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EFFICACY AND SAFETY OF TADALAFIL 5 MG ONCE DAILY IN ASIAN MALES WITH LOWER URINARY TRACT SYMPTOMS SECONDARY TO BENIGN PROSTATIC HYPERPLASIA (BPH-LUTS): INTEGRATED ANALYSIS FROM 3 ASIAN DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL STUDIES

Hypothesis / aims of study
To evaluate the efficacy and safety of tadalafil, a potent and selective inhibitor of phosphodiesterase type 5, in Asian males with BPH-LUTS using integrated data from 3 Asian randomized, placebo-controlled studies.

Study design, materials and methods
In the 3 randomized studies, Asian males ≥45 years old with BPH-LUTS and an International Prostate Symptom Score (IPSS) ≥13 were enrolled [1],[2],[3]. Each study included a screening/washout period of up to 4 weeks, a placebo lead-in for 4 weeks and double-blind period for 12 weeks. After the placebo lead-in period, patients were randomized to tadalafil 5 mg or placebo in a 1:1 ratio by a computer-generated random sequence. The primary endpoint was to evaluate the efficacy of tadalafil 5 mg once daily for 12 weeks compared with placebo in improving the total IPSS. In addition, IPSS subscores (voiding and storage) and IPSS Quality of Life (QoL) score were also examined. For safety evaluation, treatment-emergent adverse events (TEAEs), post void residual (PVR), and peak urinary flow (Qmax) were assessed. IPSS parameters were assessed by mixed-effects model repeated measures (MMRM). Subgroup analyses were performed for total IPSS according to the following subgroups: age (<65, ≥65 years); BPH-LUTS severity at baseline (mild-to-moderate [IPSS <20]/severe [IPSS ≥20]); previous use (during the 12 months before screening) of an alpha blocker (yes/no); prostate volume (<median [31mL], ≥median [31mL]). The subgroup analyses were performed by analysis of covariance (ANCOVA).

Results
Of a total of 1199 patients, 601 and 598 patients were randomly assigned to tadalafil group and placebo group, respectively. Of these, 557 (92.7%) and 569 (95.2%) patients completed the study in the tadalafil group and the placebo group, respectively. The most common reason for discontinuation in both groups was adverse event [tadalafil: 16/601 (2.7%), placebo: 11/598 (1.8%)]. At baseline, the mean age was 62.6 and 63.1 years; the mean total IPSS was 17.8 and 17.7; the proportion of patients with severe symptoms (total IPSS ≥20) was 37.4% and 37.5%; the proportion of patients with prior alpha blocker use was 38.1% and 38.8% for tadalafil and placebo, respectively. The demographic and baseline clinical characteristics were similar between the groups.
The least squares (LS) mean change in total IPSS from baseline to Week 12 was -5.3 for tadalafil 5 mg and -3.8 for placebo. Tadalafil 5 mg showed a statistically significant improvement compared with placebo (p<0.001). A statistically significant separation from placebo occurred from Week 4 and continued through Week 12 (Figure1). Tadalafil 5 mg also resulted in a statistically significant improvement compared with placebo in IPSS voiding and storage subscores and IPSS QoL score at Week 4, 8 and 12 (Table1). In subgroup analyses, the improvement in tadalafil 5 mg compared with placebo observed in patients <65 years old was greater than that observed in patients ≥65 years old with significant treatment-by-subgroup interaction (p=0.042). However, in both age categories, tadalafil 5 mg resulted in numerically greater improvements compared with placebo in total IPSS. As for other subgroup analyses based on BPH-LUTS severity, prior alpha blocker use and prostate volume, tadalafil 5 mg resulted in significant improvements in total IPSS that were greater than those observed in placebo treated patients in both subgroups, and the treatment-by-subgroup interactions were not statistically significant (Table2).
Furthermore, tadalafil 5 mg once daily demonstrated favourable tolerability and safety. Commonly reported TEAEs in tadalafil 5 mg were nasopharyngitis (29/601, 4.8%), dyspepsia (18/601, 3.0%), headache (15/601, 2.5%), and most events were either mild or moderate in severity. The numbers and percentages of patients reporting at least 1 SAE were similar for tadalafil 5 mg (4/601; 0.7%), and placebo (3/598; 0.5%). There were no significant treatment differences in tadalafil 5 mg for Qmax or PVR.

Interpretation of results
Tadalafil 5 mg once daily treatment resulted in statistically significant symptomatic improvements compared with placebo from Week 4 in Asian males with BPH-LUTS. In the subgroup analysis for age, although the improvement of total IPSS in patients <65 years old was greater than that of patients ≥65 years old, the symptom severity of patients treated by tadalafil 5 mg at the end of the treatment measured by total IPSS was similar in both age categories. In general, tadalafil 5 mg showed improvement in total IPSS throughout the subgroups analysed. For safety, the majority of TEAEs in tadalafil 5 mg were typically mild to moderate in severity, and rarely lead to study discontinuation. Tadalafil treatment is not believed to cause adverse events related to sexual dysfunction (including ejaculatory disorders and decreased libido), which are known to be associated with alpha blocker and 5-ARI.

Concluding message
These integrated analyses revealed that tadalafil 5 mg once daily is efficacious in Asian mals with BPH-LUTS across subgroups of age, BPH-LUTS severity, prior alpha-blocker use, and prostate volume. No new safety concerns were identified by the integrated analyses.
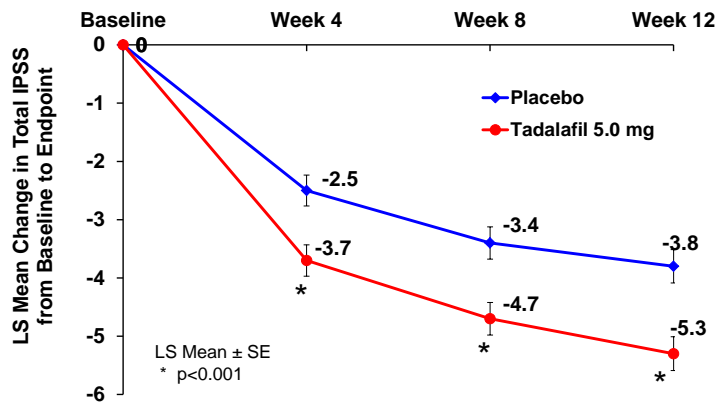
Figure1. Change from baseline to Weeks 4, 8 and 12 in total IPSS

Table1. Changes from baseline to Week 4, 8, and 12 in IPSS parameters

Measure	Week	Placebo n	Tadalafil n	Treatment Differences LS mean ± SE (95% CI)	p-value[b]
Total IPSS[a]	4	589	590	-1.2 ± 0.27 (-1.7 to -0.7)	<0.001
	8	581	576	-1.3 ± 0.29 (-1.9 to -0.7)	<0.001
	12	574	562	-1.5 ± 0.31 (-2.1 to -0.9)	<0.001
IPSS voiding subscore[a]	4	589	590	-0.9 ± 0.19 (-1.3 to -0.5)	<0.001
	8	581	576	-0.9 ± 0.20 (-1.3 to -0.5)	<0.001
	12	574	562	-1.0 ± 0.21 (-1.4 to -0.6)	<0.001
IPSS storage subscore[a]	4	589	590	-0.3 ± 0.12 (-0.5 to -0.1)	0.013
	8	581	576	-0.4 ± 0.12 (-0.6 to -0.1)	0.005
	12	574	562	-0.5 ± 0.13 (-0.8 to -0.3)	<0.001
IPSS QoL[a]	4	589	590	-0.2 ± 0.06 (-0.3 to -0.1)	0.001
	8	581	576	-0.2 ± 0.06 (-0.4 to -0.1)	<0.001
	12	574	562	-0.3 ± 0.07 (-0.4 to -0.1)	<0.001

Abbreviations: CI = confidence interval; LS = least squares; SE = standard error; n=number of patients.
a Baseline: Placebo: n = 596; Tadalafil: n = 600. b Mixed-effects model repeated measures analysis (MMRM).

Table2. Subgroup analyses of changes from baseline to Week 12 (LOCF) in total IPSS

Sugbroup categories	Placebo n	Placebo LS mean ± SE	Tadalafil n	Tadalafil LS mean ± SE	Treatment Difference LS mean ± SE (95% CI)	p-value[a]	Treatment-by-subgroup interaction[a]
Age							
<65 years old	336	-3.2 ± 0.4	356	-5.3 ± 0.4	-2.1 ± 0.4 (-2.9 to -1.3)	< 0.001	0.042
≥65 years old	262	-3.7 ± 0.4	245	-4.2 ± 0.4	-0.6 ± 0.5 (-1.5 to 0.3)	0.221	
Prior Alpha-Blocker Use							
Yes	232	-3.1 ± 0.4	229	-4.2 ± 0.4	-1.1 ± 0.5 (-2.1 to -0.2)	0.023	0.58
No	366	-3.8 ± 0.4	372	-5.5 ± 0.4	-1.6 ± 0.4 (-2.4 to -0.9)	< 0.001	
Baseline BPH-LUTS Severity							
Mild/Moderate	374	-2.8 ± 0.4	376	-3.7 ± 0.4	-1.0 ±0.4 (-1.7 to -0.2)	0.013	0.097
Severe	224	-4.6 ± 0.4	225	-6.9 ± 0.4	-2.3 ±0.5 (-3.3 to -1.3)	< 0.001	
Baseline Prostate Volume							
< 31 mL	282	-3.8 ± 0.4	307	-5.2 ± 0.4	-1.4 ±0.4 (-2.2 to -0.5)	0.001	0.921
≥31 mL	316	-3.2 ± 0.4	294	-4.6 ± 0.4	-1.5 ±0.4 (-2.3 to -0.6)	< 0.001	

Abbreviations: CI = confidence interval; LS = least squares; LOCF=Last Observation Carried Forward ;SE = standard error; n=number of patients.
a Analysis of Covariance (ANCOVA).

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