2. LVHJ Synopsis

Clinical Study Report Synopsis: Study H6D-MC-LVHJ

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multinational Study to Evaluate the Efficacy and Safety of Daily Tadalafil for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia	
Number of Investigators: This multicenter study included 28 principal investigators.	
Study Center(s): This study was conducted at 28 study centers in 5 countries.	
Publication Based on the Study: None at this time.	
Length of Study: Date of first subject enrolled: 26 February 2009 Date of last subject completed: 09 November 2009	**Phase of Development:** 3

Objectives:

The primary objective of Study LVHJ was to:

- Evaluate the efficacy of tadalafil 5 mg daily for 12 weeks compared with placebo in improving the International Prostate Symptom Score (IPSS) in men with signs and symptoms of benign prostatic hyperplasia (BPH; also referred to as BPH-LUTS [lower urinary tract symptoms]).

Secondary objectives of the study were to:

- Evaluate change from baseline of tadalafil 5 mg daily for 12 weeks compared with placebo in the treatment of men with BPH-LUTS as assessed by BPH Impact Index (BII, a key secondary objective).
- Evaluate change from baseline of tadalafil 5 mg daily for 12 weeks compared with placebo in the treatment of men with BPH-LUTS as assessed by the following measures: IPSS storage (irritative) subscore; IPSS voiding (obstructive) subscore; IPSS nocturia question; and IPSS Quality of Life (QoL) Index.
- Evaluate Patient Global Impression of Improvement (PGI-I); and Clinician Global Impression of Improvement (CGI-I), at endpoint.
- Evaluate change from baseline of tadalafil 5 mg daily compared with placebo after 1 week of treatment in men with BPH-LUTS as assessed by the Modified IPSS (mIPSS, a key secondary objective).
- Evaluate change from baseline of tadalafil 5 mg compared with placebo after 4 weeks of treatment in men with BPH-LUTS as assessed by: total IPSS and BII (both key secondary measures).
- Examine the efficacy of tadalafil 5 mg for 12 weeks compared to placebo in improving erectile function (EF) as assessed by the International Index of Erectile Function (IIEF-EF) Domain in men with both BPH-LUTS and erectile dysfunction (ED) (a key secondary objective).
- Evaluate change from baseline of tadalafil 5 mg daily for 12 weeks compared with placebo in the treatment of men with BPH-LUTS as assessed by uroflowmetry measurements.
- Assess the safety of tadalafil 5 mg for 12 weeks in the treatment of men with BPH-LUTS as examined by the following measures: adverse events (AEs); orthostatic vital signs; clinical laboratory tests; postvoid residual volume (PVR).

Study Design:
Study LVHJ was a randomized, double-blind, placebo-controlled, parallel-design, multinational, outpatient study with 3 study periods: screening/washout, placebo lead-in, and treatment. Eligible subjects entered a 4-week washout period, if needed, for washout of any prohibited BPH, overactive bladder, or ED treatment; those who did not require the 4-week washout period could immediately enter the placebo lead-in period after screening labs were reviewed. Subjects who remained eligible after the screening/washout period 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 ratio to 1 of 2 treatment groups (placebo or tadalafil 5 mg administered once daily) and began the 12-week double-blind treatment period.

Number of Subjects:
Planned: Approximately 151 per treatment group
Randomized: 161 tadalafil, 164 placebo
Treated (received at least 1 dose): 161 tadalafil, 164 placebo
Completed: 148 tadalafil, 152 placebo

Diagnosis and Main Criteria for Inclusion:
The study population consisted of men ≥45 years of age who had BPH-LUTS (as diagnosed by an urologist) for >6 months at Visit 1. 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 of ≥13 and bladder outlet obstruction as defined by a urinary peak 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. Subjects had to be ≥70% compliant during the placebo lead-in period to be eligible for randomization.

Test Product, Dose, and Mode of Administration:
One tadalafil 5 mg tablet taken orally once daily.

Reference Therapy, Dose, and Mode of Administration:
One placebo tablet, identical in form and appearance to tadalafil 5 mg, taken orally once daily.

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 primary efficacy measure was the total IPSS change from baseline to endpoint (12 weeks). Secondary efficacy measures were: the IPSS storage (irritative) and voiding (obstructive) subscores; the IPSS nocturia question; the IPSS QoL Index; the mIPSS; the BII; the PGI-I and CGI-I; and the IIEF-EF Domain.
Safety: Adverse events were assessed at each study visit following screening. Safety was also evaluated 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 (performed at beginning of placebo lead-in period, randomization, and endpoint).

Evaluation Methods:
Efficacy: Efficacy analyses were conducted in the primary analysis population (subjects who were randomized and started double-blind study medication). All efficacy analyses were performed on an intent-to-treat basis. Analysis of covariance (ANCOVA) modeling was used as the primary inferential analysis method to evaluate change from baseline, measured after a placebo lead-in period, in continuous efficacy variables. The model included terms for baseline values of the analysis variable, treatment group, region, baseline-by-treatment interaction, and treatment-by-region interaction. Interaction terms were tested at a significance level of 0.1 and were removed from the model if not significant (p-value ≥.10). Change from baseline to endpoint and the treatment difference of changes were estimated using least squares (LS) means. If analysis of the primary efficacy measure (total IPSS after 12 weeks) was significant, key secondary efficacy measures (IIEF-EF domain after 12 weeks, total IPSS after 4 weeks, BII after 12 weeks, mIPSS after 1 week, and BII after 4 weeks) were sequentially assessed in the primary analysis population for significance. Treatment differences in PGI-I and CGI-I were compared using the Cochran-Mantel-Haenszel test. All statistical tests were evaluated at a two-sided significance level of .05, unless stated otherwise.
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:
Overall, 325 subjects were randomized, 164 to placebo and 161 to tadalafil. Baseline demographics and clinical characteristics were well balanced between treatment groups. Mean age of subjects was 64.9 years. Approximately one-third of subjects (30.5%) had received previous alpha-blocker therapy for BPH. The majority of subjects (68.9%) also reported ED. Following the placebo lead-in period, the majority of randomized subjects (64.6%) were categorized as having moderate LUTS (IPSS <20) with the remainder having severe LUTS (IPSS ≥20). Approximately one-half of subjects (47.5%) had a Q_{max} between 10 and 15 mL/sec and 38.0% had a Q_{max} less than 10 mL/sec; mean PVR was 63.3 mL for placebo subjects and 44.9 mL for tadalafil subjects.

The most common reason for study discontinuation among subjects randomized to tadalafil was entry criteria not met (2.5%). The most common reason for study discontinuation among subjects randomized to placebo was discontinuation due to subject decision (2.4%).

For the primary efficacy measure, once daily dosing of tadalafil 5 mg resulted in a statistically significant improvement in total IPSS change from baseline to Week 12 (the primary efficacy measure), compared to placebo (tadalafil, -5.6; placebo, -3.6; p=.004).

Because the primary efficacy analysis was statistically significant, the key secondary efficacy measures were sequentially assessed in the prespecified order; statistical significance was only claimed if the preceding key secondary measure was statistically significant. Results of analyses for the key secondary measures were as follows:

- In sexually active subjects with ED, there was a statistically significant improvement in the IIEF-EF domain score with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, 6.7; placebo, 2.0; p<.001), after 12 weeks of treatment.
- There was a statistically significant improvement in total IPSS with once daily dosing of tadalafil 5 mg, compared to placebo (tadalafil, -5.3; placebo, -3.5; p=.003), after 4 weeks of treatment .
- There was no statistically significant difference in BII with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, -1.8; placebo, -1.3; p=.057), after 12 weeks of treatment.
- There was no statistically significant difference in the mIPSS with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, -3.4; placebo, -2.7; p=.146), after 1 week of treatment.
- There was a decrease in BII with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, -1.8; placebo, -1.2; p=.029), after 4 weeks of treatment.

Results of analyses for the additional secondary efficacy objectives were as follows:

- There was improvement in the IPSS voiding (obstructive) subscore with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, -3.3; placebo, -2.3; p=.020), after 12 weeks of treatment.
- There was improvement in the IPSS storage (irritative) subscore with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, -2.3; placebo, -1.3; p=.002), after 12 weeks of treatment.
- There was no improvement in the response to the IPSS nocturia question was with once daily dosing of tadalafil 5 mg and for placebo (tadalafil, -0.5; placebo, -0.4; p=.234), after 12 weeks of treatment.
- There was improvement in the IPSS QoL index with once daily dosing of tadalafil 5 mg compared to placebo (tadalafil, -1.0; placebo, -0.7; p=.013), after 12 weeks of treatment.
- For PGI-I and CGI-I, there was a significant difference between the 2 treatment groups in the distribution of subjects over the 7 response categories (PGI-I, p=.021; CGI-I, p=.009). Overall, a higher proportion of tadalafil subjects than placebo subjects felt their urinary symptoms were very much better, much better, or a little better at the end of the study. Clinicians also felt that a higher proportion of tadalafil subjects than placebo subjects had urinary symptoms that were very much better, much better, or a little better at the end of the study.

There were 2 serious adverse events (SAEs); both were in the tadalafil group (1 subject who died due to an acute myocardial infarction and 1 subject who had endocarditis).

The proportion of subjects reporting at least 1 treatment emergent adverse event (TEAE) was 26.1% (42 subjects) in the tadalafil group and 22.0% (36 subjects) in the placebo group. The most commonly reported TEAEs (incidence ≥ 2.0% in the tadalafil group and occurring more frequently than in the placebo group, using Medical Dictionary for Regulatory Activities [MedDRA], version 12.0 terms) in the tadalafil group were headache (tadalafil, 3.7%; placebo, 0.6%) and back pain (tadalafil, 3.1%; placebo 2.4%). Four subjects discontinued due to an AE, 3 in the tadalafil group and 1 in the placebo group.

The proportion of subjects reporting at least 1 TEAE possibly related to hypotension, including the preferred terms of headache, asthenia, and fatigue, was 6.2% (10 subjects) in the tadalafil group and 1.2% (2 subjects) in the placebo group (p=.019). Headache was the most commonly reported TEAE possibly related to hypotension both overall (n=7) and in the tadalafil group (n=6).

Overall, fewer tadalafil-treated (n=31, 19.3%) than placebo-treated subjects (n=38, 23.2%) experienced ≥1 treatment-emergent positive orthostatic test. Similar results were observed for subjects <75 years of age (tadalafil, n=25, 19.1%; placebo, n=30, 23.3%) and in subjects ≥75 years (tadalafil, n=6, 20.0%; placebo, n=8, 22.9%). No subject reported a TEAE upon standing during orthostatic assessment.

Overall, no clinically significant adverse changes were observed in laboratory values, urinalysis parameters, uroflowmetry assessments, or PVR. There was one TEAE report of urinary retention in a placebo-treated subject.

Conclusions:
Once daily tadalafil resulted in statistically significant improvement in total IPSS, the IIEF-EF domain score, the IPSS storage and voiding subscores, the IPSS QoL index, and the PGI-I and CGI-I, compared to placebo after 12 weeks. The BII was lower in the tadalafil group than in the placebo group but the difference was not statistically significant.

The safety findings from Study LVHJ for tadalafil were comparable to those in previous studies of once daily tadalafil treatment and no new safety concerns were identified.