2. LVIR Synopsis

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Clinical Study Report Synopsis: Study H6D-MC-LVIR

Title of Study: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Tadalafil Once Daily for 8 Weeks on Prostatic Blood Flow and Perfusion Parameters in Men with Signs and Symptoms of Benign Prostatic Hyperplasia	
Number of Investigators: This multicenter study included 8 principal investigators.	
Study Centers: This study was conducted at 8 study centers in 4 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first subject randomized: 04 February 2011 Date of last subject completed study: 23 July 2012	**Phase of Development:** 3

Objectives:

Primary objective: To evaluate the effect of tadalafil 5 mg once daily for 8 weeks compared with placebo on improving prostatic blood perfusion in men with signs and symptoms of benign prostatic hyperplasia (BPH), as measured by arterial resistive index (RI) in the prostate transition zone.

Secondary objectives:

- To evaluate the effect of tadalafil 5 mg once daily for 8 weeks versus placebo on blood flow and perfusion in the prostate as measured by color Doppler ultrasound pixel intensity (CPI) in the prostate transition zone and arterial RI and CPI in the prostate peripheral zone.
- To evaluate the effect of tadalafil 5 mg once daily for 8 weeks versus placebo on blood flow and perfusion parameters in the bladder neck as measured by arterial RI and CPI.
- To evaluate the effect of tadalafil 5 mg once daily for 4 weeks versus placebo on all of the above blood flow and perfusion parameters in the prostate and bladder neck.

Study Design: This randomized, double-blind, placebo-controlled study consisted of 3 periods: Screening/Wash-Out, transrectal ultrasound (TRUS) Assessment, and Treatment Period. Screening included a 4-week wash-out of BPH, overactive bladder, or erectile dysfunction treatments to assess symptoms and uroflowmetry data in the absence of therapy. Subjects were assessed for lower urinary tract symptoms (LUTS) according to the International Prostate Symptom Score (IPSS) and for bladder outlet obstruction (BOO) using uroflowmetry. At the start of the Treatment Period, eligible subjects were randomly assigned in a 1:1 ratio to one of two treatment groups (placebo or tadalafil 5 mg once daily) for 8 weeks.

Number of Subjects:

Planned: 106 (53 per treatment group).
Randomized: 97 (50 placebo, 47 tadalafil 5 mg)
Treated (at least 1 dose): 97 (50 placebo, 47 tadalafil 5 mg)
Completed: 84 subjects (45 placebo, 39 tadalafil 5 mg)

Diagnosis and Main Criteria for Inclusion:

Major inclusion criteria:

- Men ≥45 years of age, with BPH diagnosed >6 months prior to Screening.
- Lower urinary tract symptoms with a total IPSS ≥13 and BOO as defined by a urinary peak 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).
- Agree not to use any other approved or experimental pharmacologic BPH, overactive bladder, or ED treatments, including alpha blockers, 5-alpha reductase inhibitors (5-ARIs), antimuscarinics, phosphodiesterase type 5 (PDE5) inhibitors, or herbal preparations at any time during the study.

Major exclusion criteria:

- Prostate specific antigen (PSA) >10.0 ng/mL at Screening or PSA ≥4.0 to ≤10.0 ng/mL at Screening if prostate malignancy had not been ruled out to the satisfaction of a urologist.
- History of lower urinary tract malignancy or trauma, or clinical evidence of prostate cancer; evidence or medical history of Mullerian duct cysts, atonic, decompensated, or hypocontractile bladder; detrusor-sphincter dyssynergia; intravesical obstruction; interstitial cystitis; clinical evidence of urinary tract infection or inflammation, or current antibiotic therapy for urinary tract infection; current neurologic disease or condition associated with neurogenic bladder; clinically significant microscopic hematuria; history of prostate saturation biopsy; history of significant renal insufficiency.
- Current treatment with nitrates, androgens, antiandrogens, estrogens, luteinizing hormone-releasing hormone agonists/antagonists, anabolic steroids, or non-prescription products containing estrogenic or androgenic supplements, potent cytochrome P450 3A4 (CYP3A4) inhibitors, CYP3A4 inducer rifampicin; previously received pharmacological treatment for BPH-LUTS (alpha-blockers or 5-alpha reductase inhibitors) and failed to have a clinical response, or concomitant systemic dosing with CYP3A4 inhibitors.
- History of vision loss due to nonarteritic anterior ischemic optic neuropathy (NAION), only for those countries where this contraindication was in effect.

Test Product/Study Drug, Dose, and Mode of Administration:

Study Period	Blind	Dose	Dose Form	Frequency	Duration (weeks)
Wash out	—	—			4
Treatment	Double-Blind	—	Tablet	Once daily	8
		5 mg	Tablet	Once daily	8

Variables:

Efficacy: The primary endpoint was the change from Baseline to Week 8 in prostatic transitional zone RI. Changes in CPI and color pixel density (CPD) in the prostate transition zone, and change in centrally-read RI, CPI, and CPD in the prostate peripheral zone and bladder neck, were secondary endpoints.

Safety: Adverse events and vital signs.

Evaluation Methods:

Efficacy: The primary analysis was based on the change from baseline in the centrally-read prostate transitional zone RI after 8 weeks of once-daily therapy with either tadalafil 5 mg or placebo, using Primary Analysis Population. The primary test for difference between treatments at Week 8 was conducted using a mixed-model repeated-measures (MMRM) analysis. The MMRM model used to analyze the primary efficacy endpoint included fixed effects for treatment, region, visit (Week 4 and Week 8) and treatment-by-visit interaction, baseline as a covariate, a random effect of subject within treatment, and an unstructured covariance matrix. All secondary efficacy parameters were summarized using descriptive statistics. All derivations of RI, CPI, and CPD used centrally-read data. As a supportive analysis, prostate transitional zone RI at Week 8 was analyzed using the MMRM methodology with Per Protocol Population data. Changes from baseline in the secondary efficacy parameters were analyzed separately using the MMRM methodology, with Modified Intent-to-Treat Population data.

Safety: The subject incidence of treatment-emergent adverse events (TEAEs) in the double-blind treatment period was summarized in the Safety Population by treatment group, as well as for all subjects. Differences between tadalafil 5mg and placebo in the proportion of subjects experiencing at least 1 TEAE were compared using Fisher's exact test. For all randomized subjects, the change from baseline to each visit and to endpoint (last observation carried forward) for each vital sign was summarized. Treatment group differences were assessed separately for each visit and endpoint using a ranked ANOVA model with a term for treatment group.

Summary:

- The mean age of the 97 subjects randomized to study drug was 60.2 years and a majority (70.5%) of the subjects had severe BPH-LUTS (total IPSS ≥20) at baseline. Approximately 12% had received previous alpha-blocker therapy and approximately 10% had received some other previous therapy for BPH-LUTS. The majority of subjects (63.9%) reported ED at baseline.
- Tadalafil 5 mg did not have any effect compared with placebo on the primary endpoint LS mean change from baseline to Week 8 in prostate transition zone RI. There also was no effect of tadalafil 5 mg compared with placebo on the primary efficacy measure at 4 weeks, nor on any of the other secondary measures of prostate perfusion, including RI in the prostate peripheral zone or bladder neck, and CPI or CPD in the prostate transition zone, prostate peripheral zone, or bladder neck. For all measurements at each anatomical location, changes from baseline at 4 weeks and 8 weeks were small in both treatment groups; most of the changes in RI were within +/–0.02 of the baseline value.
- The mean transition zone RI values at baseline (placebo, 0.63; tadalafil, 0.65) were lower than expected based on prior studies in men with BPH-LUTS (range of prostatic RI values = 0.70 to 0.80).
- A total of 10 (21.3%) tadalafil-treated subjects reported experiencing ≥1 TEAE compared to 4 (8.0%) placebo-treated subjects; this difference was not statistically significant (p=.084). The most frequent AE in tadalafil-treated subjects was headache, and was the only TEAE reported by more than 1 subject. Headache, known to be associated with tadalafil treatment, was the AE most commonly assessed by the principal investigator as treatment-related in the tadalafil group; others were abdominal pain upper, dyspepsia, and gastric disorder, each reported by 1 subject. Four (4) tadalafil-treated subjects discontinued the study due to AEs: 2 subjects due to headache; 1 subject due to abdominal pain; and 1 subject due to gastric disorder.

Conclusions:

- Once daily treatment of men with BPH-LUTS with tadalafil 5 mg compared with placebo for 8 weeks did not result in a change in prostate or bladder neck blood flow that were detectable by changes in either the RI or the CPI as measured in the study.
- The AE profile of tadalafil 5 mg once daily was consistent with previous studies in men with BPH-LUTS, and there were no new safety findings.