2. LVHR Synopsis

Clinical Study Report Synopsis: Study H6D-MC-LVHR

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Tadalafil 2.5- and - mg Once-Daily Dosing for 12 Weeks for the Treatment of Erectile Dysfunction and Signs and Symptoms of Benign Prostatic Hyperplasia in Men with Both Erectile Dysfunction and Benign Prostatic Hyperplasia	
Number of Investigators: This multicenter study included 54 principal investigators.	
Study Centers: This study was conducted at 54 study centers in 9 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first subject enrolled: 14 April 2009 Date of last subject completed: 07 July 2010	**Phase of Development:** 3

Objectives:

The primary objective of Study H6D-MC-LVHR (Study LVHR) was to evaluate the efficacy of tadalafil once daily for 12 weeks compared with placebo in improving both International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) Erectile Function (EF) Domain in men with both erectile dysfunction (ED) and signs and symptoms of benign prostatic hyperplasia (BPH). Two doses of tadalafil (5 mg and 2.5 mg) were compared to placebo.

The key secondary efficacy objectives were as follows:

- To compare the efficacy of tadalafil 5 mg once daily for 12 weeks with placebo in improving Patient Sexual Encounter Profile (SEP) diary Question 3.
- To compare the efficacy of tadalafil 5 mg once daily for 12 weeks with placebo in improving BPH Impact Index (BII).
- To compare the efficacy of tadalafil 2.5 mg once daily for 12 weeks with placebo in improving SEP diary Question 3.
- To compare the efficacy of tadalafil 2.5 mg once daily for 12 weeks with placebo in improving BII.

Additional secondary objectives were as follows:

- To assess the safety of tadalafil 2.5 and 5 mg once daily for 12 weeks, as examined by adverse events, orthostatic vital signs, clinical laboratory tests, and postvoid residual volume (PVR).
- To compare the change in Modified IPSS (mIPSS) from baseline to 2 weeks for tadalafil 2.5 mg and tadalafil 5 mg once daily versus placebo.
- To compare the change in IPSS, IIEF EF Domain, SEP diary Question 3, and BII from baseline to 4 and 8 weeks for tadalafil 2.5 and 5 mg once daily versus placebo.
- To compare the change in IPSS subscores, IIEF Overall and Intercourse Satisfaction Domains, IIEF Questions 3 and 4, and SEP diary Questions 2, 4, and 5 from baseline to 12 weeks for tadalafil 2.5 and 5 mg once daily versus placebo.
- To examine the impact of tadalafil 2.5 and 5 mg once daily for 12 weeks compared with placebo on urinary symptoms of BPH-LUTS as assessed by Patient Global Impression of Improvement (PGI-I) and Clinician Global Impression of Improvement (CGI-I).
- To examine the impact of tadalafil 2.5 and 5 mg once daily for 12 weeks compared with placebo on improving erectile function as assessed by the EF Global Assessment Questions (GAQ).
- To compare the change in uroflowmetry parameters from baseline to 12 weeks for tadalafil 2.5 and 5 mg once daily versus placebo.

Study Design: Study LVHR was a randomized, double-blind, placebo-controlled, parallel-design, multinational outpatient study with 3 study periods: screening/washout, placebo lead-in, and treatment. Subjects who remained eligible after a 4-week wash-out period (if needed for wash-out of a prohibited BPH, overactive bladder, or ED treatment) entered a 4-week single-blind, placebo lead-in period. Subjects who remained eligible following the placebo lead-in period were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups (placebo, tadalafil 2.5 mg, or tadalafil 5 mg, administered once daily) for the 12 week double-blind treatment period.

Number of Subjects:
Planned: Approximately 184 randomized (175 evaluable) per treatment group
Randomized: 208 tadalafil 5 mg; 198 tadalafil 2.5 mg; 200 placebo
Treated (at least 1 dose): 208 tadalafil 5 mg; 198 tadalafil 2.5 mg; 200 placebo
Completed: 184 tadalafil 5 mg; 172 tadalafil 2.5 mg; 170 placebo

Diagnosis and Main Criteria for Inclusion: The study population consisted of men ≥45 years of age who had both BPH-LUTS (as diagnosed by a urologist) for >6 months and a ≥3-month history of ED at Visit 1. Subjects were to have been sexually active with an adult female partner and expected to remain sexually active with the same adult female partner for the duration of the study. Subjects were not to have taken finasteride for at least 3 months, dutasteride for at least 6 months, or any BPH (including herbal preparations), overactive bladder (OAB), or ED therapy for at least 4 weeks prior to Visit 2. At Visit 2, subjects needed to have a total IPSS ≥13 and evidence of bladder outlet obstruction as defined by a peak urine flow rate (Q_{max}) of ≥4 to ≤15 mL/second (from a prevoid total bladder volume [assessed by ultrasound] of ≥150 to ≤550 mL and a minimum voided volume of 125 mL) to continue participation. During the placebo lead-in period, subjects had to make at least 4 sexual intercourse attempts, as recorded in the SEP diary, and be ≥70% compliant with study drug to be eligible for randomization.

Study Drug, Dose, and Mode of Administration:
Tadalafil 2.5 or 5 mg/day, given orally once daily as one 2.5- or one 5-mg tablet.

Reference Therapy, Dose, and Mode of Administration: Placebo tablets identical in form and appearance to tadalafil 2.5- or 5-mg tablets, given orally once daily as 1 of each tablet for subjects assigned to placebo; or given orally as 1 tablet in conjunction with the tadalafil dose for subjects assigned to 1 of the tadalafil treatment groups (subjects assigned to tadalafil 5 mg received 1 placebo tablet identical to tadalafil 2.5 mg; subjects assigned to tadalfil 2.5 mg received 1 placebo tablet identical to tadalfil 5 mg).

Duration of Treatment: 12 weeks
Screening/washout period: up to 4 weeks
Single-blind placebo lead-in period: 4 weeks
Double-blind treatment period: 12 weeks

Variables:
Efficacy: The coprimary efficacy measures of this study were total IPSS and the IIEF EF Domain score. The key secondary efficacy measures were the SEP diary Question 3 and the BII. Additional secondary efficacy measures were the mIPSS; the IPSS storage (irritative) and voiding (obstructive) subscores; the IPSS nocturia question and IPSS QoL Index; the IIEF Intercourse Satisfaction and Overall Satisfaction Domains; the IIEF Questions 3 and 4; SEP diary Questions 2, 4, and 5; the PGI-I and CGI-I; and the EF GAQ.
Safety: In addition to adverse event reporting at each study visit following screening, safety was assessed via clinical laboratory assessments and PVR (performed at screening, randomization, and endpoint), orthostatic vital sign assessment (from beginning of placebo lead-in period to endpoint), and uroflowmetry measurements (performed at beginning of placebo lead-in period, randomization, and endpoint).

Statistical Evaluation Methods:

Efficacy:

Efficacy analyses were performed using the Primary Analysis Population, which included all subjects who were randomized and started study medication. The baseline visit for efficacy measurements was at the end of the placebo lead-in period (Visit 3). Endpoint, or final visit, was the last measurement collected prior to study discontinuation. All efficacy measures were summarized by descriptive statistics for each treatment group during the treatment period (Weeks 0 through 12).

The coprimary endpoints for the primary inferential analyses were the differences between tadalafil 5 mg and placebo in mean change from baseline (Visit 3, Week 0) to end of therapy (Visit 7 [Week 12], or last visit) in total IPSS and in IIEF EF domain score. Additionally, these coprimary endpoints were compared between tadalafil 2.5 mg and placebo. Key secondary endpoints were mean differences between tadalafil (5 and 2.5 mg) and placebo in change from baseline to Week 12 (or last visit) in the percentage of "yes" responses to SEP diary Question 3 and in BII scores. Mean differences between tadalafil treatment groups and placebo for these endpoints were evaluated within the framework of analysis of covariance models (ANCOVA) with terms for therapy, region, and a baseline covariate. Terms for region-by-treatment group interaction and baseline covariate-by-treatment group interaction were included in the model if significant at a 0.1 level ($p<0.1$). To control the familywise Type I error rate associated with the testing of the coprimary and key secondary endpoints for 2 doses of tadalafil versus placebo, pre-specified decision rules for interpreting the significance of the coprimary and key secondary analyses based on a Dunnett-Bonferroni gatekeeping procedure were developed.

Sample size estimates of 175 subjects per treatment arm were based on pre-specified alpha levels derived from the gatekeeping procedure and 80% power to detect a placebo-adjusted mean difference in IPSS of -1.9 (assuming a standard deviation [SD] of 6). This sample size was also expected to provide at least 80% power to detect placebo-adjusted differences in IIEF EF Domain score of 2.6 with a SD of 8.0. Given a projected nonevaluable rate of 5%, it was anticipated that this study would need to randomize 184 subjects per treatment group, or 552 total subjects.

Safety

The safety analysis population consisted of all randomized subjects. Subjects were analyzed according to the treatment to which they were assigned. Safety was assessed by evaluating reported AEs, orthostatic vital signs, PVR, uroflowmetry parameters, and clinical laboratory values (chemistry, hematology, and urinalysis). Adverse events were summarized using preferred terms and/or system organ classes. Differences between treatment groups in the proportion of subjects experiencing ≥1 AE were analyzed using Fisher's exact tests.

Summary:

A total of 606 subjects were randomized (200 to placebo, 208 to tadalafil 5 mg, 198 to tadalafil 2.5 mg). Baseline demographics and characteristics were well-balanced between the treatment groups. Subjects had a mean age of 62.6 years; overall, 9.2% of subjects were 75 years of age or older. At randomization 61.0% of subjects had mild to moderate LUTS (IPSS <20), with the remainder having severe LUTS (IPSS ≥20). Approximately one-half (50.6%) of subjects had a Q_{max} <10 ml/sec, and 39.9% had a Q_{max} of 10-15 ml/sec. All treatment groups were well-balanced with respect to BPH-associated characteristics (IPSS, Q_{max}, mean PVR, and mean PSA). The majority of subjects (91.6%) had ED duration of >1 year; at randomization, 48.8% of subjects had mild ED (IIEF EF Domain score, 17-30), 24.6% of subjects had moderate ED (IIEF

EF Domain score, 11-16), and 26.6% of subjects had severe ED (IIEF EF Domain score, 1-10). Prior use of an alpha blocker or a PDE5 inhibitor was reported by 23.4% and 28.5% of randomized subjects, respectively; previous use of alpha-blockers or PDE5 inhibitors was balanced across all treatment groups. Of the 606 randomized subjects, 526 (placebo, 170 [85%]; tadalafil 5 mg, 184 [88.5%]; tadalafil 2.5 mg, 172 [86.9%]) completed 12 weeks of double blind treatment.

Tadalafil 5 mg resulted in a statistically significant improvement in both total IPSS (LS mean difference of the change from baseline of -2.3, p<.001) and IIEF EF Domain score (LS mean difference of the change from baseline of 4.7, p<.001) when compared with placebo; thus the coprimary objectives were met after 12 weeks of tadalafil 5 mg once-daily dosing. For total IPSS, the LS mean changes from baseline were -6.1 for the tadalafil 5-mg group and -3.8 for the placebo group; for the IIEF-EF Domain score, the LS mean changes from baseline were 6.5 for the tadalafil 5-mg group and 1.8 for the placebo group.

The coprimary objectives were not met after 12 weeks of tadalafil 2.5 mg once-daily dosing. While a statistically significant improvement in IIEF EF Domain score was observed when compared with placebo (LS mean difference of the change from baseline of 3.4, p<.001), the decrease in total IPSS compared to placebo was not statistically significant for the tadalafil 2.5 mg group (LS mean difference of the change from baseline of -0.8, p=.181). For total IPSS, the LS mean changes from baseline were -4.6 for the tadalafil 2.5 mg group and -3.8 for the placebo group; for the IIEF-EF Domain score, the LS mean changes from baseline were 5.2 for the tadalafil 5-mg group and 1.8 for the placebo group.

As the coprimary efficacy analyses were statistically significant only for tadalafil 5 mg, the key secondary efficacy measures, SEP diary Question 3 and BII, were only assessed for statistical significance sequentially in the prespecified order for tadalafil 5 mg compared to placebo. The LS mean difference of the change in the percentage of "Yes" responses to SEP diary Question 3 was statistically significant when compared to placebo (19.7, p<.001; LS mean changes from baseline: tadalafil 5 mg, 31.7, placebo, 12). The LS mean difference of the change in the BII was also statistically significant when compared to placebo (-0.9, p<.001; LS mean changes from baseline: tadalafil 5 mg, -2.1; placebo, -1.2). While the tadalafil 2.5-mg dose group did not achieve success under criteria established in the gatekeeping procedure for the coprimary endpoints, an increase in the percentage of "Yes" responses to SEP diary Question 3 (24.6%; placebo 12.0%), and a decrease (-1.6; placebo, -1.2) in BII was observed in this group.

Results of the additional secondary analyses were consistent with, and supportive of, the primary analysis results; that is, 12 weeks of tadalafil 5-mg dosing, but not tadalafil 2.5-mg dosing, statistically significantly improved measures related to assessment of BPH-LUTS (IPSS at 2 weeks, IPSS voiding (obstructive) subscore, IPSS storage (irritative) subscore, PGI-I and CGI-I), whereas both tadalafil doses statistically significantly improved measures related to the assessment of ED (IIEF Intercourse Satisfaction Domain, the IIEF Overall Satisfaction Domain, IIEF Questions 3 and 4, SEP diary Questions 2, 4, and 5, and EF-GAQ). No statistically significant differences were observed between either tadalafil group versus the placebo group in the IPSS nocturia question or the IPSS QoL Index after 12 weeks of treatment.

Once daily dosing of either tadalafil 5 mg or 2.5 mg for 12 weeks in men with BPH-LUTS was generally well tolerated. No statistically significant differences were observed between either tadalafil treatment group and placebo in SAEs, AEs leading to discontinuation, TEAEs, treatment-related AEs, or procedure-related AEs. The incidence of discontinuations due to AEs was low and the majority of TEAEs were mild or moderate in severity. Overall, SAEs were rare; 1 resulted in death (tadalafil 2.5 mg). Overall, 57 (27.4%) tadalafil 5 mg-treated subjects and 50 (25.3%) tadalafil 2.5 mg-treated subjects reported experiencing ≥1 TEAE compared to 39 (19.5%) placebo-treated subjects (all p≥.063). The most commonly reported TEAEs (incidence ≥2% in the tadalafil treatment group and occurring more frequently than in the placebo group) were headache, back pain, and nasopharyngitis in the tadalafil 5-mg group, and nasopharyngitis in the tadalafil 2.5-mg group. TEAEs possibly related to hypotension were analyzed; similar proportions of subjects in each treatment group reported at least 1 TEAE, with no statistically significant differences between treatment groups (p>.393 for both treatment groups versus placebo).

A similar proportion of subjects in each treatment group met at least 1 of the 4 criteria for a treatment-emergent positive orthostatic test. There was no evidence of an adverse impact of tadalafil therapy on orthostatic vital signs compared to placebo. No subjects had evidence of symptomatic orthostatic hypotension (presence of a clinical symptom simultaneously with a positive orthostatic test). No clinically adverse changes were observed in laboratory parameters, uroflowmetry assessments, or PVR in the tadalafil-treated subjects compared to placebo.

Conclusions:

Efficacy results from Study LVHR demonstrated that once-daily dosing of tadalafil 5 mg statistically significantly improved the coprimary efficacy measures of total IPSS and the IIEF-EF Domain score, and the key secondary efficacy measure of percentage of "Yes" responses to SEP diary Question 3 and BII at 12 weeks. The statistically significant improvement in total IPSS shown with tadalafil 5mg in this population of men with ED and BPH-LUTS is consistent with results from other tadalafil studies conducted in men with BPH-LUTS. Similarly, the statistically significant improvement in IIEF-EF Domain score, as well as in other ED-related measures, shown with both tadalafil doses is consistent with results from other tadalafil studies conducted in men with ED. Overall, the safety results were comparable with other tadalafil studies and no new safety concerns were identified.