

Tadalafil Administered Once Daily for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Dose Finding Study

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Purpose: Phosphodiesterase type 5 inhibitors are widely used to treat erectile dysfunction. Preliminary data have suggested phosphodiesterase type 5 inhibitor efficacy in men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia.

Materials and Methods: After a 4-week placebo run-in period 1,058 men with benign prostatic hyperplasia lower urinary tract symptoms were randomly allocated to receive 12-week, once daily treatment with placebo or tadalafil (2.5, 5, 10 or 20 mg).

Results: The International Prostate Symptom Score least squares mean change from baseline to end point was significantly improved for 2.5 (−3.9, $p = 0.015$), 5 (−4.9, $p < 0.001$), 10 (−5.2, $p < 0.001$) and 20 mg (−5.2, $p < 0.001$) tadalafil compared to placebo (−2.3). International Prostate Symptom Score improvements at 4, 8 and 12 weeks were significant for all tadalafil doses and they demonstrated a dose-response relationship. Tadalafil (2.5 mg) significantly improved the International Prostate Symptom Score obstructive subscore and the International Index of Erectile Function-Erectile Function domain, the latter in sexually active men with a history of erectile dysfunction. Statistically significant improvements were noted for 5, 10 and 20 mg tadalafil compared to placebo, as assessed by the International Prostate Symptom Score irritative and obstructive subscores, International Prostate Symptom Score Quality of Life, Benign Prostatic Hyperplasia Impact Index (nonsignificant for 10 mg), Global Assessment Question and International Index of Erectile Function-Erectile Function domain. No statistically significant effect of treatment compared to placebo was noted for peak flow at any tadalafil dose. Treatment emergent adverse events were infrequent in all tadalafil groups.

Conclusions: Once daily tadalafil demonstrated clinically meaningful and statistically significant efficacy and it was well tolerated in men with benign prostatic hyperplasia lower urinary tract symptoms. Of the doses studied 5 mg tadalafil appeared to provide a positive risk-benefit profile.

Key Words: prostate; tadalafil; dose-response relationship, drug; prostatic hyperplasia; questionnaires

Men with signs of BPH may experience LUTS, such as urinary frequency, urgency, intermittence, nocturia, straining, incomplete emptying or a weak urinary stream.¹ LUTS increase with age with an overall prevalence of greater than 50% in men 50 years or older.²⁻⁴ The current standard of care in men with bothersome moderate to severe BPH LUTS is treatment with an α 1-adrenergic blocker (α -blocker) or in men with an enlarged prostate a 5 α -reductase inhibitor.⁵ Although they are effective, each of these drug classes can produce unwanted side effects, including dizziness, hypotension and sexual dysfunction. These side effects may be exacerbated by combination therapy.⁶

Since reports of ED incidence, pathophysiology and treatment have shown a possible link between BPH LUTS and ED,⁷ PDE5 inhibitors have received increased attention for treating BPH LUTS. Tadalafil (Cialis®) is a PDE5 inhibitor that is currently only approved for ED. The half-life of tadalafil is 17.5 hours,⁸ making it suitable as once daily therapy.

Although the precise mechanism of action by which PDE5 inhibitors may alleviate LUTS is not completely understood, several putative mechanisms are currently under investigation. One mechanism focuses on the accumulation of intracellular prostatic and bladder smooth muscle cyclic guanosine monophosphate following PDE5 inhibition, which may decrease tension in the smooth muscle of the prostatic stroma and capsule. This muscle relaxation results in bladder neck opening and improved voiding function,⁹ and it decreases detrusor muscle overactivity in the bladder body and neck.^{10,11} Another possible mechanism involves pelvic arterial insufficiency and ischemia, which may compromise normal bladder detrusor function and cause a change in the prostatic structure.^{12,13} Increased vascular perfusion of the lower urinary tract, especially the prostatic or bladder neck,

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could result in a beneficial therapeutic effect and decrease LUTS.^{12–14} Additional theories of PDE5 inhibition on the lower urinary tract suggest a LUTS decrease via modifications of afferent nerve signaling from the bladder, urethra and prostate.^{15–18}

In a recent proof of concept, 12-week dose titration study enrolling 281 men with BPH signs and symptoms tadalafil once daily (5 mg for 6 weeks, followed by dose escalation to 20 mg for 6 weeks) was well tolerated.¹⁹ It demonstrated statistically significant and clinically meaningful improvement of LUTS compared to that of placebo. In the current dose finding study we further examined the efficacy, dose response and safety of tadalafil in men with LUTS secondary to BPH.

MATERIALS AND METHODS

Study Design and Participants

This study was a randomized, double-blind, placebo controlled, parallel design, dose finding, 12-week study performed at 92 centers in a total of 10 countries. Men at least 45 years old with a history of LUTS secondary to BPH of 6 months or longer were eligible for this study unless 1) PSA was more than 10 ng/ml (in men with PSA 4 to 10 ng/ml prostate biopsy negative for malignancy within 12 months was required) or 2) PVR volume was 300 ml or greater at screening visit 1 (fig. 1). Patients reporting the use of other BPH or ED treatments upon study entry underwent a 4-week treatment-free screening/washout period. Otherwise patients began the placebo run-in period after screening results were reviewed. Other key inclusion criteria were a total I-PSS of 13 or greater, a Qmax of 4 to 15 ml per second from pre-void bladder volume, as assessed by ultrasound,

and between 150 and 550 ml with a voided volume of 125 ml or greater at visit 2. Men were not required to have a history of ED and the frequency of sexual intercourse was not discussed at study entry.

Excluded from enrollment were men who received recent finasteride or dutasteride treatment within 3 and 12 months, respectively, before visit 2 (the start of the placebo run-in period) and those with penile or pelvic surgery, radiotherapy, lower urinary tract malignancy, trauma or recent instrumentation, urinary retention or bladder stones, a history of urethral obstruction due to stricture, valves, sclerosis or tumor, a neurological condition affecting bladder function, detrusor-sphincter dyssynergia, intravesical obstruction secondary to the prostate median lobe, urinary tract inflammation or infection, or prostate cancer. Other exclusionary medical conditions were clinically significant renal or hepatic insufficiency, cardiovascular conditions such as significant angina, recent myocardial infarction or poorly controlled blood pressure, a 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 HbA1c greater than 9%).

The clinical study was performed in accordance with the Declaration of Helsinki and all applicable regulations. The institutional review board at each site approved the study and all men provided written informed consent before undergoing any study procedure or receiving any study therapy.

Outcomes

The primary study end point was the I-PSS change after 12 weeks of treatment with 5 mg tadalafil compared with pla-

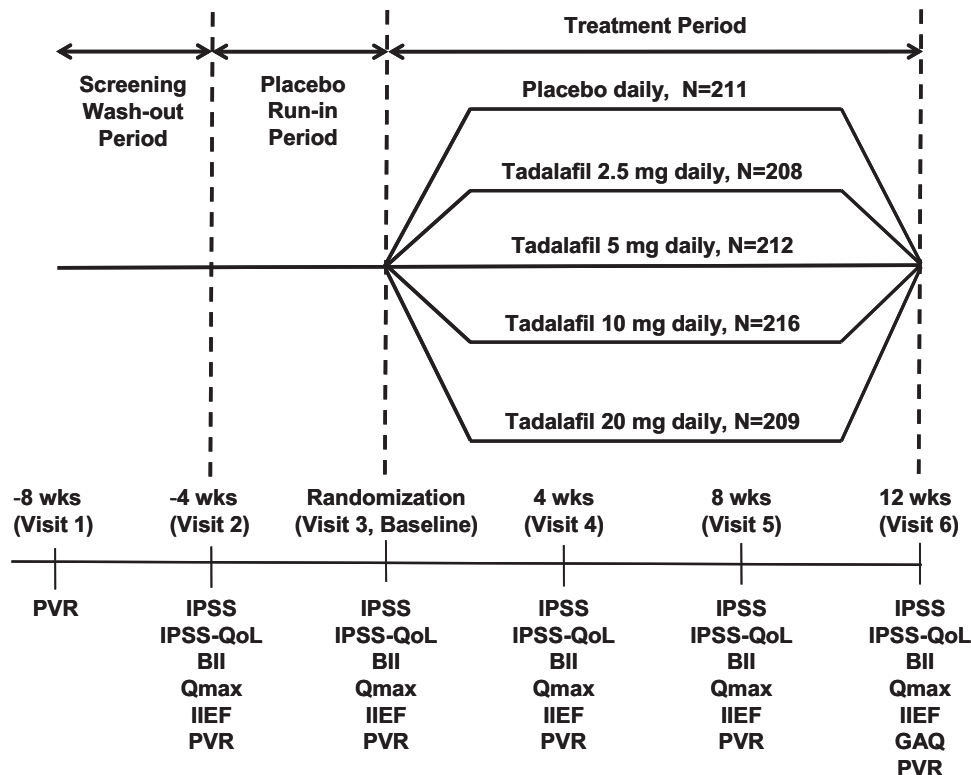


FIG. 1. Study design with schedule of events

cebo. Figure 1 shows the study design. I-PSS is a validated 7-item questionnaire about LUTS occurring within the last month. The total I-PSS range is 0 to 35 with higher scores indicating more severe symptoms.

Secondary end points were used to examine the efficacy and dose-response relationship of placebo and once daily dosing with 2.5, 5, 10 or 20 mg tadalafil, as assessed by I-PSS (questions 1 to 7), the irritative subscore (questions 2, 4 and 7), the obstructive subscore (questions 1, 3, 5 and 6) and the I-PSS QOL index, "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?" Secondary end points also included BPH-II, a validated 4-item questionnaire with a score range of 0 to 13 with higher scores indicating more bother or problems associated with urinary symptoms within the previous month, GAQ, "Has the treatment you have been taking since your last visit improved your urinary symptoms?" and uroflowmetry parameters.

Qmax, the mean urinary flow rate and voided volume parameters were recorded using a standard calibrated flowmeter. Qmax read by an investigator was used to determine study eligibility, while a central over read for each tracing was used for analysis. The mean urinary flow rate and voided volume were assessed for descriptive purposes (data not shown).

The IIEF questionnaire was administered 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?" the change in IIEF-EF was analyzed, while other IIEF domains were assessed for descriptive purposes only (data not shown).

Safety assessments included patient reported TEAEs, SAEs, vital signs, changes in clinical laboratory values, including PSA, and PVR. TEAEs were coded using the Medical Dictionary for Regulatory Activities, version 10.

Statistical Analyses

Treatment group differences compared to placebo for continuous variables were evaluated using ANCOVA adjusted for multiplicity by Dunnett's method and by permutation tests²⁰ based on a 10,000 Monte Carlo sample stratified by the randomization factors. The data presented represent ANCOVA results. Permutation test results were presented when the inference from the 2 methods was not similar.

A total of 198 patients per treatment group provided 91% power to detect a difference of 2.0 points from placebo in the I-PSS change from baseline. These calculations were based on the 2-sided t test at a significance level of 0.05.

All efficacy analyses were performed on an intent to treat basis and they included all randomized patients who had a baseline and at least 1 post-baseline measurement available.

ANCOVA using change from baseline as a response variable and including effects for treatment, baseline value of the response variable and randomization factors, that is 4 levels of geographic region, 2 levels of BPH LUTS severity and 2 levels of ED, was used to analyze continuous variables. A last observation carried forward imputation convention was used for these analyses.

Repeated measures analysis was performed for some continuous variables using mixed models with unstructured covariance matrices. These models used the change from

baseline as a response variable and they included effects for treatment, baseline value of the response variable, geographic region, BPH LUTS severity, ED history, time and treatment group by time interaction.

Secondary analysis was done to evaluate the LUTS GAQ at end point using the Cochran-Mantel-Haenszel test for general association, stratified by the randomization factors. LUTS GAQ was analyzed according to the proportion of patients with nonmissing responses at the final visit.

RESULTS

Baseline Characteristics

Of 1,813 men who were screened for eligibility 1,058 were randomly allocated to receive 1 of 4 active treatments or placebo (figs. 1 and 2). There were no significant treatment group differences in baseline characteristics or in features related to BPH (table 1). In 67 randomized men with moderate to severe LUTS, as assessed at visit 2, LUTS severity improved during the placebo run-in period from moderate or severe to mild (I-PSS 13 or greater to 8 or less, respectively).

Efficacy End Points

Primary end point. Daily dosing of 5 mg tadalafil resulted in a statistically significant improvement in the I-PSS change from baseline compared to placebo (table 2).

Secondary end points. Statistically significant improvements in the I-PSS change from baseline compared to placebo were observed for each tadalafil dose (table 2) and at all post-randomization visits (4, 8 and 12 weeks) (fig. 3, A). The 2.5 mg daily tadalafil dose resulted in significant improvements in the I-PSS obstructive subscore and IIEF-EF compared to those of placebo (table 2). Statistically significant improvements were also noted in the I-PSS irritative and obstructive subscores, the I-PSS QOL subscore, BPH-II, GAQ and IIEF-EF at tadalafil doses of 5 mg or greater, except a nonsignificant finding at the 10 mg dose for BPH-II compared to placebo ($p = 0.056$, table 2). Improvements in BPH-II were statistically significant at tadalafil doses of 5 mg or greater compared to placebo when assessed in patients completing 4, 8 and 12 weeks of treatment (fig. 3, B).

On subgroup analysis of patients with a mild to moderate BPH LUTS severity score 5 mg or greater tadalafil significantly improved I-PSS compared to placebo, while all tadalafil doses improved I-PSS in patients with severe BPH LUTS (table 2).

When analyses of covariance and permutation tests were performed, similar results were observed, except a nonsignificant treatment effect compared to placebo for BPH-II at the 5 mg dose (permutation test $p = 0.095$) and a significant treatment effect on the I-PSS irritative subscore and the I-PSS QOL subscore at the 2.5 mg dose (permutation test $p < 0.01$). No statistically significant treatment effect compared to placebo was noted for Qmax at any tadalafil dose.

Safety End Points

Individual TEAEs in the tadalafil treatment groups were infrequent. Back pain, myalgia and to a lesser degree headache were more frequent at higher tadalafil doses but no clear dose relationship was evident (table 3). One patient

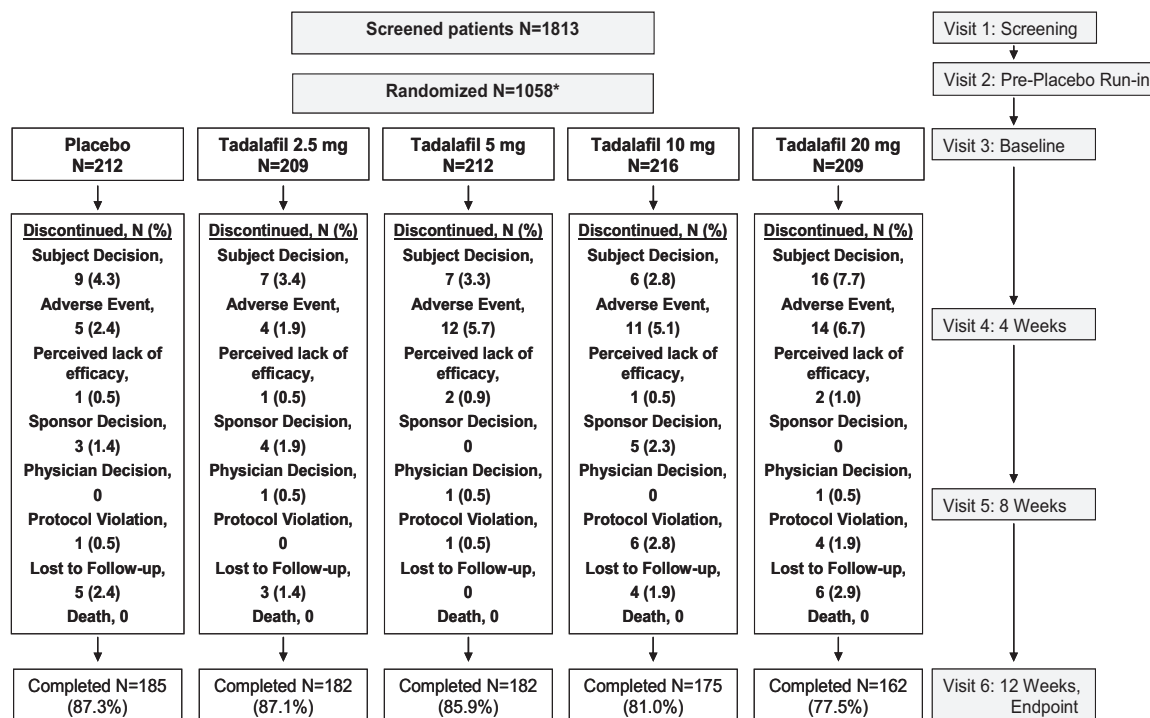


FIG. 2. Patient Consolidated Standards of Reporting Trials diagram. Asterisk indicates that 1 patient randomized at 2 sites was excluded from study and another two who were randomized did not receive study drug.

receiving placebo was catheterized because of urinary retention caused by BPH. Table 3 shows the incidence of patients experiencing SAEs or discontinuing due to TEAEs.

No clinically relevant changes in laboratory parameters, vital signs, mean PSA or mean PVR were observed. The least squares mean PVR change from baseline to week 12 was 4.81 ml in the placebo group, and 12.13, 6.63, 10.55 and -3.95 ml in the 2.5, 5, 10 and 20 mg tadalafil groups, respectively.

DISCUSSION

In this study once daily treatment with 2.5, 5, 10 or 20 mg tadalafil for 12 weeks was superior to placebo for relieving LUTS associated with clinical BPH, as measured by I-PSS. Improvement was statistically significant at 4, 8 and 12 weeks, and it was clinically meaningful according to the American Urological Association guideline of a 3-point improvement in I-PSS from baseline.^{5,21} Further improve-

TABLE 1. Baseline characteristics of all randomized patients

	Placebo	Tadalafil (mg)			
		2.5	5	10	20
No. pts	211*	208	212	216	209
Mean age (range)	61.75 (45.59–80.62)	62.03 (44.99–92.64)	61.95 (46.10–85.60)	62.22 (45.53–80.04)	62.55 (45.81–79.47)
% Younger than 65	64.93	61.06	64.62	63.89	58.85
% Race or ethnic group:					
White	84.83	88.46	84.43	86.11	84.21
Hispanic	13.74	9.62	11.79	11.11	11.96
Black	1.42	1.44	3.30	2.31	2.39
Other	0	0.48	0.47	0.46	1.44
Mean kg/m ² body mass index (range)	28.57 (20.23–44.25)	27.98 (17.46–40.76)	28.58 (20.09–48.09)	28.40 (18.35–45.42)	28.46 (19.68–53.98)
% Previous α -blocker use [†]	29.86	29.33	27.83	26.85	30.14
% Previous 5 α -reductase inhibitor use [†]	1.90	1.44	1.42	0.93	0.00
Mean \pm SD % ED history	67.30	64.90	67.92	69.44	69.38
% Sexually active [†]	80.10	80.77	84.43	80.56	77.03
Mean ng/ml PSA (range)	1.65 (0.03–9.21)	1.71 (0.19–8.78)	1.79 (0.11–6.69)	1.82 (0.21–6.83)	1.73 (0.18–5.92)
		Visit 3 (baseline)			
Mean \pm SD I-PSS	17.08 \pm 6.36	17.48 \pm 5.84	17.30 \pm 5.97	17.77 \pm 5.60	17.11 \pm 6.53
Mean \pm SD BPH-II	4.94 \pm 2.95	4.73 \pm 2.95	4.66 \pm 2.98	4.86 \pm 2.98	4.75 \pm 2.79
Mean \pm SD Qmax (ml/sec)	10.31 \pm 4.85	9.97 \pm 4.09	10.37 \pm 3.86	9.93 \pm 3.77	9.82 \pm 3.97
Mean ng/ml PSA (range)	1.73 (0.12–10.33)	1.67 (0.16–8.41)	1.79 (0.14–6.79)	1.86 (0.19–8.54)	1.73 (0.10–7.23)

* One patient randomized at 2 sites was excluded.

[†] Identified at visit 1 based on patient medical history.

TABLE 2. Change from baseline to end point in efficacy variables in all treatment groups

Measure	Placebo	Tadalafil (mg)				Tadalafil vs Placebo p Value
		2.5	5	10	20	
No. pts	210*	208*	212	216	208*	
Least squares mean ± SE I-PSS change from baseline:	-2.27 ± 0.49	-3.88 ± 0.50†	-4.87 ± 0.49‡	-5.17 ± 0.49	-5.21 ± 0.50	<0.001
Mild-moderate at baseline (701 pts)	-1.4 ± 6.44	-2.7 ± 5.18§	-4.3 ± 4.94	-4.4 ± 5.60	-3.7 ± 5.18	<0.001 (permutation test)
Severe at baseline (352 pts)	-3.9 ± 5.30	-6.5 ± 6.41	-6.2 ± 6.71	-7.3 ± 6.71	-8.4 ± 6.36	<0.05 (permutation test)
Irritative	-0.99 ± 0.23	-1.58 ± 0.23§	-1.89 ± 0.23	-1.96 ± 0.23	-2.07 ± 0.23	<0.01
Obstructive	-1.26 ± 0.33	-2.23 ± 0.33†	-2.94 ± 0.33	-3.13 ± 0.32	-3.12 ± 0.33	<0.001
QoL	-0.49 ± 0.11	-0.74 ± 0.11§	-0.86 ± 0.11	-0.92 ± 0.10	-0.88 ± 0.11	<0.01
Least squares mean ± SE BPH-II change from baseline	-0.83 ± 0.21	-0.96 ± 0.21§	-1.40 ± 0.21	-1.38 ± 0.20§	-1.45 ± 0.21	<0.05
Least squares mean ± SE Qmax change from baseline (cm/sec)	1.24 ± 0.40	1.41 ± 0.39	1.64 ± 0.39	1.58 ± 0.38	1.96 ± 0.39	Not significant
% Yes LUTS GAQ end point (Cochran-Mantel-Haenszel test)	54.8	61.9§	69.2	73.0	74.2	<0.05
Least squares mean ± SE sexually active ED IIEF-EF change from baseline (55% of pts)	2.20 ± 1.03	5.59 ± 1.01	6.97 ± 1.01	7.98 ± 1.0	8.34 ± 1.01	<0.001

* One patient randomized at 2 sites was excluded and another and 2 randomized did not receive study drug.

† p <0.05.

‡ Primary end point.

§ Not significant.

ments with tadalafil beyond that observed in the 2.5 mg group was evident in the 5 mg group with minimal additional improvement in the 10 and 20 mg groups (fig. 3, A). This dose-response relationship was mirrored in the percep-

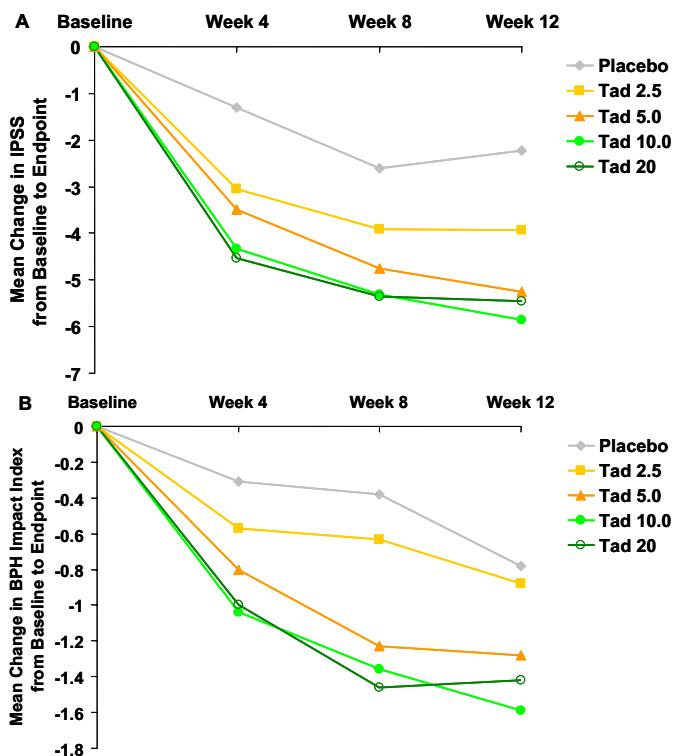


FIG. 3. Mean change from baseline to end point after 4, 8 and 12 weeks. A, I-PSS. At weeks 4, 8 and 12 vs placebo 2.5 mg tadalafil (Tad) ANCOVA p = 0.001, 0.028 and 0.007, respectively, and 5, 10 and 20 mg ANCOVA p <0.001. B, for tadalafil 2.5 mg no significance vs placebo. Vs placebo 5 and 10 mg tadalafil at week 8 ANCOVA p <0.001, and at weeks 4 and 12 ANCOVA p <0.05. Vs placebo at weeks 4 and 8, 20 mg tadalafil ANCOVA p <0.001 and at week 12 ANCOVA p <0.05.

tion of how bothered patients were by urinary symptoms during the study (fig. 3, B). While the improvement in I-PSS and BPH-II continued throughout the 12-week period, additional improvements observed after 8 weeks were minimal (fig. 3).

The 5 mg tadalafil group had an I-PSS least squares mean change compared with placebo of -2.6 points, which is similar to findings in tamsulosin studies²² and to reported I-PSS changes in a recent meta-analysis of the impact of α-blocker therapy.⁵ Likewise, when I-PSS was assessed after 6 weeks of treatment with 5 mg tadalafil once daily in a recent dose titration study, improvement was significantly greater in patients treated with tadalafil compared to placebo.¹⁹ However, differences in eligibility and study design should be considered when comparing these studies.

Decreased LUTS in men with BPH following treatment with other available PDE5 inhibitors has recently been reported.^{23,24} Caution should be applied when comparing our results with the findings of these studies due to differences in study population and study design. In particular in trials that do not include a placebo run-in period before recording baseline values the placebo effect can be substantial. Additionally, patient baseline demographics and comorbidities must be considered when extrapolating trial results to a broad population of men. The current study protocol enrolled men at least 45 years old with a history of LUTS secondary to BPH of 6 months or longer regardless of whether they had a history of ED. Patients also underwent a 4-week placebo run-in period before treatment initiation.

The significant improvements in I-PSS irritative, obstructive and QoL subscores, and GAQ were consistent with observations of the effect of tadalafil in a previous study.¹⁹

The dose-response improvement in BPH-II with time was generally similar to that observed for I-PSS. While improvement following 2.5 mg tadalafil vs placebo was insignificant, the BPH-II score improvement from baseline surpassed the clinically meaningful threshold of 0.4 in all tadalafil treatment groups.²¹

TABLE 3. TEAEs and SAEs

	No. Placebo (%)	No. mg Tadalafil (%)				Totals
		2.5	5	10	20	
Overall	211	209	212	216	209	846
TEAEs:*						
Headache	6 (2.8)	5 (2.4)	6 (2.8)	11 (5.1)	7 (3.3)	29 (3.4)
Dyspepsia	0	2 (1.0)	10 (4.7)	6 (2.8)	10 (4.8)	28 (3.3)
Back pain	1 (0.5)	3 (1.4)	2 (0.9)	10 (4.6)	12 (5.7)	27 (3.2)
Myalgia	0	3 (1.4)	3 (1.4)	6 (2.8)	6 (2.9)	18 (2.1)
Nasopharyngitis	2 (0.9)	7 (3.3)	4 (1.9)	2 (0.9)	5 (2.4)	18 (2.1)
Diarrhea	3 (1.4)	2 (1.0)	6 (2.8)	1 (0.5)	5 (2.4)	14 (1.7)
Gastroesophageal						
Reflux disease	0	2 (1.0)	2 (0.9)	6 (2.8)	3 (1.4)	13 (1.5)
Extremity pain	0	3 (1.4)	5 (2.4)	2 (0.9)	3 (1.4)	13 (1.5)
Influenza	1 (0.5)	4 (1.9)	4 (1.9)	1 (0.5)	2 (1.0)	11 (1.3)
Bronchitis	1 (0.5)	3 (1.4)	1 (0.5)	5 (2.3)	0	9 (1.1)
Muscle spasms	0	2 (1.0)	0	2 (0.9)	5 (2.4)	9 (1.1)
1 or Greater TEAE	45 (21.2)	56 (26.8)	65 (30.7)	75 (34.7)	83 (39.7)	279 (33.0)
1 or Greater SAE	6 (2.8)	3 (1.4)	1 (0.5)	2 (0.9)	5 (2.4)	11 (1.3)
1 or Greater AE leading to discontinuation	5 (2.4)	4 (1.9)	12 (5.7)	11 (5.1)	14 (6.7)	41 (4.8)

* Reported by 2% or greater of patients in any treatment group.

Qmax increased with increasing doses of tadalafil but these changes were relatively small and not statistically different compared to those in the placebo group. The lack of a significant peak flow improvement in men with BPH LUTS treated with tadalafil is consistent with previous reports of PDE5 inhibitor compounds.^{19,23,24} However, the clinical importance of the nonsignificant improvement in peak flow observed with PDE5 inhibitor therapy or the modest improvement observed with α -blocker therapy is a subject of debate. A recent study supports the hypothesis that the decrease in BPH LUTS caused by PDE5 inhibitors may be due not only to smooth muscle relaxation in the prostate, but also to a direct effect on the bladder. When 25 patients with spinal cord injury receiving chronic oxybutynin therapy were given a single dose of a PDE5 inhibitor, urodynamic parameters such as bladder capacity and detrusor overactivity volume improved.¹¹ In the current study the improvement in LUTS did not seem to be associated with decreased bladder contractility since PVR changes across treatment groups were insignificant and not clinically meaningful.

The significant improvement in IIEF-EF in men with BPH LUTS was observed across all doses. It was consistent with findings in men with BPH LUTS and ED treated with tadalafil once daily in a recent dose titration study.¹⁹

From a safety perspective all doses of tadalafil were well tolerated and few patients discontinued the study. TEAEs were few but more common in the tadalafil groups than in the placebo group. The incidence of patients with 1 or more TEAEs increased with increasing tadalafil doses. However, no clear relationship was observed between the tadalafil dose and individual AEs, except more prevalent reports of back pain and myalgia in men treated once daily with 10 or 20 mg tadalafil. SAEs in the tadalafil groups were rare. Mean PVR did not change significantly during the study. The AE profile in this BPH population was similar to that in previous reports of men with ED treated once daily with tadalafil.^{25,26}

CONCLUSIONS

In this placebo controlled, dose finding study tadalafil (2.5, 5, 10 or 20 mg) was well tolerated and effective for improving

BPH LUTS with statistical and clinically meaningful improvement after 4, 8 and 12 weeks. Of the doses studied 5 mg tadalafil provided a positive risk-benefit profile.

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APPENDIX

Trial Investigators

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Abbreviations and Acronyms

AE	=	adverse event
BPH	=	benign prostatic hyperplasia
BPH-II	=	BPH Impact Index
ED	=	erectile dysfunction
GAQ	=	Global Assessment Question
IIEF	=	International Index of Erectile Function
IIEF-EF	=	IIEF Erectile Function domain
I-PSS	=	International Prostate Symptom Score
LUTS	=	lower urinary tract symptoms
PDE5	=	phosphodiesterase type 5
PSA	=	prostate specific antigen
PVR	=	post-void residual urine
Qmax	=	peak urinary flow rate
QOL	=	quality of life
SAE	=	serious AE
TEAE	=	treatment emergent AE

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