# 2. LVIW Synopsis

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# Clinical Study Report Synopsis: Study H6D-CR-LVIW

**Title of Study:** A Phase 3b, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Evaluate the Efficacy and Safety of Tadalafil Co-administered with Finasteride for 6 Months in Men with Lower Urinary Tract Symptoms and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia

**Number of Investigators:** This multicenter study included 70 principal investigators.

**Study Centers:** This study was conducted at 70 study centers in 13 countries.

**Publications Based on the Study:** None at this time.

| **Length of Study:** | **Phase of Development:** 3b |
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| Date of first subject enrolled: 01 November 2010<br>Date of last subject completed: 10 May 2012 | |

**Objectives:**

The **primary objective** of this study was to test the hypothesis that tadalafil 5 mg once daily co-administered with finasteride is superior to placebo once daily co-administered with finasteride for 12 weeks in improving total International Prostate Symptom Score (IPSS) in men with lower urinary tract symptoms (LUTS) and prostatic enlargement secondary to benign prostatic hyperplasia (BPH).

The **secondary objectives** of the study were:

- To examine the impact of tadalafil 5 mg once daily versus placebo when co-administered with finasteride on erectile function in men with LUTS and prostatic enlargement secondary to BPH at 4, 12, and 26 weeks, as assessed by the International Index of Erectile Function-Erectile Function (IIEF-EF) Domain.
- To examine the impact of tadalafil 5 mg once daily versus placebo when co-administered with finasteride on erectile function in men with LUTS and prostatic enlargement secondary to BPH at 4, 12, and 26 weeks, as assessed by the following domains: IIEF Overall Satisfaction; IIEF Intercourse Satisfaction; IIEF Orgasmic Function; IIEF Sexual Desire; and IIEF Questions 3 and 4.
- To evaluate the change from baseline of tadalafil 5 mg once daily versus placebo when co-administered with finasteride in the treatment of men with LUTS and prostatic enlargement secondary to BPH as assessed by total IPSS score at 4 and 26 weeks.
- To evaluate the change from baseline of tadalafil 5 mg once daily versus placebo when co-administered with finasteride in the treatment of men with LUTS and prostatic enlargement secondary to BPH, as assessed by the following measures at 4, 12, and 26 weeks: the IPSS storage (irritative) subscore; IPSS voiding (obstructive) subscore; IPSS nocturia subscore; and IPSS Quality of Life (QoL) Index.
- To examine the impact of tadalafil 5 mg once daily versus placebo when co-administered with finasteride on urinary symptoms of BPH in men with LUTS and prostatic enlargement secondary to BPH, as assessed by the following measures at 26 weeks: the BPH Treatment Satisfaction Scale (TSS-BPH); Patient Global Impression of Improvement (PGI-I); and Clinician Global Impression of Improvement (CGI-I).
- To assess the safety of tadalafil 5 mg once daily versus placebo when co-administered with finasteride for 26 weeks in the treatment of men with LUTS and prostatic enlargement secondary to BPH, as examined by the following measures: adverse events (AEs) (including sexual function-related AEs); vital signs; clinical laboratory tests; and post-void residual (PVR) measurements.

The **exploratory objective** of this study was as follows:

- To evaluate the impact of tadalafil 5 mg once daily versus placebo when co-administered with finasteride on sexual function parameters and mood in men with LUTS and prostatic enlargement secondary to BPH at 4, 12, and 26 weeks, as assessed by the Psychosexual Daily Questionnaire (PDQ).

**Study Design:** Study LVIW was a multi-country, multicenter, randomized, double-blind, parallel, placebo-controlled outpatient trial with 3 study periods. This study evaluated the efficacy and safety of tadalafil 5 mg once daily when co-administered with finasteride 5 mg once daily compared with placebo once daily co-administered with finasteride 5 mg once daily in men with LUTS and prostatic enlargement secondary to BPH.

**Number of Subjects**:

Planned: Approximately 646 subjects (323 subjects per arm) were to be enrolled in this study.
Randomized: tadalafil 5 mg, 346; placebo, 350.
Treated (at least 1 dose): tadalafil 5 mg, 345; placebo, 350.
Completed 26 weeks: tadalafil 5 mg, 306; placebo, 286.

**Diagnosis and Main Criteria for Inclusion:** Men 45 years of age or older who had BPH-LUTS (as diagnosed by a qualified physician) for >6 months and prostate enlargement (defined as prostate volume 30 cc or greater on transrectal ultrasonography [TRUS]) at Visit 1; a total IPSS ≥13 and bladder outlet obstruction (as defined by a $Q_{max}$ 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]) at Visit 2; and who had not previously taken finasteride or dutasteride at any time prior to Visit 1 or any other short-acting BPH (including herbal preparations), overactive bladder (OAB), or ED therapy for at least 4 weeks prior to Visit 2.

**Study Drug, Dose, and Mode of Administration:**
Tadalafil 5 mg/day, given orally once daily as one 5-mg tablet; co-administered with finasteride 5 mg/day, given orally once daily as one 5-mg tablet.

**Comparator, Dose, and Mode of Administration:** Placebo, given orally once daily as 1 tablet; co-administered with finasteride 5 mg/day during the double-blind treatment period, given orally once daily as 1 5-mg tablet.

**Duration of Treatment:**
Placebo Lead-In Period: 4 weeks
Double-Blind Treatment Period: 26 weeks

**Variables:**

Efficacy: The primary efficacy measure of this study was total IPSS. The secondary efficacy measures were the IIEF-EF Domain; the IPSS storage (irritative) and voiding (obstructive) subscores, IPSS nocturia question, and IPSS QoL index; the IIEF Intercourse Satisfaction, IIEF Overall Satisfaction, IIEF Orgasmic Function, and IIEF Sexual Desire Domains and IIEF Questions 3 and 4; the PGI-I and CGI-I; and the TSS-BPH. The PDQ was an exploratory measure.

Safety: In addition to AE reporting at each study visit following screening, safety was assessed via clinical laboratory assessments, vital signs assessments (systolic and diastolic blood pressure, heart rate), and PVR measurements.

**Statistical Evaluation Methods:**

Efficacy: All efficacy analyses were conducted using the intention-to-treat (ITT) analysis set (defined as subjects who were randomized to study treatment by the interactive voice response system (IVRS) and received at least 1 dose of the study medication in the double-blind period) and the per-protocol analysis set (PPS; defined as subjects who met the criteria for the ITT, completed 12 weeks of treatment in the double-blind treatment period [up to Visit 5], had no major protocol violations, and had ≥70% treatment compliance rate in the double-blind treatment period [tadalafil/placebo and finasteride] up to 12 weeks of treatment Visit 5]). The primary analysis was performed on the ITT population and was analyzed according to the treatment assigned in the randomization scheme.

The primary efficacy measure was the change in total IPSS from baseline (Visit 3 [Week 0]) to Visit 5 (Week 12). Descriptive statistics for total IPSS were presented by treatment group for baseline, Week 12, and change from baseline to Week 12. The method for the primary efficacy measure was based on a mixed-effect model repeated measure (MMRM) analysis using the ITT population, with change in total IPSS from baseline to Weeks 4, 12, and 26 as the dependent variable. As a sensitivity analysis of total IPSS, history of ED was included in the MMRM model.

A fixed-sequence testing procedure to control the familywise Type I error in the primary and the multiple key

secondary endpoints for the comparison between tadalafil 5 mg and placebo was implemented. The key secondary endpoints were analyzed to compare the changes from baseline between tadalafil 5 mg and placebo by the following prespecified order: total IPSS change at 4 weeks, IIEF-EF Domain score change at 4 weeks, IIEF-EF Domain score change at 12 weeks, IIEF-EF Domain score change at 26 weeks, and total IPSS change at 26 weeks.

The sample size was based on the primary efficacy measure, the change from baseline to Week 12 in total IPSS. Approximately 646 subjects (323 subjects per arm) were to be enrolled in this study and randomly assigned to tadalafil 5 mg or placebo, administered concomitantly with finasteride following a 1:1 ratio. Assuming that approximately 10% of the subjects would not contribute to the primary analysis (missing total IPSS measurements at 12 weeks), 578 subjects (289 subjects per arm) would provide 85% power to confirm superiority of tadalafil over placebo and detect a difference of 1.5 in total IPSS. This calculation assumed an SD of 6.0 and a two-sided alpha level of 0.05. For a non-evaluable rate of 15%, approximately 550 subjects (275 subjects per arm) were expected to complete the study after 26 weeks of treatment.

Safety: Safety analyses were conducted on the as-treated population (the safety analysis set). This set included all randomized subjects who received at least 1 dose of study medication in the double-blind treatment period, and were analyzed according to the treatment which they actually received. Safety was assessed by evaluating reported AEs (including sexual function-related adverse effects), vital signs, PVR measurements, and clinical laboratory values (chemistry, hematology, and urinalysis). Adverse events were summarized using MedDRA preferred terms and/or system organ classes (SOC).

**Summary:**

- Overall, 696 subjects were randomized; 350 to placebo/finasteride and 346 to tadalafil/finasteride. Generally, baseline demographics and characteristics were well balanced between treatment groups. Mean age of subjects was 63.7 years; 41.6% were >65 years of age. At baseline (randomization, Visit 3), 31.7% of subjects were categorized as having severe LUTS (IPSS ≥20), mean prostate volume was 49.4 ml, and mean prostate-specific antigen (PSA) was 2.4 ml for all subjects. The overall mean PVR was 64.1 mL for subjects. Approximately one-third of subjects (36.6%) had received previous alpha-blocker therapy. The proportion of subjects considered compliant (compliance rate ≥70%) during the double-blind treatment phase was 98.0% for tadalafil and placebo and 96.8% for finasteride, and did not differ between the treatment groups.
- The primary objective of the study was met: once-daily dosing of tadalafil/finasteride resulted in a statistically significant improvement in total IPSS as compared to placebo/finasteride at 12 weeks (LS mean treatment difference, -1.41 [95% CI: -2.27, -0.55]; p=.001). Results of the PPS and ANCOVA analyses were consistent with that of the primary analysis population for the primary efficacy measure, as was the sensitivity analysis of total IPSS including history of ED in the statistical MMRM model.
- Once-daily dosing of tadalafil/finasteride also resulted in a statistically significant improvement in the key secondary efficacy measures (analyzed per the pre-specified fixed sequence) of total IPSS at 4 and 26 weeks, with statistically significant decreases in total IPSS observed after 4 weeks (p<.001) and 26 weeks (p=.022).
- The improvement in total IPSS was significantly better in the tadalafil/finasteride group than in the placebo/finasteride group at all visits during the 26-week treatment period, though the difference between groups gradually decreased over time. In these men with verified enlarged prostates who were treated with finasteride, tadalafil significantly improved IPSS at the first scheduled visit at 4 weeks.
- For the other key secondary efficacy measures, the IIEF-EF Domain completed by subjects who were sexually active with a female partner and who had ED at baseline, statistically significant improvement was observed in the tadalafil/finasteride group in the IIEF-EF Domain score after 4 weeks, 12 weeks, and 26 weeks (p<.001, all).

- For the additional secondary efficacy objectives, results for tadalafil/finasteride were consistent with, and supportive of, the primary analysis results. Once-daily dosing of tadalafil/finasteride statistically significantly improved measures related to assessment of BPH-LUTS (IPSS storage [irritative] subscore [Weeks 4 and 12], IPSS voiding [obstructive] subscore [Weeks 4, 12, and 26], IPSS QoL Index [Week 4], PGI-I [endpoint], and the TSS-BPH [endpoint]). The CGI-I was not statistically significantly improved in the tadalafil/finasteride group compared with placebo/finasteride.
- The statistically significant improvement in total IPSS and other secondary measures related to the assessment of BPH-LUTS shown with tadalafil 5 mg in this population of men with BPH-LUTS is consistent with results from other tadalafil studies conducted in men with BPH-LUTS, including those who also have ED.
- Once-daily dosing of tadalafil/finasteride resulted in a statistically significant improvement in sexually active men with baseline ED at Weeks 4, 12, and 26 in the IIEF-EF Domain score, Overall Satisfaction Domain, Intercourse Satisfaction Domain, Orgasmic Function Domain, Sexual Desire Domain, and Questions 3 and 4. Once-daily dosing of tadalafil/finasteride also resulted in a statistically significant improvement in all sexually active men with or without ED at Weeks 4, 12, and 26, as measured by the IIEF-EF Domain score, Overall Satisfaction Domain, Intercourse Satisfaction Domain, Orgasmic Function Domain, Sexual Desire Domain, and Questions 3 and 4.
- Tadalafil 5 mg once daily co-administered with finasteride in men with BPH-LUTS was generally well tolerated. The incidence of discontinuations due to AEs was low and not statistically significantly different between treatment groups (tadalafil/finasteride, 1.4%; placebo/finasteride, 2.3%).
- Few serious adverse events (SAEs) were reported (9 [2.6%] in tadalafil-/finasteride-treated subjects and 5 [1.4%] in placebo-/finasteride-treated subjects; the only SAE reported by more than 1 subject was urinary retention, reported by 1 subject in the tadalafil/finasteride group and 1 subject in the placebo/finasteride group. There were 3 deaths during the study (1 during the placebo lead-in period and 1 in each treatment group during the double-blind treatment period), none of which were determined by the investigator to be related to study drug.
- The incidence of TEAEs in the tadalafil/finasteride group was numerically higher than placebo/finasteride (tadalafil/finasteride, 31.3%; placebo/finasteride, 27.1%). The majority of TEAEs were mild or moderate in severity. The most commonly reported TEAEs in the tadalafil/finasteride group (incidence ≥2% and occurring more frequently than in the placebo/finasteride group) were back pain and dyspepsia. TEAEs known to be associated with finasteride monotherapy (erectile dysfunction and decreased libido) were few, with only subjects in the placebo/finasteride treatment group reporting libido decreased or loss of libido, and numerically more subjects in the placebo/finasteride group than in the tadalafil/finasteride group reporting ED.
- No clinically adverse changes were observed in laboratory parameters, uroflowmetry assessments, or vital signs in the tadalafil-/finasteride-treated subjects compared to placebo/finasteride.

**Conclusions:** In summary, results from Study LVIW demonstrated that once-daily dosing of tadalafil 5 mg co-administered with finasteride was efficacious in treating BPH-LUTS in men with prostatic enlargement, as assessed by total IPSS score and other key secondary measures related to BPH-LUTS. The efficacy of tadalafil 5 mg in treating BPH, as assessed by IPSS, is consistent with previous findings and was observed as early as 4 weeks of therapy and was maintained through 26 weeks of treatment. Tadalafil was efficacious in improving erectile function in sexually active men, as assessed by IIEF-EF. Tadalafil was also efficacious in treating ED in men with ED at baseline. The safety results are consistent with prior studies of tadalafil in men with BPH and no new safety concerns were identified. Overall, this study supports the combination of finasteride and tadalafil in order to receive early urinary symptom improvement and to improve erectile function.