2. Synopsis

Clinical Safety and Efficacy Study Synopsis: Study H6D-MC-LVGH

Title of Study: Tadalafil 5 mg Once a Day Compared to Placebo in Improving Erectile Dysfunction and Sexual Quality of Life	
Number of Investigators: This multicenter study included 26 principal investigators, all of whom entered subjects into the study.	
Study Centers: This study was conducted at 26 study centers in 5 countries.	
Publications Based on the Study: None at this time.	
Length of Study: 14 months Date of first subject entered: 14 November 2006 Date of first subject enrolled: 19 December 2006 Date of last subject completed: 03 January 2008	**Phase of Development:** 3

Objectives:

Primary Objectives:

- To evaluate the efficacy of tadalafil 5 mg compared with placebo, when taken orally once a day over 12 weeks, in improving erectile function in men with erectile dysfunction (ED) 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 Sexual Encounter Profile (SEP) diary Questions 2 and 3.
- To evaluate the effect of tadalafil 5 mg compared with placebo, when taken orally once a day over 12 weeks, in improving the sexual quality of life of the subject and their partner as measured by the Sexual Quality of Life (QOL) domain of the Sexual Life Quality Questionnaire (SLQQ).

Subject-related Secondary Objectives:

- To evaluate the efficacy of tadalafil 5 mg once a day compared to placebo as measured by the Global Assessment Questionnaire (GAQ).
- To evaluate sexual satisfaction in men treated with tadalafil 5 mg once a day compared to placebo as measured by IIEF Intercourse Satisfaction (IS) and Overall Satisfaction (OS) domains and SEP diary Question 4 (SEP4), satisfaction with hardness, and Question 5 (SEP5), satisfaction with the sexual experience.
- To evaluate treatment satisfaction of tadalafil 5 mg once a day compared to placebo as measured by the SLQQ Treatment Satisfaction domain.
- To evaluate psychosocial outcomes of tadalafil 5 mg once a day compared to placebo as measured by the total score, Sexual Relationship and Confidence domain of the Self-Esteem And Relationship (SEAR) questionnaire.

- To assess the safety of tadalafil 5 mg administered once a day compared to placebo in men with ED.

Partner-related Secondary Objectives

- To evaluate the efficacy of tadalafil 5 mg once a day compared to placebo as measured by Questions 1 and 2 of the Partner SEP (pSEP) and the Partner GAQ (pGAQ).
- To evaluate sexual satisfaction in partners of men with ED treated with tadalafil 5 mg once a day compared to placebo as measured by Question 3 of the pSEP and the Index of Female Sexual Function (FSFI) Satisfaction domain.
- To evaluate partner treatment satisfaction with tadalafil 5 mg administered once a day to subjects with ED compared to placebo as measured by the Partner SLQQ Treatment Satisfaction domain.

Study Design: The study was an international randomized, multicenter, outpatient, double-blind, placebo-controlled, parallel group study in which the efficacy and the sexual quality of life of men with ED treated with tadalafil 5 mg once a day for 12 weeks were evaluated. The sexual quality of life of their partner was also evaluated.

The study consisted of two phases. The first was a run-in phase, lasting approximately 4 weeks, the purpose of which was to obtain baseline data for analysis purposes. The second was the treatment phase in which subjects were stratified by baseline ED severity and randomized within each severity group into treatment groups with either placebo or tadalafil in a 1:3 ratio for the 12-week treatment assessment.

Number of Subjects Receiving Drug:

Screened: 530 men with ED and their female partner

Randomized: Total 342; tadalafil 264, placebo 78.

Completed: Total 307; tadalafil 243, placebo 64

Diagnosis and Main Criteria for Inclusion: The study population consisted of men at least 18 years of age who had clinical diagnosis of ED of at least 3 months duration, and who anticipated having the same adult female sexual partner during the study who was willing to participate in recording responses to efficacy questionnaires, sexual quality of life questionnaires, and other instruments used in this study.

Study Drug, Dose, and Mode of Administration: Tadalafil 5 mg, given orally once a day.

Comparator: Placebo tablet, given orally once a day.

Duration of Treatment: 12 weeks during the treatment phase of the study.

Variables:

Efficacy (co-primary):

- Erectile Function domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 of the Sexual Encounter Profile (SEP) diary.
- Sexual Quality of Life: subject and partner SLQQ-QOL domains

Efficacy (secondary):

- Subject related: subject responses for GAQ and SEAR, IIEF Intercourse Satisfaction domain and Overall Satisfaction domain scores, SEP Questions 4 and 5, and the SLQQ Treatment Satisfaction domain score.
- Partner related: partner responses for pGAQ, pSEP Questions 1, 2, and 3, FSFI Satisfaction domain score, and SLQQ Treatment Satisfaction domain score.

Safety: adverse events, changes from baseline in vital signs (pulse rate and blood pressure) in subjects only.

Evaluation Methods:

Statistical: All efficacy analyses were performed using the intent-to-treat (ITT) population, which included all randomized subjects who had both baseline and at least one postbaseline measurement. All efficacy variables were analyzed using the last-observation-carried-forward (LOCF) convention. Analysis of covariance (ANCOVA) models were used to evaluate change from baseline in efficacy variables (IIEF domains, SEP scores, SLQQ-QOL domain, SEAR domains and FSFI domains). The model incorporated terms for baseline value of the efficacy variables, treatment group, pooled sites, and baseline-by-treatment group interaction, if the latter was significant at $p \leq 0.10$. For between-group comparison, an ANCOVA model was also used to evaluate endpoint score for the SLQQ-Treatment Satisfaction domain. Responses to the GAQ were analyzed using logistic regression models. To protest against Type I error when testing multiple primary hypotheses, the hypotheses were tested in a sequential fashion using a gatekeeping strategy. The null hypotheses (no treatment effect with respect to the IIEF EF domain or SEP2 or SEP3) were each tested at a specific level of 0.05. In order to pass a serial gatekeeper, it was necessary to reject all three hypotheses. The two null hypotheses (no treatment effect with respect to subject SLQQ-QOL domain and no treatment effect with respect to partner SLQQ-QOL domain) were each tested at a significance level of 0.025.

Safety: Safety was assessed by evaluating all reported adverse events and changes from baseline to study endpoint in pulse rate and blood pressure based on all randomized subjects. The incidence of treatment-emergent adverse events (TEAEs) was analyzed using Fisher's Exact test across treatment groups for guidance purposes. The treatment effect on change from baseline to endpoint in vital signs was assessed using a one-way analysis of variance (ANOVA) on ranked data.

Subject Demographics and Disposition

This was an international randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of tadalafil 5 mg once a day compared to placebo for up to 12 weeks in male subjects with ED, and the sexual quality of life of both subjects and their female partner. The majority of the subjects were Caucasian (71.6%), 26.3% were Hispanic, and 2.1% were of African or Native American descent. The mean age was 54.3 years. Baseline demographics and erectile function characteristics were similar between treatment groups.

Of the 342 randomized patients, 307 (89.8%) completed the 12-week treatment period (82.1% in the placebo-treated group and 92% in the tadalafil-treated group), and 35 (10.2%) discontinued early for various reasons. Reasons for discontinuation during the treatment period in the placebo-treated and tadalafil-treated groups, respectively, were: subject decision (15.4% and 3%); protocol violation (1.3% and 2.3%); physician decision (1.3% and 0.4%); adverse event (0% and 1.1%); and partner decision (0% and 1.1%).

Primary Outcome Measures

Tadalafil 5 mg once a day significantly improved both erectile function as measured by all three primary efficacy endpoints and the sexual quality of life of the subject and partner ($p<0.001$) compared with placebo.

- Tadalafil 5 mg once a day significantly improved erectile function compared with placebo as measured by the IIEF EF domain (mean change from baseline, tadalafil 7.86 vs. placebo 0.65), SEP Question 2 (the percentage of positive responses at endpoint and mean change from baseline for the tadalafil-treated group was 86.8% and 28.6%, respectively, compared to 60% and 2.7% for the placebo-treated group) and SEP Question 3 (the percentage of positive responses at endpoint and the mean change from baseline was 71% and 46%, respectively, for the tadalafil-treated group compared to 37.3% and 10.8% for the placebo-treated group).
- Tadalafil 5 mg once a day compared to placebo significantly improved sexual quality of life of the subject (mean change from baseline, tadalafil 39.5 vs. placebo 12.5) and the female partner (mean change from baseline, tadalafil 32.4 vs. placebo 5) as measured by SLQQ-QOL domain.

Secondary Outcome Measures

Tadalafil 5 mg once a day compared with placebo significantly improved erectile function as measured by all secondary efficacy endpoints ($p<0.001$ for all comparisons of tadalafil treatment with placebo).

- Subject-related secondary endpoints
  - Subjects treated with tadalafil 5 mg once a day had significant improvement in erections compared with placebo as measured by GAQ1 (Has the treatment you have been taking during this study improved your erections?) and GAQ2 (Has the treatment improved your ability to engage in sexual activity?). For GAQ1 the percentage of positive responses at endpoint was 81.2% for the tadalafil-treated group and 26.4% for the placebo-treated group. For GAQ2 the percentage of positive responses was 79.1% for tadalafil-treated group and 22.2% for placebo-treated group.

- Tadalafil 5 mg once a day significantly improved intercourse satisfaction and overall satisfaction compared to placebo as measured by IIEF IS (mean change from baseline was 2.7 in the tadalafil-treated group and 0.1 in the placebo-treated group) and OS domains (mean change from baseline was 2.6 in the tadalafil-treated group and 0.5 in the placebo-treated group).

- Tadalafil 5 mg once a day also significantly improved hardness satisfaction and overall satisfaction with the sexual experience as measured by SEP Questions 4 (Were you satisfied with the hardness of your erection?) and SEP Question 5 (Were you satisfied overall with this sexual experience?). For SEP4 the mean change from baseline in "yes" responses was 49% in the tadalafil-treated group and 12.3% in the placebo-treated group. For SEP5 the mean change from baseline in "yes" responses was 48.1% in the tadalafil-treated group and 11.8% in the placebo-treated group.

- Subjects treated with tadalafil 5 mg once a day were statistically significantly more satisfied compared to subjects receiving placebo as measured by the subject SLQQ-Treatment Satisfaction domain. The endpoint score for SLQQ-Treatment Satisfaction domain was 74.7 in the tadalafil-treated group and 51.3 in the placebo-treated group.

- Subjects in the tadalafil-treated group had significant improvement in self-esteem, confidence, sexual relationship, and overall relationship compared to those in the placebo-treated group as measured by baseline to endpoint mean change in the SEAR total score (tadalafil, 30.2; placebo, 4.6), the Sexual Relationship domain (tadalafil, 34; placebo, 5.4), the Confidence domain (tadalafil, 25.1; placebo, 3.5), and the Self-Esteem (tadalafil, 29.5; placebo, 5.6) and Overall Relationship (tadalafil, 16.3; placebo, -0.7) subscales of the Confidence domain.

- Partner-related secondary endpoints

  - Partner assessment of pGAQ Questions 1 and 2 showed statistically significant improvement in the tadalafil-treated group compared to the placebo-treated group. For pGAQ1 (In your opinion, has the treatment which your partner has been taking during this dosing phase improved his erections?) the percentage of positive responses at endpoint was 79% for the tadalafil-treated group vs. 30% for the placebo-treated group. For pGAQ2 (Has the treatment improved his ability to engage in sexual activity?) the percentage of positive responses at endpoint was 76.1% for the tadalafil-treated group vs 24.3% for the placebo-treated group.

  - Partner assessment of pSEP Questions 1 and 2 showed statistically significant improvement in the tadalafil-treated group compared to the placebo-treated group. For pSEP1 (Was your partner able to achieve at least some erection?) the mean change from baseline in the percent of "yes" responses was 17.3%

tadalafil-treated group vs 3.7% for the placebo-treated group. For pSEP2 (Was your partner able to insert his penis into your vagina?) the mean change from baseline in the percent of "yes" responses was 30% for the tadalafil-treated group vs. 8.2% for the placebo-treated group.

- Partner assessment of sexual satisfaction, as measured by pSEP3 and the FSFI Satisfaction domain, also showed statistically significant improvement for the tadalafil-treated group compared to the placebo-treated group. The mean change from baseline in the percent of "yes" responses to pSEP3 (Were you satisfied overall with this sexual experience?) was 43% for the tadalafil-treated group vs. 11.3% for the placebo-treated group. The mean change from baseline in the FSFI Satisfaction domain was 0.4 in the tadalafil-treated group vs. -0.4 in the placebo-treated group.
- Partners of men treated with tadalafil 5 mg once a day in this study showed significantly more treatment satisfaction compared to partners of men treated with placebo as measured by the partner SLQQ-Treatment Satisfaction domain. The endpoint score for the partner SLQQ-Treatment Satisfaction domain was 73.3 in the tadalafil-treated group and 55.1 in the placebo-treated group.

Safety

The treatment-emergent adverse events most commonly reported (>2%) in tadalafil-treated subjects compared to placebo, respectively, were headache (8.3% vs. 3.8%), dyspepsia (4.5% vs.0%), and nasal congestion (2.7% vs. 0%). Most adverse events were mild or moderate in severity.

There were four serious adverse events during the study, three in the tadalafil-treated group (hypersensitivity, cerebrovascular accident, and gastroenteritis) and one in the placebo-treated group (pancreatitis). None of these events was considered, by the investigators, to be related to treatment.

Tadalafil 5 mg administered once daily for 12 weeks was well tolerated. The incidence of discontinuations due to adverse events was low for the tadalafil group (1.1%); there were no discontinuations due to adverse events in the placebo group. There were no deaths or treatment-related serious adverse events during the treatment phase of the study. There were no clinically significant changes noted in heart rate or blood pressure.

Conclusions:

- Tadalafil 5 mg once a day for 12 weeks compared with placebo significantly improved erectile function in men with ED resulting in improved sexual satisfaction and sexual quality of life of both male subjects and their female partners.

- Tadalafil 5 mg once a day for 12 weeks compared with placebo statistically significantly improved all subject-related and partner-related secondary outcomes.
- Tadalafil 5 mg once a day for 12 weeks was well tolerated.
- Most adverse events were mild or moderate in severity. The treatment-emergent adverse events most commonly reported in subjects who received tadalafil compared to placebo, respectively, were headache, dyspepsia, and nasal congestion.
- There were no deaths or treatment-related serious adverse events during the treatment phase of the study.
- No clinically significant changes were reported in vital signs (pulse rate and blood pressure).