#705 Effects of Tadalafil or Tamsulosin on Erectile Function in Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia: Results from a Multicenter, Double-blind, Randomized, Placebo (PLA)- controlled 12-week Study

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BACKGROUND

- Medical therapy for the signs or symptoms of benign prostatic hyperplasia (LUTS/BPH) currently consists of α_1-adrenoceptor antagonists (alpha blockers), 5α-reductase inhibitors (in men with an enlarged prostate), or combination therapy with both drugs.[1]
- Tadalafil 5 mg once daily is approved for erectile dysfunction (ED) and was recently approved in the USA for the treatment of LUTS/BPH and for the treatment of coexisting LUTS/BPH and ED.
- Data on the effects of α-blockers on sexual function have been mixed; some data, primarily from uncontrolled studies, suggest improvements in ED while other data suggest no effect.[2-5] Additionally, α-blockers with high selectivity for α_{1A}-adrenoceptors (tamsulosin and silodosin) are associated with an increased incidence of ejaculatory dysfunction.[1]
- Whereas the effect of tadalafil on ED is well-established based on assessments using the International Index of Erectile Function (IIEF) in randomized clinical studies, data for α-blockers using this instrument in randomized clinical trials are limited.

OBJECTIVE

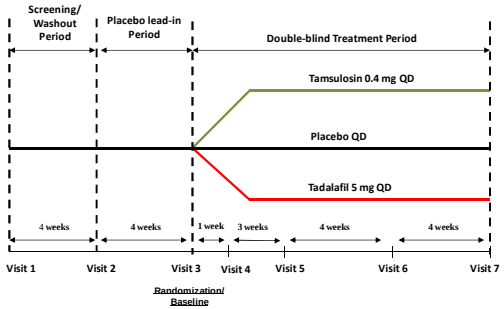
To determine the effect of monotherapy with tadalafil or tamsulosin on erectile function (EF) and sexual satisfaction assessed by the IIEF questionnaire as a secondary objective in a placebo-controlled, multinational trial in men with LUTS/BPH.

METHODS

STUDY DESIGN

- Phase III, randomized, double-blind, parallel-design, placebo- and active-controlled trial conducted at 44 centres 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



PATIENTS

Men were eligible for inclusion if they:

- Were at least 45 years of age
- Had a total IPSS ≥13 and a peak urinary flow (Q_{max}) of ≥4 to ≤15 ml/s at the beginning of the placebo lead-in period
- Had not taken finasteride therapy for at least 3 months, dutasteride therapy for at least 6 months, other experimental or off-label BPH therapy for at least ½ year, or any other BPH therapy (including herbal preparations), overactive bladder therapy, or ED therapy for at least 4 weeks prior to Visit 2.

At study entry, men could, but were not required to, have a history of ED

- Defined in the protocol as a consistent change in the quality of erection adversely affecting patient satisfaction with sexual intercourse.

For men who reported being sexually active, there was no entry criterion that specified a minimum number of sexual intercourse attempts prior to randomization.

OUTCOME MEASURES

- The primary efficacy measure was International Prostate Symptom Score (IPSS) (reported on poster #641).
- The International Index of Erectile Function (IIEF) was assessed in sexually active men with ED at baseline and again at 4, 8 and 12 weeks.
- IIEF-Erectile Function (EF) domain score was a pre-specified secondary efficacy measure.
- IIEF-Intercourse Satisfaction (IS) and Overall Satisfaction (OS) domains were pre-specified exploratory efficacy measures.

STATISTICAL ANALYSES

- IIEF was assessed as change from baseline (randomization) to endpoint (last post-baseline observation) compared to placebo using analysis of covariance (ANCOVA) models with terms for therapy, region, and a baseline covariate.
- Region-by-treatment group interaction and baseline covariate-by-treatment group interaction terms were included if p<0.1.
- Change from baseline and difference of changes during treatment were estimated using least squares (LS) means.
- A repeated measures model was applied to analyze change in IIEF scores over time in the Primary Analysis Population, with the change from baseline (Visit 3) to 4, 8, and 12 weeks as the response. The model included terms for treatment group, region, visit, centered-baseline of the parameter, visit-by-treatment interaction, centered-baseline-by-treatment interaction, and treatment-by-region interaction.

RESULTS

- Of 652 subjects screened, 511 were randomized (safety population) and 510 started study drug (efficacy population); 88.8% of subjects completed the study.
- Of the 511 randomized subjects, 310 reported ED and intended to be sexually-active during the study; this sub-population was analyzed here.

Table 1. Baseline Characteristics of Sexually-Active Subjects with BPH and ED

Characteristic	Placebo (N=105)	Tadalafil 5 mg (N=106)	Tamsulosin 0.4 mg (N=99)*
Age, mean years (range)	62.7 (45.9 – 80.6)	63.3 (45.1 – 83.1)	64.0 (45.5 – 83.5)
Region, n (%)			
European	87 (82.9)	88 (83.0)	82 (82.8)
Non-European	18 (17.1)	18 (17.0)	17 (17.2)
Erectile Dysfunction Severity, n (%)			
Mild	31 (29.5)	35 (33.0)	28 (28.3)
Moderate	58 (55.2)	56 (52.8)	50 (50.5)
Severe	16 (15.2)	15 (14.2)	21 (21.2)
Erectile Dysfunction Duration, n (%)			
< 1 year	14 (13.3)	25 (23.6)	28 (28.3)
≥ 1 year	91 (86.7)	81 (76.4)	71 (71.7)
Erectile Dysfunction Etiology, n (%)			
Psychogenic	2 (1.9)	4 (3.8)	5 (5.1)
Organic	22 (21.0)	17 (16.0)	15 (15.2)
Mixed	60 (57.1)	63 (59.4)	58 (58.6)
Unknown	21 (20.0)	22 (20.8)	21 (21.2)
Prior Erectile Dysfunction Therapy, n (%)	17 (16.2)	19 (17.9)	20 (20.2)
LUTS Symptom Severity, n (%)			
Moderate (IPSS < 20)	73 (69.5)	75 (70.8)	74 (74.7)
Severe (IPSS ≥ 20)	32 (30.5)	31 (29.2)	25 (25.3)
PSA (ng/ml), mean (SD)	2.0 (1.4)	2.0 (1.8)	2.0 (1.7)

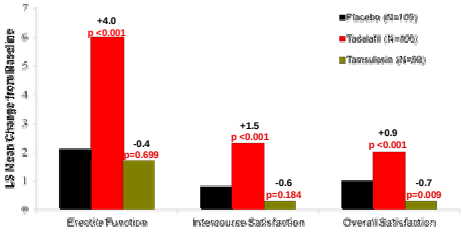
*One subject randomized to the tamsulosin group discontinued prior to taking study drug and was excluded from analyses

Table 2. Summary of IIEF Scores and Baseline to Endpoint Change

	Placebo (N=105)	Tadalafil 5 mg (N=106)	Tamsulosin 0.4 mg (N=98)	p-value TAD vs PLA	p-value TAM vs PLA
IIEF-Erectile Function					
Mean baseline	16.1	15.8	14.0		
Mean endpoint	17.1	20.9	15.3		
Change from baseline	2.1 (0.8)	6.0 (0.8)	1.7 (0.8)		
Change vs placebo		4.0 (1.0)	-0.4 (1.0)	**<0.001**	**0.699**
IIEF-Intercourse Satisfaction					
Mean baseline	7.2	6.6	6.7		
Mean endpoint	7.7	8.7	6.7		
Change from baseline	0.8 (0.3)	2.3 (0.3)	0.3 (0.4)		
Change vs placebo		1.5 (0.4)	-0.6 (0.4)	**<0.001**	**0.184**
IIEF-Overall Satisfaction					
Mean baseline	5.6	5.6	5.4		
Mean endpoint	6.3	7.2	5.5		
Change from baseline	1.0 (0.2)	2.0 (0.2)	0.3 (0.2)		
Change vs placebo		0.9 (0.3)	-0.7 (0.3)	**<0.001**	**0.009**

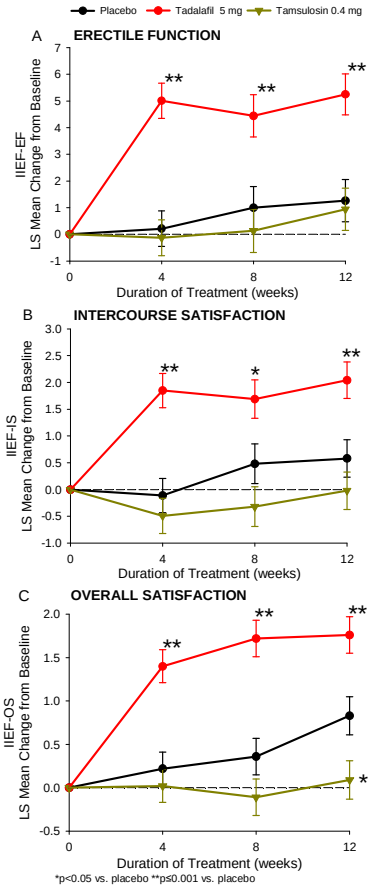
Changes are presented as least-squares mean changes (standard error) from baseline to 12 weeks using last observation carried forward. P-values are from ANCOVA. Increasing scores represent improvement.

Figure 3. Change from Baseline to Endpoint in IIEF Scores



Numbers above bars represent change versus placebo and p-values from ANCOVA. Increasing scores represent improvement.

Figure 4. Change in IIEF Scores over Time



*p<0.05 vs. placebo **ps0.001 vs. placebo

SUMMARY

- Tadalafil 5 mg once daily significantly improved the IIEF-EF domain score at endpoint compared to placebo, whereas tamsulosin 0.4 mg had no significant effect.
- In repeated measures analysis, there were statistically significant improvements in IIEF-EF in the tadalafil group compared to placebo at 4, 8 and 12 weeks (p≤0.001 at all time points); no improvement in IIEF-EF was observed with tamsulosin compared to placebo at any time point.
- Tadalafil also significantly improved both the IIEF Intercourse Satisfaction and Overall Satisfaction domains at endpoint and at 4 and 8 weeks compared to placebo.
- Tamsulosin had no significant effect at endpoint compared to placebo on the Intercourse Satisfaction domain, and the placebo group showed significantly greater mean improvement in the Overall Satisfaction domain at endpoint compared to tamsulosin (p=0.009).

CONCLUSIONS

Monotherapy with tadalafil 5 mg once daily improved erectile function and measures of intercourse and overall sexual satisfaction in men with LUTS/BPH, whereas tamsulosin 0.4 mg once daily did not improve these measures.

Acknowledgements:

Thomas Melby (PharmaNet/I3, Indianapolis, IN) assisted in the preparation of this poster. The authors would like to acknowledge all investigators and their staff, as well as the participants for their contributions to this study.

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