

*These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.*

Sponsor/Company: sanofi-aventis	Study Identifier: NCT00347061												
Drug substance: Alfuzosin (SL77.0499-10)	Study code: LTS5235												
Title of the study: A long-term safety and efficacy of SL77.0499-10 10-mg once-daily tablets in patients with lower urinary tract symptoms related to benign prostatic hyperplasia (BPH). A multicenter, 52-week, open-label, uncontrolled study.													
Study centers: Multicenter study with a total of 18 active centers in Japan.													
Study period: Date first patient enrolled: 26-May-2006 Date last patient completed: 05-Oct-2007													
Phase of development: Phase 3													
Objectives: The primary objective of this study was to assess the safety of 10 mg dose of alfuzosin administered once daily for 1 year in patients with lower urinary tract symptoms (LUTS) related to BPH. The secondary objectives were to provide supportive information on the efficacy of 10 mg alfuzosin administered once daily for 1 year in patients with LUTS related to BPH, and to document the plasma concentration of alfuzosin after repeated administrations of 10 mg alfuzosin administered once daily in patients with LUTS related to BPH.													
Methodology: Multicenter, Japanese, open-label, uncontrolled, long-term safety study													
Number of patients: <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="2" style="text-align: center;">Summary of patient analysis population</th> </tr> <tr> <th style="text-align: center;">Number of patients</th> <th style="text-align: center;">Alfuzosin 10 mg</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Planned</td> <td style="text-align: center;">150</td> </tr> <tr> <td style="text-align: center;">Exposed patients (safety population)</td> <td style="text-align: center;">148</td> </tr> <tr> <td style="text-align: center;">Modified intent-to-treat (mITT) population</td> <td style="text-align: center;">147</td> </tr> <tr> <td style="text-align: center;">Pharmacokinetic population</td> <td style="text-align: center;">147</td> </tr> </tbody> </table>		Summary of patient analysis population		Number of patients	Alfuzosin 10 mg	Planned	150	Exposed patients (safety population)	148	Modified intent-to-treat (mITT) population	147	Pharmacokinetic population	147
Summary of patient analysis population													
Number of patients	Alfuzosin 10 mg												
Planned	150												
Exposed patients (safety population)	148												
Modified intent-to-treat (mITT) population	147												
Pharmacokinetic population	147												
Diagnosis and criteria for inclusion: Males, ≥50 years of age suffering for at least 6 months from LUTS related to BPH and an International Prostate Symptom Score (IPSS) total score ≥13 at screening and Day-1.													
Investigational product: Alfuzosin (SL77.0499-10)													
Dose: 10 mg													
Administration: Oral, once daily after breakfast													
Duration of treatment: 52 weeks													
Duration of observation: Screening period: 1 to 14 days (maximum + 4days) and treatment period: 52 weeks ±7 days													

Criteria for evaluation:**Efficacy:**

The main efficacy assessment was the change from baseline (Day-1) in IPSS total score to each visit and the last available postbaseline visit (last observation carried forward [LOCF] procedure). The change in the Quality-Of-Life index (bother score) was also assessed from baseline to each visit and LOCF.

Safety:

Safety was assessed by spontaneously reported adverse events (AEs) and treatment-emergent AEs (TEAEs), vital signs assessments (blood pressure and heart rate), and clinical laboratory tests. The rate of adverse drug reactions (ADRs) with a causal relationship to the investigational product was also assessed.

Pharmacokinetic sampling times and the bioanalytical method:

Blood samples for the quantification of alfuzosin concentrations in plasma were collected on Week 12 (Visit 6), Week 28 (Visit 8) and Week 52 (Visit 11) following repeated oral administration of 10 mg alfuzosin once a day. Alfuzosin plasma concentrations were assayed using a validated liquid chromatography tandem mass spectrometry method with a limit of quantification (LOQ) of 0.500 ng/mL (DOH0252).

Statistical methods:**Efficacy:**

The primary population for the efficacy analysis was the modified ITT (mITT) population. Summary statistics of the IPSS total score as well as the IPSS subscores (irritative and obstructive) are presented by visit and the last available postbaseline value (ie LOCF procedure). The frequency and percentage of patients within the categories were summarized.

Quality-of-life bother scores are presented by visit and LOCF. Observed values and changes from baseline are presented.

Safety:

The safety population consisted of all patients who were exposed to at least 1 dose of investigational product. Treatment-emergent adverse events were defined as AEs that occurred during study treatment exposure or within 5 half lives (2 days) following the last investigational product intake. Additionally, events present before the first dose, but worsening under treatment were considered TEAEs. Treatment-emergent adverse events were analyzed by system organ class and preferred term.

Summary statistics of raw values at baseline and of changes from baseline, at each visit and at the endpoint, were provided for clinical laboratory evaluations and vital signs. Counts of postbaseline potentially clinically significant abnormalities were also provided.

Pharmacokinetics:

Blood samples for the determination of alfuzosin in plasma were collected 1 to 3, 3 to 6, 6 to 9, and 9 to 12 hours postdosing. Individual values were summarized by descriptive statistics separately by visit. Plots of mean alfuzosin plasma concentrations are presented by visit and by sampling time.

Pharmacokinetic/pharmacodynamic relationship:

Pharmacokinetic/pharmacodynamic relationships between alfuzosin plasma concentrations and IPSS total score improvement and blood pressure change from baseline, supine systolic and diastolic blood pressure, standing systolic and diastolic blood pressure, were explored in descriptive and graphical ways. Relationships with age, creatinine clearance, and weight (<65, ≥65) were also investigated. The plots of alfuzosin plasma concentrations versus each parameter are presented by visit.

Summary:**Efficacy results:**

The evaluation of efficacy was considered supportive information in this study. During treatment with 10 mg alfuzosin, IPSS total scores and quality-of-life bother scores were promptly decreased up to Week 4. From Week 4 on, both parameters continued to improve (more gradually) up to Week 52 of treatment. In this study, the efficacy of alfuzosin was maintained during long-term treatment.

Safety results:

Overall, the majority of the patients experienced at least 1 TEAE (126/148, 85.1%). The most frequently reported TEAEs by preferred terms ($\geq 10\%$) were nasopharyngitis (55/148, 37.2%), seasonal allergy (17/148, 11.5%), and orthostatic hypotension (16/148, 10.8%).

Twelve patients (12/148, 8.1%) experienced at least 1 SAE during the study period including 1 death that was unrelated to the investigational product. For 2 SAEs, the Investigators did not exclude causality to the investigative product (1 event of syncope and 1 hypoesthesia of the left upper limb, both with outcomes of "recovered"). Less than a tenth of patients discontinued study treatment due to an AE. No specific TEAEs were associated with long-term exposure.

For vital signs, 16/148 (10.8%) of patients experienced at least 1 postbaseline orthostatic changes in SBP (standing minus supine ≤ -20 mmHg). No changes were reported for the heart rate parameter.

Pharmacokinetic results:

Mean values of alfuzosin C_{1-3H} , C_{3-6H} , C_{6-9H} , and C_{9-12H} were similar across visits, (9.84, 10.4), (10.3, 12.3), (10.0, 12.6), and (6.95, 10.2) ng/mL, respectively.

Pharmacokinetic/pharmacodynamic relationships results:

Inconsistencies on the degree of relationships between plasma alfuzosin concentrations and pharmacodynamic parameters were observed across visits, whereas steady-state conditions were fully reached on Week 12.

Issue date: 10-Oct-2008