SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe B.V. (sponsor) [redacted] (co-sponsor)		
Name of Finished Product: Tamsulosin OCAS		
Name of Active Ingredient: Tamsulosin hydrochloride		
Title of Study: A randomized, double-blind, placebo-controlled study to assess the effect of Tamsulosin OCAS 0.4 mg tablets, once daily on nocturia, compared to placebo, in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia (RESTORE)		
Coordinating Investigators: [redacted] UK; [redacted] U.K		
Study Centers: 93 centers in 19 European countries		
Publication (reference): Not applicable at the time of this report		
Study Period: **Date of First Enrollment:** 25 October 2005 **Date of Last Evaluation:** 24 November 2006		**Phase of Development:** IIIb/IV
Objectives: The primary objective was to assess the effect of Tamsulosin OCAS 0.4 mg once daily compared to placebo on improvement of nocturnal voiding frequency, in patients with LUTS associated with BPH over 12 weeks. Secondary objectives were (1) to assess the effect of Tamsulosin OCAS 0.4 mg once daily compared to placebo on improvement in hours of undisturbed sleep, defined as the duration of the first period of undisturbed sleep, in patients with LUTS associated with BPH over 12 weeks; and (2) to compare the other secondary efficacy variables and the safety and tolerability of Tamsulosin OCAS 0.4 mg and placebo.		
Study Design: The study had a randomized, double-blind, placebo-controlled design with 2 treatment arms (Tamsulosin OCAS 0.4 mg and placebo). The study comprised a 2-week single-blind placebo run-in period followed by a 12-week randomized, double-blind, placebo-controlled treatment period. Patients visited the center at screening (Visit 1), at the end of the run-in period (Visit 2), and after 4, 8, and 12 weeks of double-blind treatment (Visits 3, 4 and 5).		
Diagnosis and Main Criteria for Inclusion: Eligible subjects were men aged 45 years or over who were diagnosed with LUTS associated with BPH. In addition, they had to have a total I-PSS score of ≥13; on average at least 2 voids per night over the last week; and a maximum of 4 hours of undisturbed sleep, expected per night at screening.		
Number of Subjects (planned and analyzed): 882 patients were planned to be randomized; 848 patients were randomized and 846 were treated (566 on Tamsulosin OCAS and 280 on placebo).		
Test Product, Dose And Mode of Administration: Tamsulosin OCAS tablets containing 0.4 mg Tamsulosin hydrochloride, equivalent to 0.37 mg of Tamsulosin base. One Tamsulosin OCAS 0.4 mg tablet was to be taken orally once daily in the morning. Batch number used was [redacted].		
Reference Product, Dose And Mode of Administration: Placebo tablets with same size and appearance as the Tamsulosin OCAS tablets. One placebo tablet was to be taken orally once daily in the morning. Batch number used was [redacted].		
Duration of Study and Treatment: 2-week single-blind placebo run-in period followed by a 12-week randomized, double-blind, placebo-controlled treatment period.		

Criteria for Evaluation: The primary efficacy variable was the change from baseline to Week 12 in mean number of nocturnal voids measured using the sleep diary. Secondary efficacy variables were the change from baseline to Week 12 (1) in mean hours of undisturbed sleep, defined as the time from falling asleep to first awakening to void (measured using the actigraph); (2) in Nocturia Quality of Life (N-QoL) total score, and sleep/energy and bother/concern sub-domain scores; (3) of the visual analogue scale (VAS) energy/vitality score; (4) in Leeds Sleep Evaluation Questionnaire (LSEQ) total score and sub-domain scores: getting to sleep, quality of sleep, pattern of awakening, and behaviour following awakening; (5) of the total I-PSS score; (6) of the I-PSS sub-domain scores; (7) for the QoL score on both the I-PSS and on the N-QoL. Safety was assessed from incidence and nature of adverse events, vital signs, and physical examination.

Statistical Methods: The treatment effect at Week 12 was analyzed using an analysis of covariance model including treatment and pseudo-center as fixed effects with baseline included as a covariate. A point estimate (and associated 95% confidence interval) for the contrast of Tamsulosin OCAS 0.4 mg versus placebo was calculated. The point estimate was tested against 0 by means of the corresponding t-statistic at the 2-sided significance level of 0.05. A repeated measures analysis was performed in order to investigate the effect of treatment over time. Nonparametric analyses were also performed.

RESULTS:

Analysis Sets and Subject Disposition: Three analysis sets were defined for this study: (1) The SAF comprised 846 patients who received at least 1 dose of double-blind study medication; (2) The FAS consisted of 833 patients who were randomized and who had baseline and at least one post-baseline primary efficacy measurement; (3) The PPS consisted of 646 patients who were randomized and who had a valid measurement at Week 12 for the primary efficacy variable, and had completed the study without major protocol deviations. Subject disposition is presented in Table 1.

Table 1. Number (%) of patients randomized, treated, discontinued and completing the study

	Placebo		Tamsulosin OCAS 0.4 mg	
	n	**(%)**	**n**	**(%)**
Entered				
Randomized	281	(100)	567	(100)
Treated	280	(99.6)	566	(99.8)
Discontinued	16	(5.7)	25	(4.4)
Completed	265	(94.3)	542	(95.6)

Source: Table 14.2.1.1.2

Demographics: Patients were men, predominantly of Caucasian origin, between 44 - 91 years of age.

Study Drug Exposure: The median treatment duration was 84 days (12 weeks).

Efficacy Results: The change from baseline at Week 12 in the mean number of nocturnal voids for the FAS was numerically lower in the Tamsulosin OCAS group than in the placebo group, i.e., –0.61 and -0.55 voids, respectively, but was not statistically significantly different between treatments (p=0.4482). Similar results were obtained when the analysis was repeated for the PPS, and when a nonparametric test approach was applied.

The mean number of hours of undisturbed sleep increased over time to a similar extent in both treatment groups. No statistically significant difference was observed between treatments (FAS; p=0.7060). The analysis on the PPS yielded similar results (p=0.2518).

There was a statistically significant effect of treatment on the N-QoL Total Score and the Bother/ Concern Score, and on the I-PSS Total Score and the Voiding Score in favor of Tamsulosin OCAS. Treatment comparisons on the change from baseline for the other secondary efficacy endpoints did not reach statistical significance. This was confirmed when a nonparametric approach was applied.

Safety Results: There were no untoward safety findings in the present study. There were no treatment-related serious adverse events associated with the use of Tamsulosin OCAS. Discontinuations due to adverse events were infrequent (<1%).

Overall, the incidence of adverse events was low and comparable between treatment groups (i.e., 19.3% patients in the Tamsulosin OCAS group, and 18.6% patients in the placebo group). The most commonly reported treatment-related adverse events with Tamsulosin OCAS were asthenia, headache, fatigue, dizziness, and retrograde ejaculation (all reported by <1.5% of patients).

There were no clinically relevant changes from baseline, or differences between treatment groups in vital signs and physical examination results.

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