2. LVHX Synopsis

Clinical Study Report Synopsis: Study H6D-MC-LVHX

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Assess the Efficacy and Safety of Tadalafil (LY450190) Once a Day in Subjects with Erectile Dysfunction who are Naïve to PDE5 Inhibitors	
Number of Investigators: This multicenter study included 22 principal investigators.	
Study Centers: This study was conducted at 22 study centers in five countries.	
Publications Based on the Study: None at the time of this report.	
Length of Study: 12 months Date of first subject visit (informed consent): 22 January 2009 Date of first subject enrolled (assigned to therapy): 19 February 2009 Date of last subject visit: 15 January 2010	**Phase of Development:** Phase III

Objectives: The primary objectives of this study were as follows:

- To evaluate the efficacy of tadalafil 5 mg (with possible down-titration to 2.5 mg) compared with placebo, when taken orally once a day over 12 weeks, in improving erectile function in men with erectile dysfunction (ED) who were naïve to phosphodiesterase type 5 (PDE5) inhibitors, as measured by the Erectile Function (EF) Domain (sum of Questions 1 through 5 and Question 15) of the International Index of Erectile Function (IIEF), and Questions 2 and 3 of the subject Sexual Encounter Profile (SEP) diary.
- To assess the safety of tadalafil 5 mg (with possible down-titration to 2.5 mg) administered once a day compared with placebo in men with ED who were naïve to PDE5 inhibitors, as assessed by adverse events (AEs) and vital signs measurements.

The secondary objectives of this study were as follows (in relation to tadalafil 5 mg once a day with possible down-titration to 2.5 mg):

- To evaluate the efficacy of tadalafil compared with placebo as measured by other variables, including other IIEF domains, other SEP questions, and responses to the Global Assessment Question (GAQ) 1 and 2.
- *To characterize the endothelium dysfunction profile, assessed by peripheral arterial tonometry (measured using [redacted]) and levels of endothelial dysfunction markers and indicators, in men with ED.
- *To evaluate the effect of tadalafil compared with placebo on endothelial dysfunction, assessed by peripheral arterial tonometry (measured using [redacted]) and levels of endothelial function markers and indicators, in men with ED.
- *To evaluate the relationship between endothelium dysfunction changes and erectile function changes, assessed by the efficacy measures, including nocturnal penile tumescence (NPT) assessments and morning erections changes.
- *To evaluate the effect of tadalafil compared with placebo on the NPT pattern, measured using a nocturnal electrobioimpedance volumetric assessment (NEVA) device.
- To evaluate the effect of tadalafil compared with placebo on the frequency of spontaneous morning erections.
- To evaluate subjects' treatment satisfaction with tadalafil compared with placebo as assessed by the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire.
- To evaluate psychosocial outcomes of tadalafil compared with placebo as measured by the Self-Esteem and Relationship (SEAR) questionnaire.

* Note: At the time of finalization of this clinical study report, evaluation of these parameters was ongoing, and these objectives are not assessed in the report. Descriptive summary statistics only are presented.

Study Design: This was a randomized, double-blind, parallel-group, placebo-controlled study. Subjects attended the study center at Visit 1 when informed consent was signed before screening procedures were performed. Subjects then entered a 4-week, treatment-free, run-in period, during which they were required to make at least four sexual intercourse attempts. Eligible subjects were randomized at the end of this period (Visit 2) to receive placebo or tadalafil in a 1:2 ratio. Randomization was stratified by country and ED severity. The treatment period was 12 weeks, divided into three distinct 4-week segments, with Visits 3, 4 and 5 scheduled at the end of each 4-week interval (although unscheduled visits were permitted for dose adjustment). Dosing started at 5 mg tadalafil daily (or matching placebo) and could be down-titrated to 2.5 mg tadalafil daily (or matching placebo) based on individual tolerability. (Doses could subsequently be increased back to 5 mg based on response.) All subjects were to return for a follow-up visit (Visit 6), 2 weeks after the end of the treatment period. All visits were on an outpatient basis.

Number of Subjects:

	Tadalafil		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Planned (minimum evaluable)	116		58		174	
Randomized	147	(100.0)	70	(100.0)	217	(100.0)
Treated (≥1 dose)	147	(100.0)	70	(100.0)	217	(100.0)
Completed 12 weeks treatment	134	(91.2)	66	(94.3)	200	(92.2)
Completed study	130	(88.4)	64	(91.4)	194	(89.4)
Discontinued	17	(11.6)	6	(8.6)	23	(10.6)
Primary Efficacy population	146	(99.3)	67	(95.7)	213	(98.2)
Intention-to-treat (ITT) population	146	(99.3)	69	(98.6)	215	(99.1)
Safety population	147	(100.0)	70	(100.0)	217	(100.0)

Diagnosis and Main Criteria for Inclusion: Men who were at least 18 years of age, who had received no previous or current treatment with tadalafil or any other PDE5 inhibitor, who anticipated having the same adult female sexual partner during the study, and who reported at least a 3-month history of ED (defined as the consistent inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual intercourse), could be considered for entry to the study.

Test Product, Dose, and Mode of Administration: Tadalafil 5 mg tablets, given once daily by oral administration. Doses could be titrated to 2.5 mg/day (2.5 mg tablet once daily).
Batch numbers: [redacted] (2.5 mg tadalafil tablets), [redacted] (5 mg tadalafil tablets)

Reference Therapy, Dose, and Mode of Administration: Placebo tablets, matching 5 mg and 2.5 mg tadalafil tablets, given once daily by oral administration.
Batch numbers: [redacted] (matching 2.5 mg placebo tablets), [redacted] (matching 5 mg placebo tablets)

Duration of Treatment:
Intended duration for a single subject: 12 weeks.

Variables:

Efficacy: *Primary Efficacy Measures*: IIEF EF Domain, SEP Question 2 and SEP Question 3. *Secondary Efficacy Measures*: IIEF Intercourse Satisfaction, Orgasmic Function, Sexual Desire, and Overall Satisfaction Domains; SEP Questions 1, 4 and 5; GAQ 1 and 2; morning erection diary; peripheral arterial tonometry; endothelial function markers and indicators [redacted] and high sensitivity C-reactive protein [hs CRP]); and NPT.

Treatment satisfaction: EDITS questionnaire.

Psychosocial outcomes: SEAR questionnaire.

Safety: *Primary Safety Measures*: AEs and vital signs.

Statistical Methods:

Efficacy: The co-primary efficacy variables were: change in the IIEF EF Domain from baseline to endpoint; change in Question 2 of the SEP diary from baseline to endpoint; and change in Question 3 of the SEP diary from baseline to endpoint. There was no type I error adjustment for the three co-primary efficacy measures, because all three variables had to reach statistical significance in order for the overall null hypothesis to be rejected. Analysis of covariance (ANCOVA) models were used to evaluate change from baseline to endpoint (last observation carried forward [LOCF]) in efficacy variables where baseline value of the efficacy variable, treatment group, country, and the baseline-by-treatment-group interaction were included in the model. In any model, if the interaction was not significant (that is, if $p \geq 0.10$), then the interaction term was removed from the model and the main effects model was used to calculate the between-treatment-group p-value. All continuous secondary variables were analyzed as per the primary efficacy variables. Primary and secondary efficacy analyses were done following the ITT principle. All statistical hypothesis tests were performed with two-sided type-I error level of 0.05. All variables were summarized by descriptive statistics for each treatment group.

Safety: Safety was assessed by evaluating treatment-emergent AEs (TEAEs) and changes in vital signs.

Sample size estimation: A total of 220 subjects were required to be screened in this trial assuming a rate of 20% of screening failures or nonevaluable subjects. A total sample size of 174 subjects with a ratio of 1:2 into treatment groups (58 subjects in the placebo group and 116 subjects in the tadalafil group) was calculated to give at least 95% of power to detect a significant effect between placebo and tadalafil with a type I error of 5% and a two-sided test.

Summary:

Of the 217 randomized subjects, 134/147 (91.2%) completed 12 weeks of double-blind treatment in the tadalafil group, and 66/70 (94.3%) completed in the placebo group. Mean age was 52.1 years and the majority of subjects (99.1%) were White European. Nearly half of all subjects (44.2%) had ED of mild severity; 32.1% had moderate ED and 23.7% had severe ED. The majority of subjects (70.7%) had experienced ED for ≥12 months prior to entry to the study. There were no overt differences between the treatment groups in terms of any demographic or other baseline characteristic.

There was a statistically significant difference between the tadalafil and placebo groups ($p<0.001$), in terms of mean change from baseline to endpoint, in all three primary efficacy measures (IIEF EF Domain, Question 2 and Question 3 of the SEP questionnaire), showing an improvement in erectile function in subjects who received tadalafil 5 mg once a day. Thus, the overall null hypothesis (no difference between tadalafil and placebo in the change from baseline for the IIEF EF Domain, SEP Question 2 and SEP Question 3) was rejected. Secondary efficacy analyses supported these results. There was also statistically significant higher treatment satisfaction following tadalafil once a day, recorded using the EDITS questionnaire, and statistically significant improvements in psychosocial outcomes, recorded using the SEAR questionnaire.

TEAEs were reported by 28 (19.0%) subjects in the tadalafil group and 7 (10.0%) subjects in the placebo group (p>0.05). The most commonly reported individual TEAEs in the tadalafil group were back pain (3.4%), nasopharyngitis, dyspepsia, headache and myalgia (2.7% each). Approximately half of the subjects who experienced a TEAE in both groups reported mild events. Severe TEAEs were reported by 4 (2.7%) subjects in the tadalafil group and 1 (1.4%) subject in the placebo group. TEAEs that were classed by the investigator as possibly related to study drug were reported by 14 (9.5%) subjects in the tadalafil group compared with 0 subjects in the placebo group (p=0.0057). The most commonly reported TEAEs in the tadalafil group considered possibly related were back pain and myalgia (2.7% each), dyspepsia and headache (2.0% each). Two (1.4%) subjects in the tadalafil group experienced a total of 3 SAEs (rib fracture, hemothorax and intervertebral disc protrusion), and both subjects were discontinued from the study. One (1.4%) subject in the placebo group experienced 2 SAEs (tibia fracture and ankle fracture) and was also discontinued from the study. All SAEs were considered by the investigator to be not related to study drug. Two further subjects in the tadalafil group had TEAEs leading to discontinuation (myalgia and headache), classed as possibly related to study drug. There were no deaths or other events of special interest. There were no clinically relevant changes in vital signs.

Conclusions:

- There was a statistically significant improvement in erectile function in subjects with ED, who were previously naïve to PDE5 inhibitor treatment, when tadalafil was given once a day (5 mg with possible down titration to 2.5 once a day for 12 weeks), compared with placebo, as measured by the IIEF EF Domain, Question 2 and Question 3 of the SEP questionnaire
- There were no new safety or tolerability concerns with once daily dosing of tadalafil 5 mg for 12 weeks in male subjects with ED, who were previously naïve to PDE5 inhibitor treatment. The most commonly reported AEs are well known with current tadalafil usage and there were no additional safety concerns, in terms of AEs or vital signs data.
- Tadalafil once a day resulted in statistically significant improvements in erectile function, compared with placebo, as measured by other IIEF domains, other SEP questions, GAQs, and spontaneous morning erections.
- Subject satisfaction with treatment was statistically significantly greater following tadalafil treatment, compared with placebo, as measured using the EDITS questionnaire.
- Tadalafil once a day resulted in statistically significant improved psychosocial outcomes, compared with placebo, as measured by the SEAR questionnaire.