# Summary ID# 9797

# Clinical Study Summary: Study H6D-MC-LVHG

# A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia

## Date summary approved by Lilly: 09 September 2008

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| **Title of Study:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, 5-Group, Multinational Study to Evaluate the Efficacy, Dose Response, and Safety of Tadalafil Once-a-Day Dosing for 12 Weeks in Men With Signs and Symptoms of Benign Prostatic Hyperplasia | |
| **Investigator(s):** This multicenter study included 92 principal investigators. | |
| **Study Center(s):** This study was conducted at 92 study centers in 10 countries. | |
| **Length of Study:** 14 months<br>Date of first subject enrolled: 15 August 2006<br>Date of last subject completed: 17 October 2007 | **Phase of Development:** 2/3 |

**Objectives:**

Primary Objective:

To test the hypothesis that tadalafil 5 mg once daily for 12 weeks is superior to placebo in improving the International Prostate Symptom Score (IPSS) in men with signs and symptoms of benign prostatic hyperplasia (also referred to as BPH-LUTS [lower urinary tract symptoms]).

Secondary Objectives:

To evaluate the efficacy of all tadalafil doses once daily for 12 weeks compared to placebo in the treatment of BPH-LUTS as assessed by the following measures:

- IPSS total defined as the sum of the scores for IPSS Questions 1 through 7; a decrease in score indicates improvement.
- IPSS Storage (Irritative) subscore, defined as the sum of the scores for IPSS Questions 2, 4, and 7; a decrease in score indicates improvement.
- IPSS Voiding (Obstructive) subscore, defined as the sum of the scores for IPSS Questions 1, 3, 5, and 6; a decrease in scores indicates improvement.
- IPSS Question 7 (Nocturia); a decrease in score indicates improvement.
- IPSS Quality of Life (QoL) Index
- BPH Impact Index (BII)
- LUTS Global Assessment Question (LUTS-GAQ)
- Uroflowmetry parameters: peak flow rate ($Q_{max}$), mean flow rate ($Q_{ave}$), and voided volume ($V_{comp}$)

- To examine the impact of tadalafil 2.5, 5, 10, and 20 mg once daily on erectile function (EF) in men with both BPH-LUTS and erectile dysfunction (ED), as assessed by the International Index of Erectile Function (IIEF) EF Domain (defined as the sum of the scores for Questions 1 through 5 and 15 of the IIEF questionnaire; an increase in score indicates an improvement of EF).
- To assess the safety of tadalafil 2.5, 5, 10, and 20 mg once daily for 12 weeks in the treatment of men with BPH-LUTS as examined by the following measures:
  - Adverse events (AEs)
  - Clinical laboratory tests
  - Electrocardiograms (ECGs)
  - Prostate-specific antigen (PSA)
  - Postvoid residual volume (PVR)

**Study Design:** This was a randomized, double-blind, placebo-controlled, parallel design, multinational study to compare the efficacy, dose response, and safety of tadalafil once daily at doses of 2.5, 5, 10, and 20 mg versus placebo for 12 weeks in men with BPH-LUTS.

Number of Subjects:

Planned: 990 subjects: 198 subjects per treatment group

Randomized: 1056 subjects: 845 tadalafil, 211 placebo

Completed: 886 subjects: 701 tadalafil, 185 placebo

**Diagnosis and Main Criteria for Inclusion:** The study population consisted of men 45 years of age or older, who presented with BPH-LUTS based on disease diagnostic criteria. Subjects must have had BPH-LUTS (as diagnosed by a qualified physician) for >6 months at Visit 1. Lower urinary tract symptoms included those associated with voiding (obstructive symptoms, such as incomplete emptying, intermittency, weak stream, and straining) and/or storage (irritative symptoms, such as frequency, urgency, and nocturia).

**Test Product, Dose, and Mode of Administration:**

Tadalafil 2.5 mg/day given orally once daily as one 2.5 mg tablet

Tadalafil 5 mg/day given orally once daily as one 5 mg tablet

Tadalafil 10 mg/day given orally once daily as one 10 mg tablet

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| Tadalafil 20 mg/day given orally once daily as one 20 mg tablet<br>All doses were packaged in blister packs (4 tablets) including applicable placebo tablets. |
| **Reference Therapy, Dose, and Mode of Administration:** Placebo tablets of 2.5, 5, 10, and 20 mg/day given orally once daily. Doses of placebo were provided in blister packs of 4 tablets and consisted of 4 tablets for placebo subjects or 3 tablets in conjunction with the applicable tadalafil dose. |

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| **Duration of Treatment:** 12 weeks |
| **Variables:**<br>Efficacy: The primary efficacy outcome was the change in IPSS total from baseline to Visit 6 (Week 12) for subjects taking tadalafil 5 mg once daily versus placebo. Secondary efficacy outcomes for this study were: change in IPSS total, IPSS storage (irritative) subscore, IPSS voiding (obstructive) subscore, IPSS Question 7, IPSS QoL, BII, LUTS-GAQ, uroflowmetry parameters ($Q_{max}$ $Q_{ave}$, and $V_{comp}$), and IIEF EF Domain.<br>Safety: Safety was evaluated using treatment-emergent adverse events (TEAEs), clinical laboratory values and vital signs, ECGs, PSA, and PVR). |
| **Evaluation Methods:** Statistical: For efficacy analyses, all patients with baseline and at least 1 postbaseline observation were included. Questionnaire responses were treated as continuous variables. All efficacy variables were analyzed at Visit 6 utilizing the last-observation-carried-forward (LOCF) convention. Primary analysis of IPSS data used a permutation test, which makes no assumptions about the underlying distribution of the data. Analysis of covariance (ANCOVA) models were used to evaluate change from baseline in efficacy variables and the models incorporated terms for baseline, treatment group, geographic region, and baseline of the analyzed parameter. All statistical tests were two sided and evaluated at the 0.05 level of significance. The incidence of TEAEs among treatment groups was analyzed using Fisher's exact tests. |

Demographics:

Of the 1058 subjects randomized in Study LVHG (2.5 mg: n=209, 5 mg: n=212, 10 mg: n=216, 20 mg: n=209), 2 subjects did not receive study drug and 1 subject was mistakenly double randomized. The data from this subject was not used in the efficacy analyses, but was included in the safety analyses.

The mean age of all subjects was 62 years, with the majority of subjects being Caucasian (approximately 86%) and all subjects being male. Approximately half of subjects had LUTS for >3 years (51.2%) and approximately one-third of subjects (33.5%) were categorized as having severe LUTS (IPSS ≥20) at baseline after the placebo run-in period. Overall, 27.8% of subjects reported taking previous therapy for BPH and 26.9% of subjects reported taking previous therapy for ED. 67.8% of subjects had ED at Visit 1 and of those, 84.8% reported ED duration of 1 year or more. Of those subjects with ED at Visit 1, the majority had an ED severity of mild or moderate (84.8%). There were 80.6% of subjects reporting that they were sexually active with a female partner and 55% of subjects reported that they were sexually active with a female partner and had ED.

Efficacy Results

Primary Endpoint:

The primary efficacy outcome was the change in IPSS total from baseline to Visit 6 for subjects taking once-daily tadalafil 5 mg compared to placebo. Once-daily dosing of tadalafil 5 mg resulted in a statistically significant improvement in total IPSS least-squares (LS) mean change from baseline as compared to placebo (tadalafil 5 mg: -4.83,

 

placebo: -2.23; p<.001 [ANCOVA]). For the non-parametric permutation test, the tadalafil 5-mg dose resulted in a statistically significant improvement in the total IPSS median change from baseline of -4.0 compared to -2.0 for placebo (p<.001).

Secondary Endpoints:

International Prostate Symptom Score (IPSS) Total: There were statistically significant improvements in IPSS total LS mean change from baseline as compared to placebo for tadalafil once-daily dosages (tadalafil 2.5 mg: p=.005, tadalafil 5 mg: p<.001, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared with placebo (ANCOVA). For the non-parametric permutation test, there were statistically significant improvements in the IPSS total median change from baseline for all tadalafil doses (tadalafil 2.5 mg: p=.004; tadalafil 5 mg: p<.001; tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared with placebo.

International Prostate Symptom Score (IPSS) Storage (Irritative) subscore: There were statistically significant improvements in LS mean changes from baseline as compared to placebo for the tadalafil treatment groups (tadalafil 2.5 mg: p=.025, tadalafil 5 mg: p<.001, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001 compared to placebo (ANCOVA). For the non-parametric permutation test, there were statistically significant improvements in the median change from baseline for all tadalafil doses (tadalafil 2.5 mg: p=.010, tadalafil 5 mg: p=.002, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared with placebo.

International Prostate Symptom Score (IPSS) Obstructive (Voiding) subscore: There were statistically significant improvements in LS mean changes from baseline as compared to placebo for all tadalafil treatment groups (tadalafil 2.5 mg: p=.008, tadalafil 5 mg: p<.001, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared to placebo (ANCOVA). For the non-parametric permutation test, there were statistically significant improvements in the median change from baseline for all tadalafil doses (tadalafil 2.5 mg: p=.01, tadalafil 5 mg: p<.001, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared to placebo.

International Prostate Symptom Score (IPSS) Question 7 (Nocturia): There was a statistically significant improvement in LS mean changes from baseline as compared to placebo in the tadalafil 20 mg treatment group (p=.012) compared to placebo (ANCOVA), but there were no statistically significant differences between other tadalafil treatment groups compared to placebo. For the non-parametric permutation test, there were no statistically significant differences in median change from baseline between any of the tadalafil treatment groups compared to placebo.

International Prostate Symptom Score (IPSS) QoL: There were statistically significant improvements in LS mean changes from baseline as compared to placebo for all tadalafil treatment groups (tadalafil 2.5 mg: p=.029, tadalafil 5 mg: p=.002, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared to placebo (ANCOVA). For the non-parametric permutation test, there were statistically significant improvements in the

 

median change from baseline for all tadalafil doses (tadalafil 2.5 mg: p=.010, tadalafil 5 mg: p=.006, tadalafil 10 mg: p=.002, and tadalafil 20 mg: p=.001) compared to placebo.

Benign Prostatic Hyperplasia Impact Index (BII): There were statistically significant improvements in LS mean change from baseline as compared to placebo for tadalafil 5 mg: p=.013, tadalafil 10 mg: p=.016 and tadalafil 20 mg: p=.007 compared to placebo (ANCOVA), but no statistically significant differences for the tadalafil 2.5 mg compared with placebo. For the non-parametric permutation test, there were statistically significant improvements in the median change from baseline for tadalafil 10 mg: p=.039 and tadalafil 20 mg: p=.011 compared to placebo.

Lower Urinary Tract Symptoms (LUTS)-GAQ: There were statistically significant differences in overall improvement in LUTS observed during therapy in the tadalafil 5 mg: p=.003, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001 treatment groups compared to placebo. Improvement in the tadalafil 2.5 mg treatment group was not statistically significant compared to placebo.

Uroflowmetry measures: There were no statistically significant differences observed in the mean changes from baseline for peak flow rate, mean flow rate, and mean voided volume between the tadalafil treatment groups compared to placebo in ANCOVA or non-parametric permutation tests.

International Index of Erectile Function (IIEF) EF Domain: There were statistically significant improvements in LS mean change from baseline for all tadalafil treatment groups (p<.001) compared to placebo. For the non-parametric permutation test, there were statistically significant improvements in the median change from baseline for all tadalafil treatment groups (tadalafil 2.5 mg: p<.001, tadalafil 5 mg: p<.001, tadalafil 10 mg: p<.001, and tadalafil 20 mg: p<.001) compared to placebo.

Safety Results:

No deaths occurred in this study.

During treatment in Study LVHG, 11 tadalafil- and 6 placebo-treated subjects had serious adverse events (SAEs).

Forty-six subjects (placebo: n=5, tadalafil 2.5 mg: n=4, tadalafil 5 mg: n=12, tadalafil 10 mg: n=11, and tadalafil 20 mg: n=14) discontinued due to AEs. Numerically more patients in the tadalafil 5, 10, and 20 mg treatment groups reported AEs leading to discontinuation compared with placebo. The most frequently reported AEs by subjects in the tadalafil treatment groups that led to study discontinuation were back pain (8 events, 0.9%), myalgia (7 events, 0.8%), and headache (5 events, 0.6%).

Table LVHG.1 summarizes TEAEs reported by ≥2% of tadalafil-treated subjects in any treatment group. There were statistically significant differences in the number of patients who reported at least 1 TEAE in the tadalafil 5 mg (p=.035), 10 mg (p=.003), and 20 mg (p<.001) treatment groups compared with placebo.

 

The most common TEAEs reported across all tadalafil treatment groups were headache (p=.831), dyspepsia (p=.003), back pain (p=.028), myalgia (p=.033), and nasopharyngitis (p=.397) compared to placebo.

No clinically adverse changes were observed in laboratory values, vital signs, PSA, or PVR with tadalafil treatment. Overall, there were no statistically significant mean changes from baseline to endpoint in tadalafil treatment groups in the ECG parameters.

Notable events within the cardiovascular system (including myocardial infarction, cerebrovascular accident, tachyarrhythmia, angina pectoris, and hypotensive events), vision/eyes, hepatic system, PSA, and urinary tract invasive procedures were further evaluated and no safety signal was identified. There were no reports of urinary retention in tadalafil-treated subjects, while 1 subject in the placebo treatment group was catheterized because of urinary retention caused by BPH.

**Table LVHG.1. Treatment-Emergent Adverse Events by Decreasing Frequency of Occurrence in greater than 2% of Subjects In Any Tadalafil Group**

| | Placebo (N=212) n (%) | Tadalafil 2.5 mg (N=209) n (%) | Tadalafil 5 mg (N=212) n (%) | Tadalafil 10 mg (N=216) n (%) | Tadalafil 20 mg (N=209) n (%) | All Tadalafil (N=846) n (%) | All Tadalafil Vs. Placebo |
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| Subjects with ≥1 TEAE | 45 (21.2) | 56 (26.8) | 65 (30.7) | 75 (34.7) | 83 (39.7) | 279 (33.0) | <.001 |
| Headache | 6 (2.8) | 5 (2.4) | 6 (2.8) | 11 (5.1) | 7 (3.3) | 29 (3.4) | .831 |
| Dyspepsia | 0 (0.0) | 2 (1.0) | 10 (4.7) | 6 (2.8) | 10 (4.8) | 28 (3.3) | .003 |
| Back pain | 1 (0.5) | 3 (1.4) | 2 (0.9) | 10 (4.6) | 12 (5.7) | 27 (3.2) | .028 |
| Myalgia | 0 (0.0) | 3 (1.4) | 3 (1.4) | 6 (2.8) | 6 (2.9) | 18 (2.1) | .033 |
| Nasopharyngitis | 2 (0.9) | 7 (3.3) | 4 (1.9) | 2 (0.9) | 5 (2.4) | 18 (2.1) | .397 |
| Diarrhoea | 3 (1.4) | 2 (1.0) | 6 (2.8) | 1 (0.5) | 5 (2.4) | 14 (1.7) | 1.00 |
| Gastroesophageal reflux disease | 0 (0.0) | 2 (1.0) | 2 (0.9) | 6 (2.8) | 3 (1.4) | 13 (1.5) | .083 |
| Pain in extremity | 0 (0.0) | 3 (1.4) | 5 (2.4) | 2 (0.9) | 3 (1.4) | 13 (1.5) | .083 |
| Influenza | 1 (0.5) | 4 (1.9) | 4 (1.9) | 1 (0.5) | 2 (1.0) | 11 (1.3) | .478 |
| Bronchitis | 1 (0.5) | 3 (1.4) | 1 (0.5) | 5 (2.3) | 0 (0.0) | 9 (1.1) | .697 |
| Muscle spasms | 0 (0.0) | 2 (1.0) | 0 (0.0) | 2 (0.9) | 5 (2.4) | 9 (1.1) | .218 |

Abbreviations: N = total number of subjects; n = number of subjects who reported a treatment-emergent adverse event; TEAE = treatment-emergent adverse event.