Effects of Tadalafil or Tamsulosin on Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia and on Erectile Dysfunction: Results from an International, Double-Blind, Placebo-Controlled Trial

MP-43

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BACKGROUND

- The prevalence of signs and symptoms of benign prostatic hyperplasia (LUTS/BPH) increases with age. Epidemiological links between LUTS/BPH and erectile dysfunction (ED) are well established [1,2]
- Tadalafil is a long-acting phosphodiesterase type-5 inhibitor widely approved for on-demand or once daily treatment of ED, and was recently approved in the USA for the treatment for LUTS/BPH with or without ED
- Improvements in LUTS/BPH with tadalafil 5 mg once daily have been demonstrated in several randomized, placebo-controlled studies [3-5], irrespective of ED [6]
- Given that the α-blocker tamsulosin is often used as first-line treatment for LUTS/BPH, assessing the efficacy of monotherapy with either tadalafil or tamsulosin in the same trial is of particular interest.

OBJECTIVES

Primary Objective:

- To assess the efficacy of monotherapy with tadalafil 5 mg once-daily versus placebo on LUTS/BPH at week 12

Secondary Objectives:

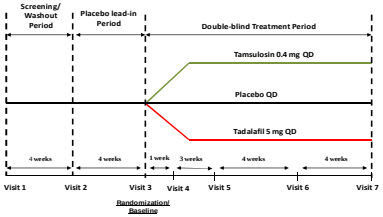
- To assess the efficacy of monotherapy with tamsulosin 0.4 mg once-daily versus placebo on LUTS/BPH as an active control
- To assess the effect of tadalafil 5 mg or tamsulosin 0.4 mg once-daily versus placebo on LUTS/BPH bother, quality of life, and treatment satisfaction
- To assess the effect of tadalafil 5 mg or tamsulosin 0.4 mg once-daily versus placebo on ED
- To assess the effects of tadalafil 5 mg or tamsulosin 0.4 mg once-daily versus placebo on maximum urinary flow rate (Q_{max}).
- To assess the safety of tadalafil 5 mg once daily or tamsulosin 0.4 mg once daily.

METHODS

STUDY DESIGN

- Phase III, randomized, double-blind, parallel-design, placebo- and active-controlled trial conducted at 44 centers in Australia, Austria, Belgium, France, Germany, Greece, Italy, Mexico, the Netherlands, and Poland.
- Single-blind placebo lead-in period, double-blind treatment period.

Figure 1: Study Design Schematic



INCLUSION CRITERIA

- Men ≥45 years of age with diagnosis of LUTS/BPH for >6 months
- Total IPSS ≥13 and Q_{max} ≥4 to ≤15 ml/s at the beginning of placebo lead-in period
- No use of finasteride for ≥3 months, dutasteride for ≥6 months, or any BPH therapy (including herbal preparations), overactive bladder therapy, or ED therapy for ≥4 weeks prior to Visit 2

EXCLUSION CRITERIA

- Prostate specific antigen >10 ng/ml, or 4 -10 ng/ml if prostate malignancy had not been ruled out
- Post-void residual (PVR) volume was ≥300 ml
- Due to inclusion of a tamsulosin dosing arm, men were excluded for planned cataract surgery, history of symptomatic orthostatic hypotension, recurrent dizziness, vertigo, loss of consciousness, or syncope

EFFICACY AND SAFETY MEASURES

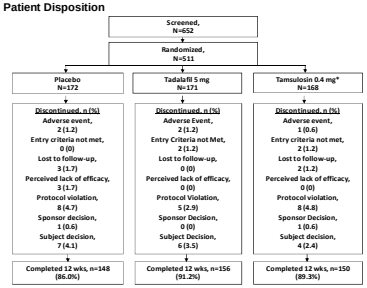
- The primary efficacy measure was total IPSS, while BPH Impact Index (BII) was a key secondary efficacy measure. A Week-1 IPSS (mIPSS) used questions beginning with "Since your last visit. The IPSS-Quality-of-Life index (QoL) , BPH-Treatment Satisfaction Scale (TSS-BPH), Patient and Clinician Global Impression of Improvement scales (PGI-I and CGI-I), and International Index of Erectile Function – Erectile Function domain (IIEF-EF) were also assessed as secondary measures.
- Uroflowmetry was performed using standard calibrated devices at screening, baseline, and endpoint visits. Traces were centrally read for the baseline and endpoint visits. Valid Q_{max} measurements required pre-void total bladder volume (assessed by ultrasound) of ≥150 to ≤550 ml and voided volume (V_{void}) of ≥125 ml.
- Safety assessments included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and PVR.
- Safety and uroflowmetry were assessed in all randomized patients. Efficacy was assessed in all randomized patients who received at least 1 dose of study drug.

STATISTICAL ANALYSES

- The primary endpoint comparison was between tadalafil and placebo, tamsulosin was included as an active control. The study was not powered for direct comparison between active treatments.
- Continuous efficacy measures, Q_{max} and PVR were evaluated as change from baseline (randomization) to Week 12/last-observation-carried-forward (LOCF) endpoint. Analyses for 1 or 4 weeks did not use LOCF imputation. Continuous efficacy measures were assessed using analysis of covariance. For CGI-I and PGI-I , the 7 response-category questionnaire was administered, however data collapsed to 3 categories for presentation.
- A fixed-sequence testing procedure was used to control Type I error in analyses of primary and key secondary outcomes for tadalafil (but not tamsulosin), using the following pre-specified order: total IPSS at endpoint; total IPSS after 4 weeks; BII at endpoint; mIPSS after 1 week; and BII after 4 weeks. Statistical significance was interpreted only if results of preceding analysis were significant at the 0.05 level. However, the results of all primary and key secondary analyses achieved statistical significance under this procedure; therefore results were presented independent of this sequence.

RESULTS

Figure 2: Patient Disposition



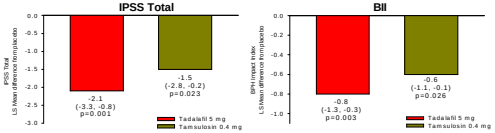
* One subject randomized to tamsulosin did not take at least one dose of study drug and was excluded from the efficacy analyses.

Table 1: Baseline Characteristics of All Randomized Patients

Characteristic	Placebo (N=172)	Tadalafil 5 mg (N=171)	Tamsulosin 0.4 mg (N=168)
Age, mean years (range)	63.7 (45.9, 88.6)	63.5 (45.1, 83.1)	63.5 (45.5, 83.4)
Race, n (%)			
White	131 (76.2)	130 (76.0)	131 (78.0)
Black or African American	0	1 (0.6)	0 (0)
American Indian/Alaska Native*	41 (23.8)	40 (23.4)	37 (22.0)
Region, n (%)			
Europe	123 (71.5)	121 (70.8)	120 (71.4)
Non-Europe	49 (28.5)	50 (29.2)	48 (28.6)
BMI, mean kg/m² (range)	28.1 (19.2, 40.2)	27.1 (17.2, 43.4)	27.9 (18.3, 39.0)
Prior therapy (last 12 months), n (%)			
α-blocker use	45 (26.2)	41 (24.0)	43 (25.6)
Other BPH-LUTS therapy	8 (4.7)	6 (3.5)	9 (5.4)
ED therapy	23 (13.4)	21 (12.3)	21 (12.5)
BPH-LUTS severity, n (%)			
Mild (IPSS<8)	6 (3.5)	3 (1.8)	4 (2.4)
Moderate (IPSS ≥8 - <20)	112 (65.1)	120 (70.2)	115 (68.5)
Severe (IPSS ≥20)	54 (31.4)	48 (28.1)	49 (29.2)
Q_{max} category, n (%)**			
<10 ml/s	79 (45.9)	92 (53.8)	105 (62.5)
10-15 ml/s	69 (40.1)	63 (36.8)	53 (31.5)
>15 ml/s	18 (10.5)	12 (7.0)	7 (4.2)
PSA, ng/ml (mean ± SD)	2.0 ± 1.7	2.1 ± 1.8	1.9 ± 1.6
Q_{max} ml/s (mean ± SD)**	10.5 ± 4.1	9.9 ± 3.6	9.4 ± 3.3
IPSS total (mean ± SD)**	17.4 ± 6.0	17.2 ± 4.9	16.8 ± 5.3
IPSS QoL (mean ± SD)	3.6 ± 1.4	3.6 ± 1.2	3.4 ± 1.2
BII (mean ± SD)	5.0 ± 3.3	4.8 ± 2.8	4.7 ± 3.1
IIEF-EF domain (mean ± SD)	16.1 ± 8.5	15.8 ± 8.4	14.0 ± 7.7

* Some subjects enrolled in Mexico self-reported their race as American Indian/Alaska Native.
** Values were obtained at randomization/baseline (Visit 3) following the placebo lead-in period; subjects with improvements in IPSS or Q_{max} during placebo lead-in were not excluded.

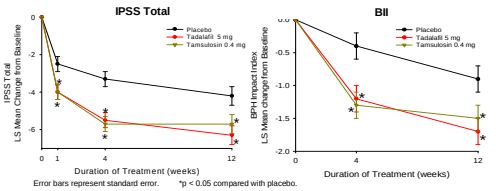
Figure 3: Placebo-adjusted Change in Primary and Key Secondary Measures at Endpoint



Data labels show value for LS mean difference from placebo (95% confidence interval) and p-value versus placebo.

- For the IPSS voiding sub-score, changes from baseline to endpoint versus placebo were statistically significant for tadalafil (p=0.001) and for tamsulosin (p=0.026). Changes were not significant versus placebo for the IPSS voiding sub-score for either tadalafil or tamsulosin (each p=0.055), nor were they significant for the IPSS nocturia sub-score for tadalafil (p=0.08) or for tamsulosin (p=0.118). (IPSS QoL shown in Table 2)

Figure 4: Change in Efficacy Measures over Time



Error bars represent standard error. *p < 0.05 compared with placebo.

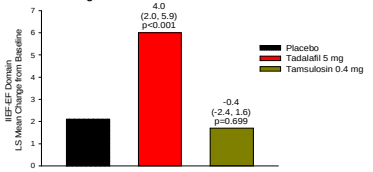
Table 2: IPSS QoL, TSS-BPH, and CGI-I and PGI-I

Measure	Placebo (N=172)	Tadalafil 5 mg (N=171)	Tamsulosin 0.4 mg (N=168)
IPSS QoL	n=172	n=171	n=165
Change from Baseline	-1.0 ± 0.1	-1.3 ± 0.1	-1.1 ± 0.1
Change vs. placebo (95% CI)		-0.3 ± 0.1	-0.1 ± 0.1
P-value vs. placebo		**0.022**	**0.546**
TSS-BPH	n=159	n=163	n=156
Mean ± SD	31.7 ± 17.5	26.9 ± 17.7	30.4 ± 16.5
Median	28.9	22.2	28.9
Median diff. vs. placebo (95% CI)		-4.4 (-8.9, -2.2)	-2.2 (-4.4, 2.2)
P-value vs. placebo [1]		**0.005**	**0.457**
CGI-I	n=160	n=163	n=157
Improvement	100 (62.5)	124 (76.1)	109 (69.4)
No change	51 (31.9)	32 (19.6)	40 (25.5)
Worsening	9 (5.6)	7 (4.3)	8 (5.1)
P-value vs. placebo [2]		**0.013**	**0.216**
PGI-I	n=159	n=160	n=157
Improvement	100 (62.9)	125 (78.1)	113 (72.0)
No change	51 (32.1)	28 (17.5)	36 (22.9)
Worsening	8 (5.0)	7 (4.4)	8 (5.1)
P-value vs. placebo [2]		**0.005**	**0.116**

Abbreviations: N = number of subjects in the analysis population; n = number of subjects evaluable; IPSS = International Prostate Symptom Score; QoL = quality of life; TSS-BPH = Treatment Satisfaction Scale-BPH; CGI-I = Clinician Global Impression of Improvement; PGI-I = Patient Global Impression of Improvement. [1] van Elteren test for differences in medians (for differences versus placebo). [2] Cochran-Mantel-Haenszel test

- The IIEF-EF domain was assessed in the 309 men in the efficacy population who reported ED at baseline and intended to be sexually-active during the study.

Figure 5: IIEF-EF Domain Change from Baseline



Data labels show LS mean difference from placebo (95% confidence interval) and p-value versus placebo.

Table 3: Q_{max} and PVR

Measure	Placebo (N=172)	Tadalafil 5 mg (N=171)	Tamsulosin 0.4 mg (N=168)
Q_{max} (ml/s)	n=147	n=156	n=144
Baseline	10.5 ± 4.1	9.9 ± 3.6	9.4 ± 3.3
Mean change	1.2 ± 4.8	2.4 ± 5.5	2.2 ± 4.1
P-value vs. placebo [1]		**0.009**	**0.014**
PVR (ml)	n=157	n=163	n=156
Baseline	50.2± 50.9	53.3 ± 50.4	61.5 ± 59.0
Mean change	-1.2 ± 56.5	-4.6 ± 47.0	-10.2 ± 59.2
P-value vs. placebo [1]		**0.303**	**0.146**

Abbreviations: N = number of subjects in the analysis population; n = number of subjects evaluable; Q_{max} = maximum urinary flow rate; PVR = post-void residual urine volume. Data are mean ± standard deviation.
[1] Changes from baseline compared using a ranked analysis of variance

Table 4: Adverse Events

	Placebo (N=172)	Tadalafil 5 mg (N=171)	Tamsulosin 0.4 mg (N=168)
Subjects with ≥1 TEAE, n (%)	35 (20.3)	40 (23.4)	40 (23.8)
Most common TEAEs, n (%)			
Headache	2 (1.2)	5 (2.9)	7 (4.2)
Nasopharyngitis	8 (4.7)	5 (2.9)	3 (1.8)
Back Pain	1 (0.6)	4 (2.3)	2 (1.2)
Dizziness	3 (1.7)	4 (2.3)	6 (3.6)
Dyspepsia	0	4 (2.3)	3 (1.8)
Subjects discontinuing due to an AE, n (%)	2 (1.2)	2 (1.2)	1 (0.6)
Subjects with ≥1 SAE, n (%)	0	2 (1.2)	2 (1.2)

N = number of subjects in the analysis population; n = number of subjects with an event; TEAE = treatment emergent adverse event; AE = adverse event; SAE = serious adverse event.

SUMMARY

- In comparison to placebo, tadalafil 5 mg and tamsulosin 0.4 mg each resulted in statistically significant and clinically meaningful[7] improvements in the primary efficacy measure of change in total IPSS at endpoint. Total IPSS also improved significantly versus placebo for both tadalafil and tamsulosin at 1 and 4 weeks.
- Tadalafil and tamsulosin also each improved BII compared with placebo at 4 and 12 weeks.
- Tadalafil 5 mg and tamsulosin 0.4 mg each improved Q_{max} significantly at endpoint compared with placebo.
- Tadalafil, but not tamsulosin, showed significant improvements versus placebo on the IPSS QoL, TSS-BPH, and PGI-I and CGI-I instruments.
- Tadalafil significantly improved the IIEF-EF domain score at endpoint compared with placebo, whereas tamsulosin did not.
- The incidence of TEAEs was numerically higher in both the tadalafil (23.4%) and tamsulosin (23.8%) groups compared with placebo (20.3%).

CONCLUSIONS

Both tadalafil and tamsulosin significantly improved LUTS/BPH as measured by IPSS as early as 1 week, and both improved Q_{max} at endpoint. Only tadalafil significantly improved secondary LUTS/BPH measures of QoL, global improvement, and treatment satisfaction, and only tadalafil improved ED.

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