with a score range of 0 to 35, in which higher scores indicate more severe LUTS. The IPSS obstructive subscore was defined as the sum of the scores for Questions 1, 3, 5, and 6; the IPSS irritative subscore was defined as the sum for Questions 2, 4, and 7; and the IPSS nocturia subscore was defined as the score from Question 7. In addition, quality of life was assessed using the IPSS QoL (“If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?”) relating to LUTS. The impact of urinary problems on overall health and activity within the previous month was assessed via the BII, a 4-item validated, self-administered questionnaire with a score range of 0 to 13, with higher scores representing an increased perceived impact of BPH-LUTS on overall health.

To assess the baseline severity of urinary symptoms, the Patient Global Impression of Severity (PGI-S) and the Clinician Global Impression of Severity (CGI-S), patient- and clinician-rated 4-point scale instruments, were administered at the beginning of the placebo run-in period [13,14]. The PGI-S asks subjects to “Check the one number that best describes how your urinary symptoms are now”; the CGI-S asks clinicians “Considering your clinical experience with this particular population, how severe are the patient’s urinary symptoms at this time?” Both instruments provide numbered responses, ranging from 1, “normal,” to 4, “severe.”

The PGI-I and CGI-I, patient- and clinician-rated instruments, respectively, are 7-point scales that were administered at endpoint to measure improvement in subjects’ symptoms [13,14]. The PGI-I asks subjects to “Check the one number that best describes how your urinary symptoms are now, compared
with how they were before you began taking medication in this study”; the CGI-I asks clinicians to “Rate the total change in urinary symptoms, whether or not in your judgment it is entirely due to drug treatment. Compared to patient’s condition at the study entry how much has it changed?” Both instruments provide numbered responses, ranging from 1, representing “very much improved,” to 7, “very much worse,” which were grouped into the following 3 derived categories: “Worse” (Categories 5 to 7), “No change” (Category 4), and “Better” (Categories 1 to 3).

Maximum urinary flow rate ($Q_{\text{max}}$) was recorded using a standard calibrated flowmeter. All uroflowmetry data was read by both the principal investigator and a central reader, both of whom were blinded to treatment assignment; Visit 2 uroflowmetry data was interpreted by the principal investigator to assess subject eligibility. Statistical analyses were performed using central reader uroflowmetry data. Uroflowmetry results were considered valid only if the prevoid total bladder volume (assessed by ultrasound) was $\geq 150$ to $\leq 550$ mL and the voided volume was $\geq 125$ mL.

Safety assessments included reported adverse events, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PVR, and urinalysis for 12 weeks. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 10.

Statistical Analysis

A sample size of 45 completed subjects per treatment group ensured that the half-width of a 2-sided 95% confidence interval (CI) for change from baseline to endpoint for therapies was 2.5 (assuming a common 6.0 unit standard deviation of change from baseline in total IPSS). 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. As this study was a pilot study, no attempts were made to power this study on the primary endpoint. All data were analyzed using Statistical Analysis Software (SAS)$^{\circledR}$, Version 9.0.
Visit 3 (post-placebo run-in) values were defined as baseline for efficacy analyses. All efficacy analyses were performed on an intent-to-treat basis and they included all randomized subjects with a baseline and at least 1 postbaseline measurement, and compared tadalafil or tamsulosin responses with placebo. Safety analyses included all randomly assigned subjects. An ANCOVA model, which included effects for treatment, prior alpha-blocker use, and a baseline covariate (that is, baseline of the parameter being analyzed), was used to analyze the primary endpoint and secondary continuous efficacy variables (IPSS, IPSS subscores, IPSS Question 7 [nocturia], IPSS QoL, BII, and Q$_{\text{max}}$). A baseline-by-treatment interaction term was evaluated and included in the model if it was significant. Treatment differences based on the 3 grouped responses of PGI-I and CGI-I data (Worse, No change, and Better) were tested using Cochran-Mantel-Haenszel (CMH) statistics with modified ridit scores controlling for alpha-blocker use (yes/no) and LUTS severity as stratification factors.

Fisher’s exact test was used to compare reported treatment-emergent adverse events (TEAEs) between the tadalafil or tamsulosin groups and placebo. Change in PVR from baseline to end of therapy was analyzed by an ANCOVA model similar to the model employed for the primary analysis. A ranked ANOVA model with effects of treatment was used to analyze the change from baseline to end of therapy in clinical laboratory parameters and ECG parameters. Vital signs change from baseline was analyzed using a ranked ANOVA model with effect of treatment. All statistical tests were evaluated at a 2-sided significance level of 0.05.

Wilcoxon rank sum test was used to analyze PGI-S and CGI-S data regarding baseline symptom severity.
RESULTS

Of 196 men who were screened for eligibility, 151 were randomly assigned to receive tadalafil 5 mg, tamsulosin 0.2 mg, or placebo (Figure 2). Treatment groups were generally balanced with respect to baseline demographics and parameters related to BPH-LUTS (Table 1); however, at baseline, 71% of placebo subjects, 59% of tadalafil subjects, and 49% of tamsulosin subjects reported history of ED. Over the 3 treatment groups, at baseline 74.5% to 87.8% of subjects rated their symptoms (PGI-S) as being moderate to severe; according to clinician assessment (CGI-S), over 96% of subjects across all 3 treatment groups had either moderate or severe symptoms. The distribution of subjects at baseline across the PGI-S and CGI-S categories in the tadalafil (p=0.866 and p=0.337 vs. placebo, respectively) or tamsulosin (p=0.903 and p=0.258 vs. placebo, respectively) groups was not statistically different from that in the placebo group. The mean PSA was higher in the tamsulosin treatment group compared to the tadalafil and placebo groups (Table 1); the impact of this difference on efficacy is expected to be minimal, based on available literature from both tamsulosin and tadalafil studies. At least 92% of subjects in each treatment group completed the study.

Decreases in total IPSS for the 12 weeks from baseline to endpoint were observed in all 3 treatment groups: tadalafil (-5.8), tamsulosin (-5.4) and placebo (-4.2) (Table 2). Although both tadalafil and tamsulosin treatments resulted in numerically greater decreases in total IPSS compared to placebo, these decreases were not statistically significant for either treatment compared to placebo, or for either treatment when compared to each other. Including the 4-week placebo run-in period, total IPSS changes after 16 weeks were greatest in the tadalafil group (-7.7) followed by the tamsulosin group (-6.6) and placebo (-5.9) group.

Figure 3 illustrates the time course of mean change in total IPSS together with the standard error at each post-randomization visit for each treatment group. Compared to placebo response, numerically greater decreases in total IPSS were seen in tadalafil- and tamsulosin-treated men as early as 4 weeks, which continued throughout the 12-week treatment period; however, neither treatment response was
statistically significant from placebo at any time point. Subjects in all treatment groups reported reduced symptoms, as assessed by the IPSS obstructive and irritative subscores, IPSS QoL score, and BII from baseline to endpoint (Table 2). The decreases in these scores were largest in the tadalafil group, but they were not statistically significant when compared to placebo for tadalafil or tamsulosin. Changes from baseline to endpoint for the IPSS nocturia subscore were small and nearly identical for all 3 treatment groups.

For both the tadalafil and tamsulosin groups, improvements in $Q_{max}$ following 12 weeks of therapy were small and not significantly different than placebo (Table 2); the change in $Q_{max}$ was largest in the tadalafil group (2.5 mL/s) followed by the placebo (2.3 mL/s) and tamsulosin (2.1 mL/s) groups.

The majority of subjects in each treatment group reported that their urinary symptoms were better at endpoint as assessed by the PGI-I (Table 2). Of the 3 treatment groups, improvement was reported by 87.8% in the tadalafil group, 79.2% in the tamsulosin group, and 77.1% in the placebo group; the difference between either the tadalafil or tamsulosin group and placebo was not statistically significant. For the CGI-I, clinicians also rated the total change in subjects’ urinary symptoms at endpoint as being better for the majority of subjects in all 3 treatment groups (Table 2). However, in contrast to the PGI-I results, the largest percent of subjects rated by the clinicians as having better symptoms at endpoint was in the placebo group (89.6%), followed by subjects in the tadalafil group (83.7%) and tamsulosin group (83.3%).

Adverse events reported during the treatment period are shown in Table 3. Overall, the percentage of subjects reporting at least 1 TEAE was greater in the tamsulosin (26.5%) than in the tadalafil (13.7%) and placebo (3.9%) groups. This difference was statistically significant for tamsulosin ($p=.002$) but not for tadalafil ($p=0.16$), compared with placebo. Individual TEAEs were infrequent in both the tadalafil and tamsulosin treatment groups. The most commonly reported adverse event in the tadalafil treatment group was myalgia; the most commonly reported event in the tamsulosin treatment group was
nasopharyngitis. Three subjects reported adverse events that led to study discontinuation; 2 were in the tadalafil group (1 due to preexisting back pain which worsened in severity during the placebo run-in period, and 1 due to pleural effusion) and 1 was in the tamsulosin group (due to an acute myocardial infarction). Two subjects in the tadalafil group reported serious adverse events; 1 reported pleural effusion and metastatic lung adenocarcinoma, and 1 reported lumbar spinal stenosis. Two subjects in the tamsulosin group reported a serious adverse event (1 each with acute myocardial infarction and inguinal hernia). No subjects in the placebo group reported a serious adverse event. There were no deaths during the study and no reports of hypotension-related adverse events or urinary retention in any treatment group. No clinically adverse changes were observed during the study in laboratory values, urinalysis parameters, vital signs, ECG abnormalities, or ECG intervals with tadalafil or tamsulosin treatment (data not shown). Decreases in PVR from baseline to endpoint were small and not significantly different from placebo; the change in PVR was largest in the tadalafil group (-5.0), followed by the tamsulosin group (-4.5), and the placebo group (0.6).
DISCUSSION

In this small pilot study in Korean men with BPH-LUTS, the decrease in IPSS with tadalafil (5 mg once daily) was numerically greater but not statistically significant compared to placebo. Subjects treated with tadalafil also had numerically greater changes in secondary efficacy outcomes compared to subjects treated with placebo (except for CGI-I); however, none of these numeric improvements were statistically significant from placebo. Tadalafil was well tolerated, but TEAEs were more prevalent in the tadalafil treatment group than in those treated with placebo. Tamsulosin 0.2 mg once daily also resulted in a numerically greater decrease in IPSS from baseline but this decrease was not statistically significant compared to placebo. Subjects treated with tamsulosin had numerically better secondary efficacy outcomes than subjects treated with placebo, except for CGI-I, BII and $Q_{\text{max}}$ outcomes; none of the differences reached statistical significance. Treatment-emergent adverse events were more prevalent in the tamsulosin treatment group than for those treated with placebo.

According to the American Urological Association (AUA) guidelines [5,15], a $\geq$3-point decrease in total IPSS from baseline is indicative of a clinically meaningful improvement in an American population. In this study of Korean men, all 3 treatment groups had improvements in total IPSS from baseline considered clinically meaningful by this guideline. The magnitude of the change in IPSS associated with tadalafil was consistent with that observed in other published tadalafil trials [11], but the change was not statistically significantly different from placebo. The lack of statistical significance in this study may be explained by the relatively large mean change in total IPSS from baseline for the placebo group (-4.2) compared to previous results observed in a larger dose-finding study (-2.3) [11]. Additional studies are needed to fully understand the efficacy of tadalafil therapy in Asian men with BPH-LUTS.

One explanation for the large difference in placebo effect may be cultural, as the current study enrolled all Korean subjects, whereas the populations for other tadalafil BPH-LUTS studies were primarily Caucasian [11,16]. Though a high placebo response is typically observed in subjects who are treatment
naïve, this may not apply to this study, since 45% of the subjects reported previous alpha blocker use, in contrast to 30% of subjects in the tadalafil dose-finding study [11].

To the knowledge of the authors, the size of the placebo effect in a Korean BPH population has not been previously reported. However, a placebo-controlled, double-blind, 12-week study of silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily, or placebo in Japanese men with moderate to severe BPH-LUTS was recently published [17]. In this study, the mean change in total IPSS from baseline was compared between men receiving silodosin and tamsulosin, and between men receiving silodosin and placebo. The mean change in total IPSS from baseline was -8.3, -6.8, and -5.3 for the silodosin, tamsulosin, and placebo groups, respectively, demonstrating a -1.5 difference between the tamsulosin and placebo groups. Although this finding is consistent with the -1.2 difference in the change in total IPSS reported between the tamsulosin and placebo groups in the current study, the tamsulosin and placebo effect seen in the Japanese study is not based on a formal statistical comparison and should be interpreted with caution.

In this study, a large proportion of men reported a history of ED at baseline in all treatment groups. Given that PDE5 inhibitors are known to improve erectile function, the potential confounding of BPH responses for patients with a history of ED has been a subject of debate. The current study was not designed to measure any impact of ED on BPH responses, but a recent placebo-controlled global study showed that changes in BPH-LUTS after 12 weeks of treatment with placebo or various doses of once-daily tadalafil were similar in men with or without co-morbid ED [18].

The increase in $Q_{\text{max}}$ observed with tadalafil was small and not significantly different, compared to placebo. The lack of a significant improvement in $Q_{\text{max}}$ is consistent with previous reports for tadalafil and other PDE5 inhibitor compounds [16]. Similar to tadalafil, tamsulosin treatment did not result in a statistically significant improvement in $Q_{\text{max}}$ compared to placebo. In fact, the improvement in $Q_{\text{max}}$ in the tamsulosin treatment group was numerically smaller than placebo (Table 2). Small improvements in
\(Q_{\text{max}}\), which were not significantly different from placebo, have been observed with PDE5 inhibitor treatment in a number of clinical trials, suggesting that increased peak flow is not a significant contributing factor to the improvements in LUTS that have been consistently reported by men treated with once-daily tadalafil [11,19,20]. A number of mechanisms, including smooth muscle, neuronal, or vascular effects in the prostate and/or bladder, have been proposed to mediate symptomatic improvements in urinary function [21]. This is the first reported placebo-controlled clinical trial with both tadalafil and tamsulosin treatment arms, and the comparable magnitude of change in \(Q_{\text{max}}\) may warrant further investigation.

Clinical Global Impression (CGI) and PGI data collected in this study indicate that clinicians may tend to rate the severity of BPH-LUTS higher than the subjects themselves. When subjects at study entry rated the severity of their urinary symptoms as assessed by the single question in the PGI-S (Table 1), moderate to severe symptoms were reported by 74.5% in the tadalafil treatment group, 87.8% in the tamsulosin group, and 82.4% in the placebo treatment group. In contrast, when the clinicians rated the severity at study entry, as assessed by the CGI-S (Table 1), moderate to severe symptoms were reported for 96.1% in the tadalafil treatment group, 97.96% in the tamsulosin group, and 96.1% in the placebo treatment group. The clinicians tended to rate the observed improvement, as assessed by CGI-I, higher than the subjects, as assessed by PGI-I, in the placebo and tamsulosin treatment groups; whereas subjects treated with tadalafil more frequently rated their symptoms as improved, compared with the clinicians’ observations (Table 2).

Both tadalafil and tamsulosin were generally well tolerated, and very few subjects discontinued the study. The incidence of subjects reporting at least 1 TEAE was low in the tadalafil group; however, it was 3 times greater than the number of subjects reporting at least 1 TEAE in the placebo group. No new safety concerns were identified with either treatment. However, the overall number of men reporting at least 1 TEAE when treated with tadalafil or placebo in this pilot study was lower than reported by men in a global study treated with the same tadalafil dose or placebo [11]. The most commonly reported TEAE
in the tadalafil treatment group was myalgia, and none of the subjects reported dyspepsia or back pain. The number of subjects reporting at least 1 TEAE in the tamsulosin group was more than 6 times greater than that of subjects in the placebo group. The most commonly reported TEAE in the tamsulosin treatment group was nasopharyngitis. There were no adverse event reports related to hypotension or urinary retention in any treatment group. The changes in PVR from baseline to endpoint were small in each treatment group, and not clinically meaningful. The safety findings in this small pilot study should be assessed in future studies with larger sample sizes as well.

This pilot study was designed to provide estimates of the change from baseline and variability of change from baseline for efficacy measurements of BPH in order to plan future possible clinical studies in Asian men. It was not powered to show efficacy for the primary endpoint. As such, the findings from this study must be interpreted with caution. The lack of significant differences in LUTS measures between tadalafil or tamsulosin and placebo treatment may have been related to the smaller sample sizes in this pilot study. The 0.2 mg dose of tamsulosin once daily is approved for treatment of men with urination disorder associated with prostatic hyperplasia in Korea and other Asian countries; however, some Asian countries such as Taiwan have also approved tamsulosin 0.4 mg for the treatment of men with urination disorder associated with prostatic hyperplasia. In other parts of the world, 0.4 mg is generally the lowest approved dose. It is unknown if similar results would have been observed in this study with other doses of tamsulosin. Additionally, since this study enrolled only men from Korea, the results may not be generalizable to other Asian populations or to non-Asian populations.

**CONCLUSION**

In this pilot study, men with BPH-LUTS treated with tadalafil 5 mg or tamsulosin 0.2 mg once daily experienced a reduction in BPH-LUTS, which was numerically, but not statistically significantly, better than placebo. Tadalafil was well tolerated, and very few subjects discontinued the study due to TEAEs. Larger studies in Asian men with BPH-LUTS treated with PDE5 inhibitors are needed.
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Table 1: Subject demographics and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 51)</th>
<th>Tadalafil 5 mg (N = 51)</th>
<th>Tamsulosin 0.2 mg (N = 49)</th>
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<tr>
<td>Age (years, Mean ± SD)</td>
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<td>Age ≥65 yrs</td>
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<td>BII (Mean ± SD)</td>
<td>6.2 ± 2.8</td>
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BPH-LUTS Severity

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<th>Tamsulosin 0.2 mg (N = 49)</th>
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<tr>
<td>Moderate (IPSS &lt;20)</td>
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<td>68.6%</td>
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<td>Severe (IPSS ≥20)</td>
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<td>32.7%</td>
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<td>PVR (mL, Mean ± SD)</td>
<td>34.4 ± 35.7</td>
<td>30.9 ± 33.8</td>
<td>42.0 ± 59.6</td>
</tr>
<tr>
<td>Erectile Dysfunction (Yes)</td>
<td>70.6%</td>
<td>58.8%</td>
<td>49.0%</td>
</tr>
<tr>
<td>CGI-S, Mild</td>
<td>17.65%</td>
<td>25.49%</td>
<td>12.24%</td>
</tr>
<tr>
<td>CGI-S, Moderate</td>
<td>47.06%</td>
<td>35.29%</td>
<td>55.10%</td>
</tr>
<tr>
<td>CGI-S, Severe</td>
<td>35.29%</td>
<td>39.22%</td>
<td>32.65%</td>
</tr>
<tr>
<td>CGI-S, Mild</td>
<td>3.92%</td>
<td>3.92%</td>
<td>2.04%</td>
</tr>
<tr>
<td>CGI-S, Moderate</td>
<td>56.86%</td>
<td>66.67%</td>
<td>71.43%</td>
</tr>
<tr>
<td>CGI-S, Severe</td>
<td>39.22%</td>
<td>29.41%</td>
<td>26.53%</td>
</tr>
</tbody>
</table>

N=number of randomized subjects per treatment group
Table 2: Change in IPSS, BII and urinary parameters from baseline to endpoint.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 51)</th>
<th>Tadalafil 5 mg (N = 51)</th>
<th>P-value</th>
<th>Tamsulosin 0.2 mg (N = 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td>p-value</td>
<td>Mean ± SE</td>
<td>p-value</td>
</tr>
<tr>
<td>Total IPSS</td>
<td>-4.2 ± 0.6</td>
<td>-5.8 ± 0.6</td>
<td>0.07</td>
<td>-5.4 ± 0.7</td>
<td>0.19</td>
</tr>
<tr>
<td>IPSS, obstructive subscore</td>
<td>-2.7 ± 0.4</td>
<td>-3.7 ± 0.4</td>
<td>0.10</td>
<td>-3.6 ± 0.5</td>
<td>0.15</td>
</tr>
<tr>
<td>IPSS, irritative subscore</td>
<td>-1.5 ± 0.3</td>
<td>-2.1 ± 0.3</td>
<td>0.15</td>
<td>-1.8 ± 0.3</td>
<td>0.52</td>
</tr>
<tr>
<td>IPSS, nocturia subscore</td>
<td>-0.4 ± 0.1</td>
<td>-0.5 ± 0.1</td>
<td>0.77</td>
<td>-0.5 ± 0.1</td>
<td>0.73</td>
</tr>
<tr>
<td>IPSS QoL</td>
<td>-0.9 ± 0.2</td>
<td>-1.2 ± 0.2</td>
<td>0.21</td>
<td>-1.0 ± 0.2</td>
<td>0.59</td>
</tr>
<tr>
<td>BII</td>
<td>-2.0 ± 0.3</td>
<td>-2.2 ± 0.3</td>
<td>0.69</td>
<td>-1.6 ± 0.3</td>
<td>0.42</td>
</tr>
<tr>
<td>Qmax (mL/s)</td>
<td>2.3 ± 0.7</td>
<td>2.5 ± 0.7</td>
<td>0.84</td>
<td>2.1 ± 0.7</td>
<td>0.83</td>
</tr>
<tr>
<td>PVR (mL)</td>
<td>0.6 ± 32.5</td>
<td>-5.0 ± 34.7</td>
<td>0.33</td>
<td>-4.5 ± 51.5</td>
<td>0.37</td>
</tr>
<tr>
<td>PGI-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse (%)</td>
<td>2.1</td>
<td>2.0</td>
<td></td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>No change (%)</td>
<td>20.8</td>
<td>10.2</td>
<td>0.18</td>
<td>14.6</td>
<td>0.92</td>
</tr>
<tr>
<td>Better (%)</td>
<td>77.1</td>
<td>87.8</td>
<td></td>
<td>79.2</td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>10.4</td>
<td>16.3</td>
<td>0.43</td>
<td>8.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Better</td>
<td>89.6</td>
<td>83.7</td>
<td></td>
<td>83.3</td>
<td></td>
</tr>
</tbody>
</table>

N=number of randomized subjects per treatment group. For Total IPSS, IPSS obstructive subscore, IPSS irritative subscore, IPSS nocturia subscore, and PVR the number of subjects with non-missing data at baseline and at least one postbaseline visit per treatment group was n = 50 for placebo, n = 50 for tadalafil, n = 49 for tamsulosin. For IPSS QoL, BII, Qmax, PGI-I, and CGI-I the number of subjects with non-missing data at baseline and at least one postbaseline visit per treatment group was n = 48 for placebo, n = 49 for tadalafil, n = 48 for tamsulosin. P-values compare each treatment group (tadalafil or tamsulosin) with placebo.
### Table 3: Treatment emergent adverse events

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Placebo (N = 51)</th>
<th>Tadalafil 5 mg (N = 51)</th>
<th>Tamsulosin 0.2 mg (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men reporting ≥1 TEAE</td>
<td>2 (3.9%)</td>
<td>7 (13.7%)</td>
<td>13 (26.5%)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Epigastic discomfort</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gastric ulcer hemorrhage</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Intentional overdose</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Lumbar spinal stenosis</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0 (0.0%)</td>
<td>3 (5.9%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>

N=number of randomized subjects per treatment group; n = number of subjects reporting adverse events
References


Figure 1. Study design with schedule of events

-8
Week
Visit

Screening/
Wash-out
Period
Placebo
Run-in
Period
Treatment Period

Screening
PVR
ECG
Vital signs
Clinical
laboratory tests
including
urinalysis

IPSS
PGI-S
CGI-S
PVR
Vital signs
Clinical
laboratory tests
including
urinalysis

Randomization
(Baseline)

Tadalafil 5 mg once a day
Placebo
Tamsulosin 0.2 mg once a day

IPSS
BII
PGI-S
Uroflowmetry
PVR
Vital signs
Clinical
laboratory tests
including
urinalysis

IPSS
PVR
Vital signs

IPSS
PVR

IPSS
BII
PGI-I
CGI-I
Vital signs
ECG

Vital signs
Clinical
laboratory tests
including
urinalysis
Figure 2: Disposition of subjects

a Based on Placebo run-in period
Figure 3: Time course of changes in total IPSS from baseline to endpoint.