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Sponsor/Company: sanofi-aventis **Drug substance**: Alfuzosin (SL77.0499-10)	**Study Identifier**: NCT00399464 **Study code**: EFC5791

Title of the study:

Efficacy and safety of SL77.0499-10 10 mg once daily in comparison with placebo and tamsulosin hydrochloride 0.2 mg in patients with lower urinary tract symptoms related to benign prostatic hyperplasia (BPH). A multicenter, randomized, placebo and active drug controlled, parallel group, 12-week, double-blind study.

Study centers:

Multicenter study with a total of 80 active centers in Japan.

Study period:

Date first patient enrolled: 23-Oct-2006
Date last patient completed: 30-Oct-2007

Phase of development: Phase 3

Objectives:

The primary objective of this study in patients with lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) was to demonstrate the superiority of alfuzosin 10 mg extended release tablets once daily over placebo, and non-inferiority versus tamsulosin hydrochloride 0.2 mg orally disintegrating tablets after 12 weeks of treatment, using the change from baseline value in the international prostate symptom score (I-PSS) total score.

The secondary objectives were to assess the efficacy of SL77.0499-10 in comparison with placebo and tamsulosin hydrochloride, using changes in I-PSS and Quality of Life (QOL) score from baseline to each visit and changes in peak flow rate (PFR) and residual urine volume from baseline at Day 84 (in a subset of patients only), and to assess the safety of SL77.0499-10 in the patients with LUTS related to BPH in comparison with placebo and tamsulosin hydrochloride.

Methodology:

Multicenter, randomized, placebo and active drug controlled study carried out on a double blind double dummy basis in 3 parallel groups.

Number of patients:
Planned: Approximately 1155
Randomized: 1177; Treated: 1177
Evaluated: Efficacy: 1172; Safety: 1177

Diagnosis and criteria for inclusion:

Japanese males, ≥50 years of age with symptomatic BPH diagnosed clinically by digital rectal examination and ultrasonography within the last 6 months and who suffered from LUTS related to BPH for at least 6 month.

Investigational product: SL77.0499-10extended release tablets and matching placebo tablets

Dose: 10 mg SL77.0499-10

Administration: Oral, once daily after breakfast

Reference therapy: Tamsulosin hydrochloride orally disintegrating tablets and matching placebo tablets

Dose: 0.2 mg tamsulosin hydrochloride

Administration: Oral, once daily after breakfast

Duration of treatment: 12 weeks

Duration of observation: 14 weeks (2 weeks of placebo run-in period + 12 weeks of double blind treatment period)

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the change in I-PSS total score from baseline to endpoint (Day 84 or last available post-baseline assessment).

The main secondary efficacy endpoints were changes from baseline to each visit in I-PSS total score and QOL score, and changes from baseline to endpoint (Day 84 or last available post-baseline assessment) of residual urine volume and PFR.

Safety:

Safety evaluations were the assessment of adverse events (AEs) focusing on treatment emergent adverse events (TEAEs), defined as AEs that occurred during study treatment exposure or within 5 half lives (3 days).

Statistical methods:

The sample size for this study was based upon the estimated differences of I-PSS total score improvement (SL77.0499-10 versus placebo and tamsulosin versus placebo).

Primary analysis:

SL77.0499-10 superiority versus placebo and non-inferiority versus tamsulosin hydrochloride was assessed for the modified intent to treat (mITT) population using the ANCOVA model with I-PSS total score change from baseline to last available post baseline value as response, treatment as a fixed effect, and I-PSS total score at baseline as a covariate. Pair wise comparison was performed within the framework of the ANCOVA model, and least square mean difference and two-sided 95% confidence interval (95%CI) is presented.

In order to keep the global significance level at 5%, a hierarchical testing procedure was applied as follows: first, SL77.0499-10 was compared with placebo. If the upper limit of the 95%CI of least square mean difference (=SL77.0499-10 - placebo) was not more than 0 point, SL77.0499-10 would be regarded as superior to placebo. Only if SL77.0499-10 superiority to placebo was demonstrated would SL77.0499-10 be compared with tamsulosin hydrochloride. If the upper limit of the 95%CI of least square mean difference (= SL77.0499-10 - tamsulosin hydrochloride) was not more than 1.0 point, SL77.0499-10 would be regarded as non-inferior to tamsulosin hydrochloride.

Summary:

Efficacy results:

The mean change in I-PSS total score from baseline to end of study (last observation carried forward [LOCF]) was -5.96 for placebo, -7.38 for alfuzosin, and -8.03 for tamsulosin. Alfuzosin showed superiority compared to placebo (95% CI: -2.166 to -0.434) which was statistically significant (p=0.0033). Though not statistically significant, non-inferiority compared to tamsulosin for the I-PSS total score change from baseline (95% CI: -0.101 to 1.314) was not demonstrated (p=0.2751).

The improvement of QOL score was statistically significant in both the alfuzosin and tamsulosin groups compared to the placebo group. Both groups exhibited a rapid onset of action, with improvements in I-PSS total score and QOL score. A trend toward improvement was observed for PFR and residual urine volume in both the alfuzosin and tamsulosin groups although these effects were not statistically significant compared to the placebo group. The alfuzosin group showed very similar results in QOL, PFR, and residual urine volume compared to the tamsulosin group, which further demonstrates comparability between the 2 active agents.

Safety results:

The numbers of patients who experienced at least 1 TEAE were similar among the 3 treatment groups (placebo: 93/235, 39.6%; alfuzosin: 215/471, 45.6%; tamsulosin: 215/471, 45.6%).

There were 13 patients who experienced at least 1 serious AE (SAE) during the study period. The percentage of patients who experienced at least 1 SAE was similar between the alfuzosin group (9/471, 1.9%) and placebo group (4/235, 1.7%).

Approximately 40 patients withdrew from the study due to TEAEs: 10 in the placebo group (4.3%), 23 in the alfuzosin group (4.9%), and 11 in the tamsulosin group (2.3%).

The incidence of vasodilatory events in the alfuzosin group (47/471, 10%) and the tamsulosin group (37/471, 7.9%) were comparable with the placebo group (10/235, 4.3%) and were for the most part due to postural dizziness, syncope, and orthostatic hypotension in the alfuzosin and tamsulosin groups.

No clinically relevant changes were observed in all groups for laboratory tests and ECG parameters.

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