2. LVID Synopsis

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Clinical Study Report Synopsis: Study H6D-MC-LVID

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Global Multicenter Study to Evaluate the Efficacy and Safety of Tadalafil Once Daily Dosing for 12 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia

Number of Investigators: This multicenter study included 44 principal investigators.

Study Centers: This study was conducted at 44 study centers in 10 countries.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 3
Date of first subject enrolled: 07 December 2009 Date of last subject completed: 27 January 2011	

Objectives:

The primary objective of Study H6D-MC-LVID (Study LVID) was to evaluate the efficacy of tadalafil 5 mg once daily (QD) for 12 weeks compared with placebo in improving total International Prostate Symptom Score (IPSS) in men with signs and symptoms of BPH (benign prostatic hyperplasia; also referred to as BPH-LUTS [lower urinary tract symptoms]).

The secondary objectives of this study were as follows:

- To evaluate the efficacy of tamsulosin 0.4 mg QD for 12 weeks compared with placebo in improving total IPSS in men with BPH-LUTS.
- To evaluate the efficacy of tadalafil 5 mg QD compared with placebo and tamsulosin 0.4 mg QD compared with placebo for 12 weeks in the treatment of men with BPH-LUTS, as assessed by the following measures:
    - BPH Impact Index (BII)
    - IPSS storage (irritative) subscore
    - IPSS voiding (obstructive) subscore
    - IPSS nocturia question
    - IPSS Quality of Life (QoL) Index
    - Patient Global Impression of Improvement (PGI-I)
    - Clinician Global Impression of Improvement (CGI-I)
    - The Treatment Satisfaction Scale - BPH (TSS-BPH)
- To evaluate the efficacy of tadalafil 5 mg QD compared with placebo and tamsulosin 0.4 mg QD compared with placebo after 1 week of treatment in men with BPH-LUTS, as assessed by the modified IPSS (mIPSS).
- To evaluate the efficacy of tadalafil 5 mg QD compared with placebo and tamsulosin 0.4 mg QD compared with placebo after 4 weeks of treatment in men with BPH-LUTS, as assessed by IPSS and BII.
- To evaluate the efficacy of tadalafil 5 mg QD compared with placebo and tamsulosin 0.4 mg QD compared with placebo after 12 weeks of treatment in men with BPH-LUTS and ED as assessed by the International Index of Erectile Function (IIEF) Erectile Function (EF) Domain.
- To evaluate the effect of tadalafil 5 mg QD compared with placebo and tamsulosin 0.4 mg QD compared with placebo for 12 weeks in the treatment of men with BPH-LUTS as assessed by uroflowmetry measurements.
- To assess the safety of tadalafil 5 mg QD and tamsulosin 0.4 mg QD for 12 weeks in the treatment of men with BPH-LUTS as examined by the following measures:
    - Adverse Events (AEs)
    - Vital signs
    - Clinical laboratory tests
    - Postvoid residual volume (PVR)

Study Design: Study LVID was a randomized, double-blind, placebo-controlled, parallel-design, global multicenter outpatient study with 3 study periods: screening/washout, placebo lead-in, and treatment. Subjects who remained eligible after a 4-week washout period (if needed for washout of a prohibited BPH, overactive bladder [OAB], or erectile dysfunction [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 (tadalafil 5 mg, tamsulosin 0.4 mg, or placebo) for the 12-week double-blind treatment period.

Number of Subjects:

Planned: Approximately 151 subjects randomized (143 evaluable) per treatment group.
Randomized: 171, tadalafil 5 mg; 168, tamsulosin 0.4 mg; 172, placebo.
Treated (at least 1 dose): 171, tadalafil 5 mg; 167, tamsulosin 0.4 mg; 172, placebo
Completed: 156, tadalafil 5 mg; 150, tamsulosin 0.4 mg; 148, placebo

Diagnosis and Main Criteria for Inclusion: The study population consisted of men ≥45 years of age who had BPH-LUTS (as diagnosed by a qualified physician) for >6 months at Visit 1. Subjects were not to have taken finasteride therapy for at least 3 months, dutasteride therapy for at least 6 months, other experimental or off-label BPH therapy (such as injectable therapies with a protracted effect) for at least 1/2 year, and any BPH therapy (including herbal preparations), OAB therapy, 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 be ≥70% compliant with study drug to be eligible for randomization.

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

Reference Therapy, Dose, and Mode of Administration:
Tamsulosin 0.4 mg/day, given orally once daily as one 0.4-mg capsule.

A placebo tablet identical in form and appearance to a tadalafil 5-mg tablet and a placebo capsule identical in form and appearance to a tamsulosin 0.4-mg capsule, given together orally once daily as 1 dose for subjects assigned to placebo; or given orally as 1 tablet or capsule in conjunction with the tamsulosin or tadalafil dose for subjects assigned to the tadalafil and tamsulosin groups, respectively (that is, subjects assigned to tadalafil 5 mg received 1 placebo capsule identical to tamsulosin 0.4 mg; subjects assigned to tamsulosin 0.4 mg received 1 placebo tablet identical to tadalafil 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 primary efficacy measure of this study was total IPSS. The key secondary efficacy measures were mIPSS and BII. Additional secondary efficacy measures were the IPSS storage (irritative) and voiding (obstructive) subscores, IPSS nocturia question; and the IPSS QoL Index; the IIEF EF Domain; the PGI-I and CGI-I; and the TSS-BPH. The IIEF Intercourse Satisfaction Domain and Overall Satisfaction Domain were exploratory efficacy measures.

Safety: In addition to AE reporting at each study visit following screening, safety was assessed via clinical laboratory assessments, PVR, vital sign assessment, and uroflowmetry measurements.

Statistical Evaluation Methods:

Efficacy:

Efficacy analyses were performed using the Primary Analysis Population, which included all subjects who were randomized and started double-blind 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.

Statistical tests for treatment group differences were conducted for the difference between tadalafil 5 mg QD and placebo. Treatment group differences between tamsulosin 0.4 mg QD and placebo were also provided for reference comparison. Any reference to statistical tests to treatment group differences implied these 2 specific comparisons.

The primary endpoint was the difference between tadalafil 5 mg and placebo in the change from baseline to the end of therapy in total IPSS. The key secondary analyses comparing the changes from baseline between tadalafil 5 mg and placebo were performed in the following pre-specified order at 2-sided significance level of 0.05: total IPSS after 4 weeks of treatment, BII after 12 weeks of treatment (end of therapy using last observation carried forward [LOCF]), mIPSS after 1 week of treatment (Visit 4), and BII after 4 weeks of treatment. Additionally, the primary and key secondary measures were compared between tamsulosin 0.4 mg and placebo as secondary analyses and performed without regard to significant results in other endpoints. For continuous efficacy variables, the primary inferential analysis method to assess a difference in change from baseline to endpoint between an active treatment group with placebo was an analysis of covariance (ANCOVA) model which included terms of centered parameter baseline, treatment group, region, centered-baseline-by-treatment interaction and treatment-by-region interaction. Interaction terms were kept in the model if the interaction was significant at a <0.1 level ($p<0.1$).

A total of 143 subjects per treatment arm was expected to provide at least 80% power to detect a placebo-adjusted mean difference in IPSS of 2.0 (assuming a standard deviation of 6) using a 2-sided t-test at 0.05 level of significance. Given a projected non-evaluable rate of 5%, it was anticipated that this study would randomize 151 subjects per treatment group, or 453 total subjects. Assuming the same standard deviation for tadalafil and tamsulosin data, this sample size had sufficient power to show the superiority of tamsulosin to placebo.

Safety:

The Safety Analysis Population for the double-blind treatment period consisted of all randomized subjects, according to the treatment to which they were assigned. Safety was assessed by evaluating reported AEs, vital signs, PVR, uroflowmetry parameters, and clinical laboratory values (chemistry, hematology, and urinalysis). Adverse events were summarized using *Medical Dictionary for Regulatory Activities* (MedDRA, Version 13.1) 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 511 subjects were randomized (172 to placebo, 171 to tadalafil 5 mg, and 168 to tamsulosin 0.4 mg). Generally, baseline demographics and characteristics were well-balanced between treatment groups. Mean age of subjects was 63.6 years. At baseline, a majority (70.5%) of randomized subjects had a total IPSS <20. At Visit 3, 7.2% of randomized subjects had a Q_{max} >15 mL/sec (tadalafil group, 7.0%; tamsulosin group, 4.2%; placebo group, 10.5%). The mean PVR was 50.9 mL for placebo-treated subjects, 54.6 mL for tadalafil-treated subjects, and 59.8 mL for tamsulosin-treated subjects. Approximately one-quarter of subjects (25.2%) had received previous alpha-blocker therapy. The majority of subjects (69.9%) also reported ED, and 60.5% of subjects had both ED and reported that they were sexually active. Of the

511 randomized subjects, 454 subjects (placebo, 148 [86.0%]; tadalafil 5 mg, 156 [91.2%]; tamsulosin 0.4 mg, 150 [89.3%]) completed 12 weeks of double-blind treatment.

Tadalafil 5 mg resulted in statistically significant improvement in total IPSS (LS mean difference of the change from baseline of –2.1; p=.001) when compared with placebo; thus, the primary objective was met after 12 weeks of tadalafil 5-mg once-daily dosing. For total IPSS, the LS mean changes from baseline were –6.3 for the tadalafil 5-mg group and -4.2 for the placebo group. Results of the Per-Protocol Population analysis and analysis adjusting for baseline ED status were similar to that of the Primary Analysis Population for the primary efficacy measure.

As the primary efficacy analysis was statistically significant, the key secondary efficacy measures were assessed sequentially. Once-daily dosing of tadalafil 5 mg resulted in a statistically significant improvement in all of the key secondary efficacy measures, analyzed in the following pre-specified fixed sequence: total IPSS after 4 weeks (tadalafil, -5.5; placebo, -3.3; LS mean difference of the change, -2.2; p<.001), BII after 12 weeks (tadalafil, -1.7; placebo, -0.9; LS mean difference of the change, -0.8; p=.003), mIPSS after 1 week (tadalafil, -4.0; placebo, -2.5; LS mean difference of the change, -1.5; p=.003), and BII after 4 weeks (tadalafil, -1.2; placebo, -0.4; LS mean difference of the change, -0.8; p<.001).

In general, results of the analyses of additional secondary efficacy measures were consistent with, and supportive of, the primary endpoint results; that is, 12 weeks of tadalafil 5-mg dosing statistically significantly improved measures related to assessment of BPH-LUTS when compared to placebo (IPSS voiding [obstructive] subscore, IPSS QoL Index, PGI-I, CGI-I, and TSS-BPH). No statistically significant differences were observed between the tadalafil 5-mg group and the placebo group after 12 weeks in the IPSS storage (irritative) subscore or IPSS nocturia question.

Once-daily dosing of tadalafil 5 mg also improved measures of ED after 12 weeks of treatment compared with placebo in sexually active subjects with ED in the Primary Analysis Population, as demonstrated by statistically significant improvements in IIEF EF Domain score (tadalafil, 6.0; placebo, 2.1; LS mean difference of the change, 4.0; p<.001). Statistically significant improvements in the tadalafil 5-mg group compared with placebo were also observed in the exploratory measures of IIEF Intercourse Satisfaction Domain (p<.001) and the IIEF Overall Satisfaction Domain (p<.001).

The active control, once-daily dosing with tamsulosin 0.4 mg, also statistically significantly improved measures related to assessment of BPH-LUTS when compared to placebo as measured by the IPSS primary efficacy measure and all key secondary efficacy measures. Tamsulosin 0.4 mg resulted in statistically significant improvement in total IPSS when compared with placebo (p=.023). Once-daily dosing of tamsulosin 0.4 mg also resulted in a statistically significant improvement in all of the key secondary efficacy measures: total IPSS after 4 weeks (p<.001), BII after 12 weeks (p=.026), mIPSS after 1 week (p=.005), and BII after 4 weeks (p<.001). Once-daily dosing of tamsulosin 0.4 mg resulted in a statistically significant improvement in the secondary efficacy measure of IPSS voiding (obstructive) subscore after 12 weeks of treatment compared to placebo (p=.026); there was no statistically significant

difference between the tamsulosin group and the placebo group for any other secondary efficacy measures related to assessment of BPH-LUTS . Tamsulosin 0.4 mg administered once daily had no statistically significant effect on ED compared to placebo, as measured by the IIEF EF Domain score (p=.699).

Once-daily dosing of tadalafil 5 mg for 12 weeks in men with BPH-LUTS was generally well tolerated. No statistically significant differences were observed between the tadalafil treatment group and placebo in SAEs, AEs leading to discontinuation, TEAEs, or treatment-related AEs. Overall, SAEs were rare, and none resulted in death. The incidence of discontinuations was low and most TEAEs were mild or moderate in severity. A total of 40 (23.4%) tadalafil-treated subjects reported experiencing ≥1 TEAE compared to 35 (20.3%) placebo-treated subjects. 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, dizziness, and dyspepsia.

No statistically significant differences were observed between the tamsulosin treatment group and placebo in SAEs, AEs leading to discontinuation, TEAEs, or treatment-related AEs. Overall, SAEs were rare, and none resulted in death. The incidence of discontinuations was low and most TEAEs were mild or moderate in severity. A total of 40 (23.8%) tamsulosin-treated subjects reported experiencing ≥1 TEAE compared to 35 (20.3%) placebo-treated subjects. The most commonly reported TEAEs (incidence ≥2% in the tamsulosin treatment group and occurring more frequently than in the placebo group) were headache and dizziness.

Treatment-emergent AEs possibly related to hypotension (based on pre-specified MedDRA terms) were analyzed; similar proportions of subjects in each treatment group reported at least 1 of these TEAEs (most of which were dizziness), with no statistically significant difference between tadalafil and placebo (p=1.00) or tamsulosin and placebo (p=.539).

There was no evidence of any statistically significant or clinically adverse effects of tadalafil or tamsulosin on baseline to endpoint changes in blood pressure or heart rate when compared to placebo, and no tadalafil- or tamsulosin-treated subjects met the pre-specified criteria for potentially clinically significant low blood pressure during the double-blind treatment phase. No clinically adverse changes were observed in laboratory values, urinalysis parameters, uroflowmetry assessments, or PVR in the tadalafil- or tamsulosin-treated subjects compared to placebo. No subjects in either treatment group had a PVR ≥300 mL post-randomization, and there were no TEAEs of urinary retention reported in any tadalafil- or tamsulosin-treated subject. There were statistically significant improvements from baseline to endpoint in Q_{max} in the tadalafil group (2.4 mL/sec, p=.009) and the tamsulosin group (2.2 mL/sec; p=.014) compared with placebo (1.2 mL/sec).

Conclusions:

The results from Study LVID demonstrated that once-daily dosing of tadalafil 5 mg was efficacious in treating men with BPH-LUTS, with statistically significant improvement observed when compared to placebo for the primary efficacy measure of total IPSS at 12 weeks, and the key secondary efficacy measures of total IPSS at 4 weeks, BII at 12 weeks and 4 weeks, and mIPSS. The efficacy of tadalafil 5 mg in treating BPH was observed as early as 1 week of

therapy, and was maintained through 12 weeks. Tadalafil also improved erectile function in sexually active men with both BPH-LUTS and ED as assessed by IIEF EF Domain scores. The statistically significant improvement in total IPSS shown with tadalafil 5 mg in this study is consistent with results from other tadalafil studies conducted in men with BPH-LUTS. Once-daily dosing of tamsulosin 0.4 mg also demonstrated efficacy compared with placebo in treating BPH-LUTS, as evidenced by statistically-significant improvements in the primary and key secondary efficacy measures, but it was not efficacious in treating ED. Overall, the safety results were consistent with other tadalafil studies in men with BPH-LUTS, and no new safety concerns were identified.