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Proprietary Drug Name UROXATRAL®	**INN:** Alfuzosin HCl 10 mg extended-release tablets	**Therapeutic area and FDA approved indications:** For the treatment of the signs and symptoms of benign prostatic hyperplasia

Name of Sponsor/Company: Sanofi-Synthelabo Inc.; a member of the sanofi-aventis group.

Title of Study: Protocol L-8472: The Efficacy, Onset of Effect, and Safety of Alfuzosin Once Daily in the Treatment of Lower Urinary Tract Symptoms of Benign Prostatic Hyperplasia: A Randomized, Placebo-Controlled Trial Using an Acute International Prostate Symptom Score (Alf-Acute)

Principal Study Investigators: Martin J. Resnick, MD
Chairman, Department of Urology/Lester Persky
Professor of Urology
Case Western Reserve University
Cleveland, Ohio

Study centre(s): Fifty-two centers in the United States enrolled patients into the study.

Publications:

Resnick M, Roehrborn C. Alfuzosin 10 mg once daily rapid onset of effect in the treatment of BPH: preliminary results of randomized, placebo-controlled trial. *BJU Int*. 2004;94 Suppl 2:84.

Resnick M, Seftel A, Rosen RC, Roehrborn CG. Alfuzosin 10 mg improves sexual function in BPH patients: preliminary results of a placebo controlled trial. *BJU Int*. 2004;94 Suppl 2:69.

Study period (years): (date of first enrolment) (date of last completed) (10 January 2003) (18 August 2003)	**Phase of development:** Phase IIIB

Objectives:

Primary Objectives:

- Demonstrate that alfuzosin 10 mg once daily (QD) dose offers symptom relief using the Acute International Prostate Symptom Score (I-PSS) after 7 days of treatment in patients with symptomatic benign prostatic hyperplasia (BPH) as compared with placebo.
- Demonstrate that alfuzosin 10 mg QD has a rapid effect on peak urinary flow rate (Q_{max}) after 7 days of treatment in patients with symptomatic BPH as compared with placebo.

Secondary Objectives:

- Demonstrate that alfuzosin 10 mg QD offers improvement in the Bother Score after 28 days of treatment in patients with symptomatic BPH as compared with placebo.
- Demonstrate that alfuzosin 10 mg QD maintains or improves symptom relief after 28 days of treatment in patients with symptomatic BPH as compared with placebo using the Acute I-PSS.
- Demonstrate that alfuzosin 10 mg QD offers improvement in the Bother Score after 7 days of treatment in patients with symptomatic BPH as compared with placebo.
- Demonstrate that alfuzosin 10 mg QD improves Q_{max} after 1 day and maintains or improves Q_{max} after 28 days of treatment in patients with symptomatic BPH as compared with placebo.
- Demonstrate that alfuzosin 10 mg QD improves or maintains sexual function after 28 days of treatment in patients with symptomatic BPH as compared with placebo using the Danish Prostate Symptom Score (DAN-PSSsex) and Men's Sexual Health Questionnaire (MSHQ).
- Demonstrate that alfuzosin 10 mg QD reduces residual urine volume after 28 days of treatment in patients with symptomatic BPH as compared with placebo.
- Demonstrate that alfuzosin 10 mg QD improves quality of life (QOL) after 28 days using the BPH Impact Score in patients with symptomatic BPH as compared with placebo.

Methodology:

This was a 2-arm, parallel, randomized, double-blind, multicenter, placebo-controlled clinical trial. A total of 384 patients were planned for enrollment (or approximately 8 patients per site). For each patient, the total duration of study participation was 8 weeks. Patients underwent a 4-week (28-day) placebo run-in period followed by 1 month (28 days) on randomized study medication. All patients who met study entry criteria were randomized to either alfuzosin or placebo using a 1:1 ratio across the entire study population. Patients received either alfuzosin 10 mg QD or matching placebo QD.

Number of patients (planned and analyzed): 384 patients were to be enrolled. A total of 372 male patients with symptoms of BPH were enrolled into this study.

Diagnosis and main criteria for inclusion:

- Noninstitutionalized males aged ≥50 years.
- Patient had given their written informed consent prior to participating in the trial.
- Patient had lower urinary tract symptoms (LUTS) associated with BPH for ≥6 months and had a digital rectal examination during Screening and a transrectal ultrasonography (TRUS) examination of the prostate performed within 12 months before Day 1.
- Patient had a history of micturition disturbances with various degrees of the following symptoms for at least the past 6 months prior to Day -28:

Storage symptoms (Irritative symptoms)	Voiding symptoms (Obstructive symptoms)
- daytime frequency	- difficulty initiating micturition
- nocturia	- impaired quality of the stream
- urgency	- feeling of incomplete voiding
	- interruption of the stream

- Patient had an Acute I-PSS score of ≥13 and a Bother Score of ≥3 on Day -28.
- Patient had a Q_{max} between 5 mL/sec and 12 mL/sec at Day -28 and a voided volume of at least 150 mL on this day.
- Patient had a residual urine volume ≤350 mL on Day -28.

Test product, dose and mode of administration, batch number:

Alfuzosin, 10 mg QD at end of evening meal, oral, CL-04678

Duration of treatment:
All patients were treated for approximately 1 month.

Reference therapy, dose and mode of administration, batch number :

Matching placebo, Once daily at end of evening meal, Oral, CL-04673

Criteria for evaluation:

Efficacy was evaluated by the following: Q_{max}, voided volume, and flow time as assessed by uroflowmetry; residual volume as assessed by transabdominal ultrasonography; and scores from the Acute I-PSS (including the Bother Score), the DAN-PSSsex, the BPH Impact Index, and the MSHQ. Study Days 8 and 29 were the primary time points for evaluation.

Safety was assessed by the results of the following: vital signs (supine and standing blood pressure and heart rate); physical including digital rectal examinations; clinical laboratory testing; 12-lead electrocardiograms (ECGs); and by monitoring the incidence of adverse events (AEs).

Statistical methods:

Summary statistics included the number (N), mean, standard deviation (SD), median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

For all variables, the last measurement before the start of double-blind treatment was used as the Baseline value. Because the first dose of double-blind treatment was taken the evening of Day 1, variables with measurements scheduled on Day 1 used the Day 1 value as the Baseline value. If the Day 1 value was missing and the Day -28 value was available, then the Day -28 value was used as the Baseline value. Variables with measurements scheduled only on Day -28 (Screening) used the Day -28 value as the Baseline value.

Multiple evaluations on the same day were averaged for the summary tables for continuous variables.

The study success was based on an “and/or” logic using 2 primary endpoints. Thus, the Bonferroni-adjusted type I error rate of 0.025 was applied to 2 primary endpoints to account for multiple comparisons and to control the overall type I error rate of 0.05. Unless otherwise specified, all other statistical tests had type I errors of 0.05 and 2-sided tests were used.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Acute I-PSS Total Score:

Primary: Analysis of the primary endpoint, reduction in Acute I-PSS Total Score at Day 8 on the ITT population, revealed that at Day 8, patients in the alfuzosin group had a greater mean reduction from Baseline of 3.4 points compared with 2.7 points for the placebo group. A trend toward significance (p=0.07) occurred at Day 8 and the mean reduction was highly significant (p=0.003) by Day 29 (see secondary endpoint). The analysis of Acute I-PSS Total Score reduction from Baseline to Day 8 by categorized groups (reduction <0%, reduction =0% and <20%, reduction =20% and <50%, and reduction =50%) also revealed no statistically significant differences between treatment groups, although a trend toward significance was observed (p=0.082) for the alfuzosin group.

When the reduction in Acute I-PSS Total Score at Day 8 was evaluated for the Per-Protocol population, results were similar to the results observed for the ITT population. Patients in the alfuzosin group had a greater mean reduction from Baseline of 3.6 points compared with 2.6 points in the placebo group. No statistically significant difference between treatment groups was observed. The Per-Protocol population analysis of Acute I-PSS Total Score reduction from Baseline to Day 8 by categorized groups (reduction <0%, reduction =0% and <20%, reduction =20% and <50%, and reduction =50%) also revealed no statistically significant differences between treatment groups, although a trend toward significance was observed (p=0.082) for the alfuzosin group.

Secondary: The analysis of reduction in Acute I-PSS Total Score at Day 29 showed a statistically significant difference between treatment groups (p=0.003). Patients in the alfuzosin group had a significantly greater reduction from Baseline (4.5 points) than patients in the placebo group (3.1 points). Additionally, a statistically significantly higher percentage of patients in the alfuzosin group (44.3%) demonstrated maintenance of reduction in Acute I-PSS Total Score compared with placebo (32.6%) (p=0.028). Patients in the alfuzosin group also had statistically significantly greater reductions from Baseline to Day 29 for the irritative, obstructive, and nocturia subscores of the I-PSS (p=0.016, p=0.004, and p=0.042, respectively) compared with placebo. For the nocturia subscore, patients in the alfuzosin group also had a statistically significantly greater reduction from Baseline at Day 8 compared with placebo (p=0.046), which suggests that alfuzosin patients experienced a greater decrease in the number of times they had to get up during bedtime to urinate.

Peak urinary flow rate (PFR or Q_{max}):

Primary: Analysis of the primary endpoint, improvement in peak flow rate (PFR) at Day 8, revealed that at Day 8, a statistically significant difference in improvement from Baseline between treatment groups was observed (p<0.001). Patients in the alfuzosin group had a significantly greater mean improvement from Baseline (1.92 mL/sec) than patients in the placebo group (0.39 mL/sec). The analysis of PFR improvement from Baseline to Day 8 by categorized groups (improvement <0%, improvement =0% and <20%, improvement =20% and <50%, and improvement =50%) showed that patients in the alfuzosin group had a statistically significantly

greater improvement at Day 8 compared with placebo ($p<0.001$).

Improvement in Q_{max} from Baseline to Day 8 was also evaluated for the Per-Protocol population. Prior to database lock, it was decided that Q_{max} measurements were not reliable when voided volume was <125 mL. As a result, Q_{max} was set to "missing" if a patient's voided volume was <125 mL. However, this was not a criterion for exclusion from the Per-Protocol population. Therefore, patients with a voided volume <125 mL were included in the overall Per-Protocol population but excluded from the summary table for Q_{max} at Day 8. The decision was made by the Senior Medical Director to exclude 1 patient (Patient 010/1205) from the Q_{max} at Day 8 Per-Protocol analysis due to the patient's voided volume of <125 mL, resulting in an overall population of 284 patients for this particular analysis (as opposed to the 285 patients for the total Per-Protocol population). Results were similar for the Per-Protocol population compared with the ITT population. A statistically significant mean difference between treatment groups was observed ($p<0.001$). Patients in the alfuzosin group had a mean improvement in Q_{max} from Baseline to Day 8 of 2.01 mL/sec compared to an improvement of 0.41 mL/sec in the placebo group. The Per-Protocol population analysis of PFR improvement from Baseline to Day 8 by categorized groups (improvement <0%, improvement =0% and <20%, improvement =20% and <50%, and improvement =50%) showed that patients in the alfuzosin group had a statistically significantly greater improvement at Day 8 compared with placebo ($p=0.008$).

Secondary: The analysis of PFR also revealed that patients in the alfuzosin group showed greater improvement from Baseline at both Day 2 and Day 29 than patients in the placebo group. The difference between treatment groups was statistically significant at both time points ($p=0.021$ at Day 2 and $p<0.001$ at Day 29). Additionally, a statistically significantly higher percentage of patients in the alfuzosin group showed maintenance of improvement in PFR compared with placebo ($p=0.006$).

Bother Score:

Analysis of the main secondary endpoint, reduction in I-PSS Bother Score at Day 29, revealed that patients in both treatment groups had a similar reduction from Baseline to Day 29 (0.7-point reduction for the alfuzosin group and 0.6-point reduction for the placebo group); no statistically significant difference between treatment groups was observed.

Other Secondary Endpoints:

Analysis of the remaining secondary objectives and their corresponding endpoints revealed the following:

- The analysis of reduction in Bother Score at Day 8 showed that patients in both treatment groups had a similar reduction from Baseline to Day 8. No statistically significant difference between treatment groups was observed.
- The analysis of improvement in DAN-PSSsex questionnaire results from Baseline to Day 29 revealed that alfuzosin patients demonstrated a statistically significantly ($p=0.015$) greater improvement for the 1A individual score ("Can you get an erection?") than placebo patients, whose scores actually worsened. No other statistically significant differences between treatment groups were observed for any of the other individual scores of the DAN-PSSsex.

- The analysis of reduction in residual urine volume at Day 29 showed that patients in the alfuzosin group demonstrated a greater mean reduction from Baseline (reduction of 14.2) compared with a reduction of 4.6 in the placebo group. No statistically significant difference between treatment groups was observed.
- The analysis of improvement in quality of life at Day 29 using BPH Impact Score showed that patients in the alfuzosin group demonstrated a statistically significantly (p=0.020) greater mean reduction from Baseline (0.9) than patients in the placebo group (0.5).
- The correlation analysis between MSHQ measures and Acute I-PSS Total Score showed that all the correlation coefficients for each of the 19 MSHQ questions were negative, which indicates consistency with the scoring scales for the I-PSS (where higher scores indicate more severe problems) and for the MSHQ (where higher scores indicate better sexual health conditions). Some MSHQ questions were significantly correlated to the Acute I-PSS Total Score.

SAFETY RESULTS:

Overall, the number of patients who experienced treatment-emergent adverse events (TEAEs) was similar between treatment groups. Most TEAEs were mild or moderate in severity. The most frequently reported TEAE in the alfuzosin group was dizziness, which was reported in 11 (5.9%) patients. The most frequently reported TEAE in the placebo group was orthostatic hypotension, which was reported in 4 (2.2%) patients.

Treatment-emergent AEs of dizziness (11 [5.9%] patients in the alfuzosin group) and orthostatic hypotension (3 [1.6%] patients in the alfuzosin group and 4 [2.2%] patients in the placebo group) were categorized as vasodilatory disorders. No other TEAEs associated with vasodilatory disorders were reported.

No deaths were reported in this study. One patient from the alfuzosin group reported 1 serious adverse event (SAE) of noninsulin-dependent diabetes mellitus.

No clinically meaningful trends were observed in clinical laboratory test results, vital sign measurements, physical examination findings, digital rectal examination findings, or 12-lead ECG results.

Date of the report: 22 June 2005