
Tadalafil Relieves Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

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Purpose: We assessed the efficacy and safety of tadalafil dosed once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia.

Materials and Methods: Following a 4-week, single-blind, placebo run-in 281 men were randomly assigned (1:1) to 5 mg tadalafil for 6 weeks, followed by dose escalation to 20 mg for 6 weeks or 12 weeks of placebo.

Results: Tadalafil significantly improved the mean change from baseline in International Prostate Symptom Score at 6 weeks (5 mg tadalafil -2.8 vs placebo -1.2) and at 12 weeks (5/20 mg tadalafil -3.8 vs placebo -1.7). Larger changes were observed with inclusion of the placebo run-in at 12 weeks (5/20 mg tadalafil -7.1 vs placebo -4.5). Significant improvements were also seen in the International Prostate Symptom Score irritative and obstructive domains, the International Prostate Symptom Score quality of life index, a question about urinary symptom improvement and the Benign Prostatic Hyperplasia Impact Index (significant at 12 weeks) vs placebo. International Prostate Symptom Score and International Index of Erectile Function erectile function domain scores significantly improved in the 56% of men with lower urinary tract symptoms/benign prostatic hyperplasia who were sexually active and had erectile dysfunction. Changes in uroflowmetry parameters were similar in the placebo and tadalafil groups. Commonly reported (2% or greater) treatment emergent adverse events were "erection increased," dyspepsia, back pain, headache, nasopharyngitis and upper respiratory tract infection (each 5.1% or less). No change in post-void residual volume was seen with tadalafil treatment.

Conclusions: Tadalafil once daily was well tolerated and demonstrated clinically meaningful and statistically significant symptomatic improvement for lower urinary tract symptoms/benign prostatic hyperplasia. Tadalafil also improved erectile function in men with lower urinary tract symptoms and erectile dysfunction.

Key Words: prostate, urination disorders, prostatic hyperplasia, impotence, tadalafil

Lower urinary tract symptoms secondary to BPH include increased urinary frequency, urgency, hesitancy, nocturia, incomplete emptying and a weak urinary stream.¹ An estimate of LUTS prevalence is that it occurs in greater than 50% of men 50 years old or older.² Treatment with α -ad-

renergic receptor antagonists (α -blockers) is recommended for symptomatic patients. Combined therapy with an α -blocker and a 5 α -reductase inhibitor is recommended when symptoms are accompanied by benign prostate enlargement.³

Tadalafil is a PDE5 inhibitor that effectively treats ED.⁴ The half-life of tadalafil is 17.5 hours with steady-state plasma concentrations achieved after 5 days of once daily dosing.⁵ PDE5 inhibition leads to increased cGMP, which is a second messenger in certain cellular signaling pathways.⁶ PDE5 inhibition partially reversed prostatic tissue strip contraction, supporting a role for cGMP in prostatic smooth muscle tension.⁷ Increasing cGMP also had an antiproliferative effect on cultured human prostatic smooth muscle cells.⁸ Several reports described LUTS improvement in patients undergoing ED treatment with PDE5 inhibitors.⁹⁻¹⁰ In this clinical trial we assessed the efficacy and safety of tadalafil dosed once daily to treat patients with LUTS secondary to BPH.

MATERIALS AND METHODS

Study Design

This double-blind, placebo controlled, randomized, parallel arm, phase 2 study was performed at 21 centers in the

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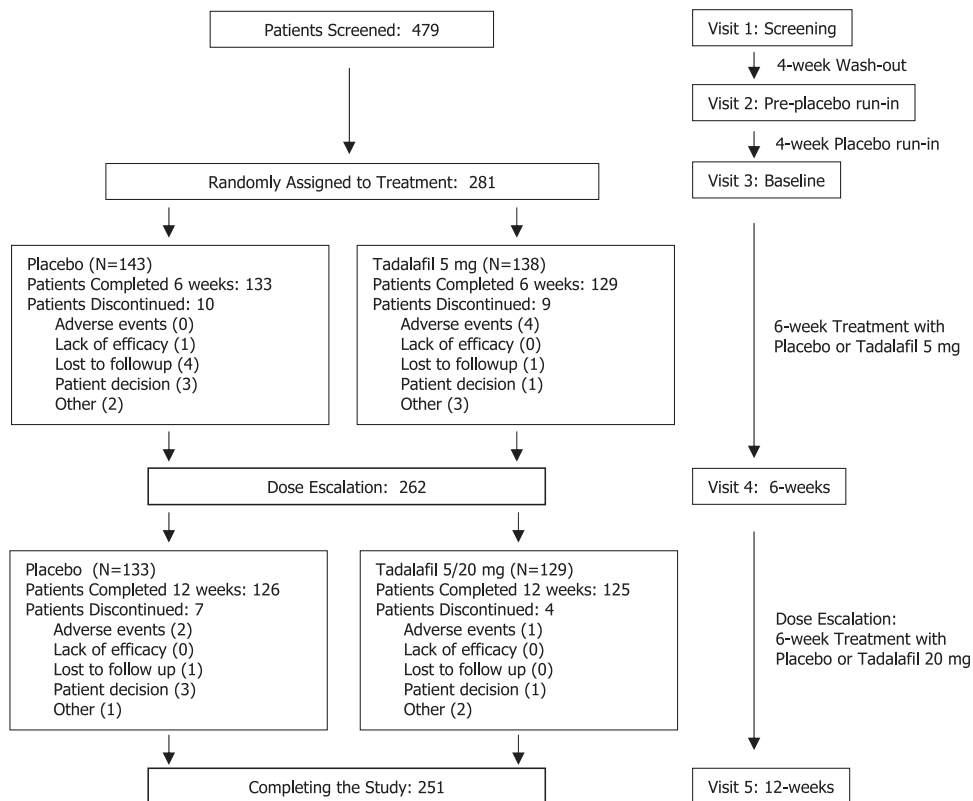


FIG. 1. Patient disposition and study design

United States from November 2004 to July 2005. Following a screening visit (visit 1) patients using other BPH treatments, including α -blockers, anticholinergics, sympathomimetic medications, antihistamines and herbal preparations, or PDE5 inhibitors underwent a 4-week treatment-free washout period (fig. 1). At visit 2 an I-PSS of 13 or greater and a Qmax of 4 to 15 ml per second on a voided volume of 125 ml or greater were required for study continuation. Eligible patients entered a 4-week single-blind run-in period with placebo dosed once daily. At visit 3 (baseline) patients demonstrating treatment compliance during the placebo run-in (70% or greater of doses administered) remained eligible. After stratification by baseline LUTS severity (moderate—I-PSS less than 20 and severe—I-PSS 20 or greater) and prior α -blocker therapy patients were randomly assigned in geographic regions to 6 weeks of once daily dosing with 5 mg tadalafil, followed by dose escalation to 20 mg tadalafil for an additional 6 weeks (total 12 weeks of treatment) or to 12 weeks of treatment with placebo (1:1 tadalafil-to-placebo ratio). Visit 4 was after 6 weeks of treatment and visit 5 was after 12 weeks (study end).

Patients were instructed to ingest study medication at the same time every day without regard to meal timing. Dosing compliance was monitored at visits 3 to 5.

I-PSS (questions 1 to 7), I-PSS QOL index (question 8, “If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?”) and BII were administered at visits 2 to 5.^{3,11,12} The IIEF questionnaire was administered at visits 2 to 5 to patients answering yes at visit 2 to the question, “Are you sexually active with a female partner and expect to remain so for the duration of the study?”¹³ A LUTS GAQ (“Has the

treatment you have been taking since your last visit improved your urinary symptoms?”) was asked at visits 3 to 5. PVR and the uroflowmetry parameters Qmax, Qave and Vcomp were recorded at visits 2 to 5. Automated readings were used for analyses. PVR was measured immediately after voiding using a portable ultrasound device. Uroflowmetry parameters were recorded using a standard calibrated flowmeter with patients standing to void.

The clinical study was performed in accordance with the Declaration of Helsinki. Institutional review boards approved the study protocol for each site and patients provided written informed consent.

Study Population

Men 45 years old or older with a history of LUTS secondary to BPH of 6 months or longer were eligible for this study. Patients agreed not to use other BPH medications during the study.

Study exclusion criteria were PSA more than 10 ng/ml (for men with PSA 4 to 10 ng/ml a recent prostate biopsy negative for malignancy was required); recent finasteride (prior 3 months) or dutasteride (prior 12 months) treatment; history of radical prostatectomy or other pelvic surgery; neurological condition affecting bladder function; recent lower urinary tract instrumentation, urinary retention or bladder stones; history of urethral obstruction due to stricture, valves, sclerosis or tumor; detrusor-sphincter dyssynergia; urinary tract inflammation or infection; intravesical obstruction secondary to the prostate median lobe; prostate cancer; PVR 200 ml or greater at visit 2; certain cardiovascular diseases, for example unstable angina, recent myocar-

dial infarction or poorly controlled blood pressure; clinically significant renal or hepatic insufficiency; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens or a potent cytochrome P450 3A4 inhibitor; or uncontrolled diabetes (glycosylated HbA_{1c} greater than 9%).

Efficacy Measures

Primary efficacy end points were I-PSS change from baseline (visit 3) to 6 and 12 weeks. Secondary efficacy end points were change from baseline to 6 and 12 weeks in I-PSS irritative domain (questions 2, 4 and 7), I-PSS obstructive domain (questions 1, 3, 5 and 6), I-PSS QOL index, BII, LUTS GAQ, Qmax, Qave and Vcomp. Post-hoc analyses were done to examine changes at 6 and 12 weeks vs visit 2, before the placebo run-in.

In sexually active patients EF was assessed using the IIEF EF domain (questions 1 to 5 and 15).¹³ Scores are presented for the patient subset that was sexually active and had ED with ED assessed by the investigator at visit 1. Post-hoc analyses were done to examine I-PSS in this patient subset.

Safety

Medical history was obtained and electrocardiogram was done at study entry. Physical examinations were performed at study entry and week 12 or study discontinuation. Safety was assessed by monitoring the incidence of patient reported adverse events and changes in clinical laboratory values (including PSA), PVR and vital signs. TEAEs were coded with Medical Dictionary for Regulatory Activities, version 8.0 preferred terms.

Statistical Analyses

The primary analysis population for efficacy included all randomly assigned patients with baseline and 1 or more post-baseline measurements. Analyses of 12-week data used the last observation carried forward convention. Safety analyses included all randomly assigned patients. Analyses of uroflowmetry values included all measurements collected on voided volumes of 112 ml or greater (required volume 125 ml minus 10% variance based on manufacturer specifications). The study was designed to provide 80% power to detect a difference of 2.0 for change in I-PSS, assuming an SD of 6.0 and a 1-sided α of 0.05. The purpose of this study was to establish proof of principle in anticipation of subsequent larger and more definitive trials. As such, this protocol prespecified the use of 1-sided tests of significance for evaluating the efficacy end points. No adjustments were made for multiple comparisons.

Visit 3 (post-placebo run-in) values were defined as baseline. Change from baseline for I-PSS end points, BII and uroflowmetry measurements were analyzed as continuous variables using ANCOVA models with terms for baseline I-PSS, previous α -blocker therapy, treatment group (tadalafil or placebo), geographic region and baseline by treatment group interaction (if significant, $p < 0.1$). Similar models were used for IIEF EF domain scores except the baseline term was the IIEF EF domain score. Pairwise comparisons of tadalafil vs placebo were based on LS mean estimates. For LUTS GAQ logistic regression

TABLE 1. Patient characteristics

	Placebo	Tadalafil
No. pts randomly assigned	143	138
Mean age (range)	61 (45.0–82.3)	62 (45.1–82.4)
No. older than 65 (%)	44 (30.8)	48 (34.8)
No. ethnicity/race (%):		
Black	12 (8.4)	15 (10.9)
White	119 (83.2)	109 (79.0)
Hispanic	10 (7.0)	9 (6.5)
Other	2 (1.4)	5 (3.6)
No. previous α -blocker use (%)	36 (25.2)	31 (22.5)
No. LUTS severity at baseline visit 3 (%):		
Moderate (I-PSS less than 20)	89 (62.2)	90 (65.2)
Severe (I-PSS 20 or greater)	54 (37.8)	48 (34.8)
No. sexually active (%)	121 (84.6)	107 (77.5)
No. ED (%) [*]	84 (59.2)	99 (71.7)
No. sexually active with ED (%)	76 (53.1)	80 (58.0)
No. ED 1 yr or greater (%)	74 (52.1)	85 (61.6) [†]

^{*} Identified at visit 1 based on patient medical history.

[†] Two patients had ED less than 3 months in duration.

models with terms for baseline I-PSS, previous α -blocker therapy, treatment group and geographic region were used. As specified in the study protocol, 1-sided p values are reported for efficacy end points. Statistical analyses used SAS®, version 9.13SP3.

RESULTS

Patient Characteristics

Of 479 patients screened for this study 281 were randomly assigned to treatment (fig. 1). The overall study completion rate was 89.3%. Of 281 men entering the first 6-week treatment period 93.2% completed and of 262 entering the second treatment period 95.8% completed. The most common reason for discontinuation in the tadalafil group was an adverse event (5 men or 3.6%) and in the placebo group it was patient decision (6 or 4.2%).

Baseline (visit 3) characteristics were generally well balanced between treatment groups (table 1). Mean patient age was 62 years, 24% of patients reported previous α -blocker therapy and 81% were sexually active. Mean baseline I-PSS (post-placebo run-in) was 17.9 (range 4 to 34) and mean Qmax was 11.5 ml per second (range 3 to 53). Dose compliance data were collected on 97% of the patients and all were compliant (70% or greater of doses ingested during the treatment period). The mean number of doses weekly was 6.9 for each treatment group.

Efficacy

Tadalafil significantly improved the I-PSS change from baseline at 6 and 12 weeks compared with placebo. Treatment effects (difference between change from baseline I-PSS for tadalafil and placebo) were 1.7 (95% CI 0.5, 2.9) at 6 weeks and 2.1 (95% CI 0.9, 3.3) at 12 weeks ($p = 0.003$ and < 0.001 , respectively, table 2). The proportion of patients with an I-PSS change from baseline of 3 points or greater (responder analysis) was greater in the tadalafil group than in the placebo group at 6 weeks (49.3% vs 36.4%, $p = 0.03$) and at 12 weeks (60.9% vs 42.7%, $p < 0.01$). At 6 and 12 weeks tadalafil also significantly improved the I-PSS change from visit 2 compared with placebo (each $p < 0.001$, table 2). As expected, the change

TABLE 2. Efficacy variables I-PSS, I-PSS QOL, LUTS GAQ and BII

	Mean ± SE Placebo, 6 Wks	Mean ± SE 5 mg Tadalafil, 6 Wks	p Value (ANCOVA 1-sided)	Mean ± SE Placebo, 12 Wks	Mean ± SE 5/20 mg Tadalafil, 12 Wks	p Value (ANCOVA 1-sided)
<i>No. randomly assigned pts</i>						
I-PSS:*,†,‡	143	138		143	138	
Visit 3 (baseline)	18.5	17.4		18.3	17.5	
End point	17.0	14.5		16.1	13.3	
Change visit 3–end point (LS)	-1.2 ± 0.5	-2.8 ± 0.5	0.003	-1.7 ± 0.5	-3.8 ± 0.5	<0.001
Change visit 2–end point (LS)	-3.9 ± 0.6	-6.2 ± 0.6	<0.001	-4.5 ± 0.6	-7.1 ± 0.6	<0.001
I-PSS obstructive domain:*,†,‡						
Change visit 3–end point (LS)	-0.8 ± 0.3	-1.7 ± 0.3	0.01	-1.0 ± 0.3	-2.2 ± 0.3	0.003
Change visit 2–end point (LS)	-2.5 ± 0.4	-4.0 ± 0.4	0.001	-2.8 ± 0.4	-4.4 ± 0.4	<0.001
I-PSS irritative domain:*,†,‡						
Change visit 3–end point (LS)	-0.4 ± 0.2	-1.1 ± 0.2	0.003	-0.7 ± 0.3	-1.7 ± 0.3	0.002
Change visit 2–end point (LS)	-1.4 ± 0.3	-2.2 ± 0.3	0.01	-1.8 ± 0.3	-2.7 ± 0.3	0.005
I-PSS QOL index:*,†,‡						
Visit 3 (baseline)	3.8	3.6		3.8	3.6	
End point	3.5	3.1		3.3	2.8	
Change visit 3–end point (LS)	-0.2 ± 0.1	-0.5 ± 0.1	0.017	-0.3 ± 0.1	-0.7 ± 0.1	0.008
Change visit 2–end point (LS)	-0.5 ± 0.1	-0.9 ± 0.1	0.007	-0.7 ± 0.1	-1.1 ± 0.1	0.004
% LUTS GAQ, yes, end point*	32.6	55.9	<0.001	37.7	57.4	<0.001
BII:*,†,‡						
Visit 3 (baseline)	5.2	5.2		5.2	5.1	
End point	4.7	4.3		4.5	3.6	
Change visit 3–end point (LS)	-0.4 ± 0.2	-0.7 ± 0.2	0.107	-0.6 ± 0.2	-1.3 ± 0.2	0.008
Change visit 2–end point (LS)	-1.6 ± 0.2	-1.6 ± 0.3	0.507	-1.8 ± 0.3	-2.2 ± 0.3	0.091
<i>No. sexually active LUTS + ED</i>						
I-PSS:*,†	76	80		76	80	
Change visit 3–end point (LS)	-0.7 ± 0.7	-3.2 ± 0.7	0.001	-1.8 ± 0.7	-4.4 ± 0.7	0.001
Change visit 2–end point (LS)	-3.0 ± 0.8	-6.5 ± 0.7	<0.001	-4.2 ± 0.8	-7.6 ± 0.8	<0.001
IIIEF EF domain score:*,†,‡						
Visit 3 (baseline)	13.7	14.3		13.7	14.3	
Change visit 3–end point (LS)	0.6 ± 0.9	6.0 ± 0.9	<0.001	1.4 ± 1.0	7.7 ± 0.9	<0.001
Change visit 2–end point (LS)	0.7 ± 1.1	6.7 ± 1.0	<0.001	1.6 ± 1.1	8.4 ± 1.1	<0.001

* Number of patients with baseline and post-baseline data I-PSS 136, 135, 138 and 136 for visit 3, end point and visit 3–end point; 135, 135, 137 and 136 for visit 2–end point; I-PSS obstructive 136, 135, 138 and 136; I-PSS irritative 138, 136, 138 and 136 for visit 3–end point; 137, 136, 137 and 136 for visit 2–end point; LUTS GAQ, I-PSS QOL 138, 136, 138 and 136; BII 137, 130, 138 and 133 for visit 3, end point, visit 3–end point; and 137, 133, 138 and 136 for visit 2–end point; and for subset with LUTS/BPH who were sexually active with ED I-PSS 73, 80, 74 and 80 for visit 3–end point; 72, 80, 73 and 80 for visit 2–end point; IIIEF EF domain 74, 78, 74 and 78 for visit 3, visit 3–end point; and 74, 77, 74 and 77 for visit 2–end point, respectively.

† Decrease corresponds to improvement in I-PSS (possible score 0 to 35), I-PSS obstructive domain (possible score 0 to 20), I-PSS irritative domain (possible score 0 to 15), I-PSS QOL (possible score 0 to 6) and BII (possible score 0 to 13), and increase corresponds to improvement in IIIEF EF domain (possible score 1 to 30) and LUTS GAQ (possible score 0% to 100%).

‡ Visit 2—pre-placebo run-in, visit 3—baseline, end point—visit 4 (6 weeks) and visit 5 (12 weeks).

in I-PSS for the tadalafil and placebo groups was larger when measured from visit 2 due to the inclusion of the placebo run-in and treatment periods (table 2 and fig. 2).

Tadalafil also significantly improved responses on most secondary efficacy measures compared with placebo (table 2). They included I-PSS irritative and obstructive domains, and I-PSS QOL index, measured as the change from baseline (visit 3) at 6 and 12 weeks. There was a numerical decrease (improvement) in BII at 6 weeks, which attained statistical significance at 12 weeks. Mean changes in these secondary efficacy variables from visit 2 (pre-placebo run-in) were larger but consistent with those measured from baseline (visit 3) (table 2). The proportion of patients answering yes to LUTS GAQ at 6 and 12 weeks was significantly greater in the tadalafil than in the placebo group (table 2).

Numerical improvements were observed in the tadalafil and placebo groups at 6 and 12 weeks compared with baseline for the uroflowmetry parameters Qmax, Qave and Vcomp (table 3). However, the differences were not significant when comparing tadalafil with placebo. Including the placebo run-in period provided consistent results, in that improvements from baseline were larger, but again they did not differ significantly between the tadalafil and placebo groups.

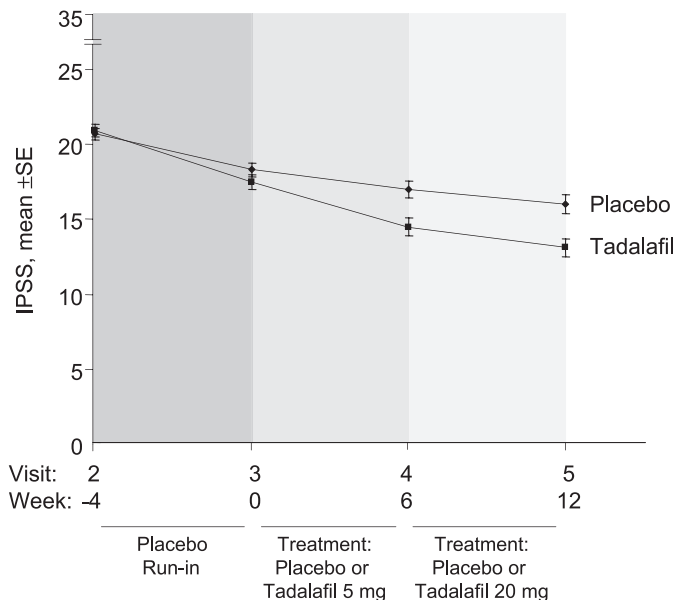


FIG. 2. Mean I-PSS (IPSS) for tadalafil and placebo. For each visit mean ± SE I-PSS was summarized for all randomly assigned patients with I-PSS data for that visit. Number of patients in placebo group at visits 2 to 5 was 141, 143, 136 and 130, while for tadalafil group it was 138, 138, 135 and 127, respectively. Possible I-PSS range was 0 to 35.

TABLE 3. Uroflowmetry parameters Qmax, Qave and Vcomp, and PVR

	Mean ± SE Placebo, 6 Wks	Mean ± SE 5 mg Tadalafil, 6 Wks	p Value (ANCOVA 1-sided)	Mean ± SE Placebo, 12 Wks	Mean ± SE 5/20 mg Tadalafil, 12 Wks	p Value (ANCOVA 1-sided)
Qmax (ml/sec):*,†						
Visit 3 (baseline)	11.2	11.7		11.1	11.8	
End point	11.8	12.2		12.1	12.3	
Change visit 3–end point (LS)	1.0 ± 0.6	1.1 ± 0.6	0.46	0.9 ± 0.5	0.5 ± 0.5	0.72
Change visit 2–end point (LS)	2.2 ± 0.4	2.2 ± 0.5	0.49	2.3 ± 0.5	1.7 ± 0.5	0.81
Qave (ml/sec):*,†						
Visit 3 (baseline)	6.2	6.3		6.1	6.3	
End point	6.4	6.8		6.5	6.5	
Change visit 3–end point (LS)	0.2 ± 0.3	0.7 ± 0.3	0.10	0.3 ± 0.3	0.2 ± 0.3	0.66
Change visit 2–end point (LS)	0.9 ± 0.3	1.2 ± 0.3	0.15	1.1 ± 0.3	0.9 ± 0.3	0.79
Vcomp (ml):*,†						
Visit 3 (baseline), mean	235	246		231	246.6	
End point	238.5	270.3		253.1	256.8	
Change visit 3–end point (LS)	11.0 ± 11.7	34.8 ± 11.9	0.06	24.8 ± 13.1	14.9 ± 13.3	0.72
Change visit 2–end point (LS)	10.9 ± 10.7	37.7 ± 11.1	0.03	23.1 ± 11.7	24.7 ± 12.1	0.46
PVR (ml):‡,§						
Visit 3 (baseline)	58.5	58.0		58.2	58.0	
End point	53.8	57.2		54.2	57.9	
Change visit 3–end point (LS)	0.1 ± 6.7	3.6 ± 7.0	0.66	−2.6 ± 6.2	1.4 ± 6.5	0.69
Change visit 2–end point (LS)	0.4 ± 5.8	1.3 ± 6.1	0.54	−2.5 ± 5.5	−1.2 ± 5.7	0.57

* Number of patients with baseline and post-baseline data 111, 110, 121, 116 for visit 3, end point and visit 3–end point; and 121, 122, 132 and 128 for visit 2–end point (includes all uroflow measurements on voided volumes 112 ml or greater).

† Visit 2—pre-placebo run-in, visit 3—baseline, end point—visit 4 (6 weeks) and visit 5 (12 weeks).

‡ Patients with baseline and post-baseline data 135, 132, 136 and 132 for visit 3, end point and visit 3–end point; and 136, 132, 137 and 132 for visit 2–end point.

Of the 281 men with LUTS in this study 156 (56%) were sexually active and had ED. In this subset of patients tadalafil significantly improved I-PSS and IIEF EF domain scores compared with placebo (table 2). Correlations between change from baseline in IIEF EF domain score and in I-PSS were not statistically significant for this subset of patients after treatment with tadalafil. Pearson correlation coefficients (2-sided p values) at 6 weeks were −0.329 (placebo p = 0.005) and −0.184 (5 mg tadalafil p = 0.106), and at 12 weeks they were −0.146 (placebo p = 0.214) and −0.145 (5/20 mg tadalafil p = 0.205).

Safety

The proportion of patients discontinuing due to TEAEs was 3.6% in the tadalafil group (4 at weeks 0 to 6 and 1 at weeks 6 to 12) and 1.4% in the placebo group (2) (fig. 1). Table 4 lists TEAEs with a frequency of 2% or greater. The most common TEAEs were “erection increased,” dyspepsia, back pain and headache. All reports of “erection increased” were from 1 study site, reported in response to specific questioning by the investigator and described as secondary to sexual stimulation. There were no reports of

priapism and no patient discontinued due to “erection increased.” There was only 1 serious adverse event, which occurred in the placebo group, and no deaths were reported. There were no clinically relevant changes in vital signs, laboratory values (including mean PSA) or mean PVR and no reports of acute urinary retention (table 3).

DISCUSSION

Tadalafil once daily improved LUTS secondary to BPH, as demonstrated by significant improvement in I-PSS compared with placebo. Improvement was observed after treatment for 6 weeks with 5 mg tadalafil and after treatment for an additional 6 weeks with 20 mg tadalafil.

The magnitude of I-PSS improvement observed with tadalafil was comparable to results reported in α -blocker studies. For 5/20 mg tadalafil the LS mean change in I-PSS from baseline to 12 weeks was −3.8 compared with −1.7 for placebo. Using an alfuzosin study as a comparator, the mean change in I-PSS at 12 weeks was −3.6 for 10 mg alfuzosin and −3.4 for 15 mg alfuzosin compared with −1.6 for placebo.¹⁴ Although the magnitude of the I-PSS

TABLE 4. TEAEs and serious adverse events

	No. Placebo, 6 Wks (%)	No. 5 mg Tadalafil, 6 Wks (%)	No. Cumulative Placebo, 12 Wks (%)	No. Cumulative 5/20 mg Tadalafil, 12 Wks (%)
Randomly assigned pts	143	138	143	138
TEAE*				
Erection increased	2 (1.4)	5 (3.6)	2 (1.4)	7 (5.1)
Dyspepsia	0	3 (2.2)	0	6 (4.3)
Back pain	0	3 (2.2)	2 (1.4)	5 (3.6)
Headache	1 (0.7)	3 (2.2)	1 (0.7)	4 (2.9)
Nasopharyngitis	0	2 (1.4)	0	3 (2.2)
Upper respiratory tract infection	1 (0.7)	2 (1.4)	1 (0.7)	3 (2.2)
Serious adverse events	0	0	1 (0.7)	0

* In any treatment group 2% or greater.

change reported in individual α -blocker studies varies with therapy and study design, the tadalafil response observed in this study at 12 weeks is comparable with the 2 to 2.5 point improvement in symptom score compared with placebo observed in the American Urological Association meta-analysis of α -blocker efficacy.³ A 3-point improvement in I-PSS (not placebo corrected) was suggested as the minimum perceived by patients. Thus, the 3.8 point improvement from baseline observed for 5/20 mg tadalafil at 12 weeks should translate into symptomatic benefit.¹⁵

Improvement in I-PSS was also reported following treatment with another PDE5 inhibitor, sildenafil citrate (sildenafil).¹⁶ The sildenafil study used an ED study design that also collected BPH secondary end points, including the change in I-PSS. ED was required for study entry and the study did not use a placebo run-in period. Given the differences in study design, any comparisons must be interpreted with caution. An improvement in I-PSS (LS mean change) of 6.3 was reported in sildenafil treated patients vs 1.9 in placebo treated patients. In the current study a comparable improvement in I-PSS of 7.1 (LS mean change) was observed for tadalafil treatment from visit 2 (pre-placebo run-in) to week 12 vs 4.5 for placebo.

I-PSS QOL, BII and LUTS GAQ measure patient QOL related to LUTS/BPH and they were significantly improved after 12 weeks treatment with 5/20 mg tadalafil. Comparing responses to these quality of life measures after tadalafil and after other LUTS/BPH therapies is difficult because patient perception of improvement depends on a number of factors, including their baseline scores.¹⁷ However, the relative 2-fold improvement at 12 weeks in I-PSS QOL and BII in this study was similar to that reported in a meta-analysis of α -blocker therapy for LUTS.³

For I-PSS QOL, BII and LUTS GAQ the responses at 12 weeks (5/20 mg tadalafil) were numerically greater than the responses at 6 weeks (5 mg tadalafil). Since this was a dose escalation study, it cannot be determined whether this improvement was due to the longer dosing period (12 vs 6 weeks) and/or the increase in tadalafil dose (20 vs 5 mg). A parallel arm, dose ranging study is under way to address this question.

In this study tadalafil treatment did not improve uroflowmetry measures compared with placebo. No differences in Qmax, Qave or Vcomp were detected after 6 or 12 weeks of treatment with tadalafil compared with placebo. Currently approved therapies, including α -blockers, generally demonstrate modest improvements in uroflowmetry parameters.³ The lack of improvement in Qmax following tadalafil treatment was unexpected but it was also recently reported for sildenafil and it may indicate a new mechanism of action.¹⁶ Potential mechanisms of action underlying improved LUTS with chronic PDE5 inhibitor therapy include prostatic smooth muscle relaxation, anti-proliferative effects, improved pelvic blood flow and an effect on afferent sensory nerve signaling from the prostate or bladder.^{7,8,18,19}

The relationship between LUTS and ED has received increased attention recently because the 2 diseases are prevalent, frequently co-associate in aging men and impact quality of life. New data have emerged to indicate potential links in epidemiological, pathophysiological and treatment aspects of these 2 diseases.²⁰ In the current study tadalafil

therapy for sexually active men with LUTS/BPH plus ED resulted in marked improvement in EF (IIEF EF domain scores), in addition to improving LUTS (I-PSS). However, it is unlikely that LUTS relief was simply a psychological benefit accruing collaterally to ED relief because changes in I-PSS and IIEF EF domain scores did not correlate significantly following tadalafil treatment.

CONCLUSIONS

Tadalafil resulted in statistically significant and clinically relevant improvement in LUTS secondary to BPH. Improvement was observed in obstructive and irritative symptoms, and in QOL assessments. There was no improvement observed in uroflowmetry parameters. In the subset of patients with LUTS who were sexually active and had ED tadalafil significantly improved EF as well as LUTS. Tadalafil was well tolerated. Further evaluation of tadalafil dosed once daily for the treatment of men with LUTS secondary to BPH is warranted.

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APPENDIX

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Abbreviations and Acronyms

BII	=	BPH Impact Index
BPH	=	benign prostatic hyperplasia
cGMP	=	cyclic guanosine monophosphate
ED	=	erectile dysfunction
EF	=	erectile function
GAQ	=	general assessment question
IIEF	=	International Index of EF
IPSS	=	International Prostate Symptom Score
LS	=	least squares
LUTS	=	lower urinary tract symptoms
PDE5	=	phosphodiesterase 5
PSA	=	prostate specific antigen
PVR	=	post-void residual volume
Qave	=	average flow rate
Qmax	=	maximal flow rate
QOL	=	quality of life
TEAE	=	treatment emergent adverse events
Vcomp	=	voided volume

REFERENCES

1. Wei JT, Calhoun E and Jacobsen SJ: Urologic diseases in America project: benign prostatic hyperplasia. *J Urol* 2005; **173**: 1256.
2. Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E et al: Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). *Eur Urol* 2003; **44**: 637.

3. American Urological Association (AUA) Clinical guideline on the management of benign prostatic hyperplasia (BPH). Available at <http://www.auanet.org/guidelines/bph.cfm>. Accessed December 2005.
4. Carson CC, Rajfer J, Eardley I, Carrier S, Denne JS, Walker DJ et al: The efficacy and safety of tadalafil: an update. *BJU Int* 2004; **93**: 1276.
5. Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE et al: Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2005; **61**: 280.
6. Francis SH, Blount MA, Zoraghi R and Corbin JD: Molecular properties of mammalian proteins that interact with cGMP: protein kinases, cation channels, phosphodiesterases, and multi-drug anion transporters. *Front Biosci* 2005; **10**: 2097.
7. Uckert S, Kuthe A, Jonas U and Stief CG: Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. *J Urol* 2001; **166**: 2484.
8. Guh JH, Hwang TL, Ko FN, Chueh SC, Lai MK and Teng CM: Antiproliferative effect in human prostatic smooth muscle cells by nitric oxide donor. *Mol Pharmacol* 1998; **53**: 467.
9. Sairam K, Kulinskaya E, McNicholas TA, Boustead GB and Hanbury DC: Sildenafil influences lower urinary tract symptoms. *BJU Int* 2002; **90**: 836.
10. Hopps CV and Mulhall JP: Novel agents for sexual dysfunction. *BJU Int* 2003; **92**: 534.
11. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK et al: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992; **148**: 1549.
12. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL and Mebust WK: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of the American Urological Association. *Med Care*, suppl., 1995; **33**: AS145.
13. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J and Mishra A: The International Index of Erectile Function (IIEF): a multidimensional scale for the assessment of erectile dysfunction. *Urology* 1997; **49**: 822.
14. Roehrborn CG: Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo-controlled trial. *Urology* 2001; **58**: 953.
15. Barry MJ: Evaluation of symptoms and quality of life in men with benign prostatic hyperplasia. *Urology*, suppl., **58**: 25, 2001.
16. McVary KT, Camps J, Henry GD, Conner SD, Tseng LJ and Van Den Ende G: Sildenafil improves erectile function and urinary symptoms in men with erectile dysfunction and concomitant lower urinary tract symptoms. *J Urol*, suppl., 2006; **175**: 527, abstract 1637.
17. Barry MJ, Williford WO, Chang Y, Machi M, Jones KM, Walker-Corkery E et al: Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol* 1995; **154**: 1770.
18. Pinggera GM, Schuster A, Frauscher F, Herwig R, Rehder P, Bartsch G et al: Increased perfusion in the prostate after administration of PDE-inhibitor sildenafil. *J Urol*, suppl., 2004; **171**: 425, abstract 1612.
19. Yoshimura N, Seki S and De Groat WC: Nitric oxide modulates Ca^{+2} channels in dorsal root ganglion neurons innervating rat urinary bladder. *J Neurophysiol* 2001; **86**: 304.
20. McVary KT: Erectile dysfunction and lower urinary tract symptoms secondary to BPH. *Eur Urol* 2005; **47**: 838.