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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00409357
Drug substance(s):	alfuzosin	**Study Code:**	DRI5234
		Date:	20 November 2006

Title of the study:	A multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose ranging study of SL77.0499-10 once daily tablets in patients with lower urinary tract symptoms related to benign prostatic hyperplasia (BPH)
Investigator(s):	Seiji Naito, MD, Kyushu University, Fukuoka, Japan (Coordinating Investigator)
Study center(s):	41 active centers in Japan
Publications:	None
Study period: **Date first patient enrolled:** 11 November 2004 **Date last patient completed**: 18 August 2005	**Phase of development:** Phase 2
Objectives: *Primary:*	The primary objective was to assess the dose-response relationship of SL77.0499-10 (alfuzosin hydrochloride, ie, alfuzosin) 5 mg, 10 mg, 15 mg, and placebo once daily during a 12-week oral administration period for the efficacy [International Prostate Symptom Score (IPSS) total score improvement] in patients with lower urinary tract symptoms (LUTS) related to BPH.
Secondary:	Secondary objectives were to assess the efficacy of each dose of alfuzosin as compared with placebo and to assess the safety of each dose of alfuzosin.
Methodology:	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study carried out in 4 parallel groups.

Number of patients:

Summary of patient analysis populations

Number of patients	Placebo	Alfuzosin (mg)			Overall
		5	10	15	
Planned	110	110	110	110	440
Randomized patients	121	119	117	116	473
Exposed patients (safety population)	121	119	117	116	473
Modified Intent-to-treat (mITT) pop	121	118	116	116	471
Per-protocol population	116	111	114	111	452

Diagnosis and criteria for inclusion:

Males ≥50 years-of-age:

- suffering from LUTS related to BPH for at least 6 months;
- having an IPSS ≥13;
- having a urinary peak flow rate (PFR) 5.0 to 12.0 mL/s for a voided volume of at least 150 mL;
- having a residual urine volume ≤200 mL.

Investigational product:	Alfuzosin	
Dose:	5 mg, 10 mg, or 15 mg extended–release (ER) tablets once daily	
Administration:	Oral administration after breakfast	
Duration of treatment: 12 weeks		**Duration of observation:** 14 weeks
Reference therapy:	Placebo matching tablets	
Dose:	Not applicable	
Administration:	Oral administration after breakfast	
Criteria for evaluation:		
Efficacy:	The primary efficacy assessment was the change from baseline in IPSS total score at the end-of-study (EOS) visit. Secondary assessments included changes from baseline in: • IPSS total score by visit; • IPSS irritative and obstructive subscores at the EOS visit and by visit; • urinary PFR at EOS and by visit; • residual urine volume at EOS and by visit. Secondary assessments also included the percentage of patients whose baseline: • IPSS total score improved ≥3 points at EOS; • urinary PFR improved ≥2 mL/sec at EOS.	
Pharmacokinetics:	Not applicable	
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 reactions with a causal relationship to the investigational product was also assessed.	
Statistical methods:		
Efficacy:	The primary population was the modified ITT (mITT) population. In addition, the per-protocol population was used for confirmatory analyses. The primary efficacy analysis was a one-way analysis of variance (ANOVA) with IPSS total score improvement that the EOS [Day 84 with the last observation carried forward (LOCF) procedure] as response and treatment as a fixed effect. A monotonic dose-response relationship between the placebo and 5, 10, and 15 mg alfuzosin groups was tested at the two-sided 5% level within the model using a contrast test with contrast coefficients [3, 1, -1, -3] for treatment. Placebo-adjusted least square means and 95% confidence intervals (CIs) were also presented.	
Safety:	The safety population consisted of all randomized patients who were exposed to at least 1 dose of double-blind investigational product. Summary statistics of raw values at baseline and of changes from baseline, at each visit and at the endpoint, were provided by treatment group for clinical laboratory evaluations and vital signs. Counts of postbaseline potentially clinically significant abnormalities (PCSAs) were also provided.	

Statistical methods (continued):

Safety (continued): All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 8.0). Treatment-emergent AEs were defined as AEs that occurred during double-blind study treatment exposure or within 5 half-lives (2 days) following the last double-blind investigational product intake. Additionally, events present before the first dose, but worsening under treatment were considered TEAEs. TEAEs were analyzed by system organ class (SOC) and preferred term (PT).

Summary:

Efficacy results: The treatment groups were well balanced at baseline (placebo versus 5, 10, and 15 mg alfuzosin):

- number of patients per treatment group (121 vs 118, 116, and 116);
- mean±SD age (65.2±6.8 vs 65.0±7.2, 67.1±6.4, and 65.1±8.0);
- mean±SD IPSS total score (18.4±5.0 vs 17.0±4.7, 18.3±4.8, and 18.7±5.1);
- mean±SD PFR at selection in mL/sec (8.69±2.30 vs 8.87±2.10, 8.38±2.07, and 8.29±2.25).

For the mITT population, the linear trend test in IPSS total score improvement (primary analysis) was statistically significant (p=0.0326). At the endpoint, the largest mean decrease of the IPSS total score was found in the 10 mg alfuzosin group. The results on the improvement of urinary PFR were consistent with these results with a significant linear trend test (p=0.0007) and the 10 mg alfuzosin dose giving the best results.

Similar results were observed for the per-protocol population. It is important to note that the per-protocol analyses fully supported the analyses of the mITT population for all efficacy parameters.

Summary of IPSS total score (LOCF) - mITT population

	Placebo (N=121)	Alfuzosin 5 mg (N=118)	Alfuzosin 10 mg (N=116)	Alfuzosin 15 mg (N=116)
Mean (SD) at baseline	18.4 (5.0)	17.0 (4.7)	18.3 (4.8)	18.7 (5.1)
Mean (SD) at last visit	12.1 (6.2)	9.8 (5.5)	10.4 (6.0)	10.9 (7.5)
Mean change from baseline (SD) at last visit	-6.3 (6.0)	-7.2 (5.3)	-7.9 (5.5)	-7.8 (6.5)
p-value of trend test	0.0326			
Lsmean difference from placebo (SE)	-	-0.8 (0.8)	-1.6 (0.8)	-1.5 (0.8)
95% CI	-	-2.3 ; 0.6	-3.1 ; -0.1	-3.0 ; 0.0
p-value	-	0.2646	0.0362	0.0541
p-value adjusted by Hochberg's method	-	0.2646	0.1083	0.1083

Liner contrast [-3 -1 1 3] was used for trend test within an ANOVA model framework.
Pairwise comparisons were performed using appropriate contrasts within an ANOVA model framework.

For additional secondary efficacy parameters, positive linear trend tests were also observed for:

- IPSS obstructive score (p=0.0381);
- urinary PFR responder patients (≥2 mL/sec improved at endpoint) (p=0.0019);
- residual urine volume (p=0.0012).

Summary (continued):

Safety results: Number (%) of randomized and exposed patients who experienced at least 1 TEAE

	Placebo (N=121) n (%)	Alfuzosin 5 mg (N=119) n (%)	Alfuzosin 10 mg (N=117) n (%)	Alfuzosin 15 mg (N=116) n (%)	Alfuzosin Total (N=352) n (%)
Patients with any TEAE (including SAEs)	69 (57.0)	58 (48.7)	64 (54.7)	79 (68.1)	201 (57.1)
Patients with any SAE (including SAEs leading to death)	3 (2.5)	3 (2.5)	1 (0.9)	0 (0)	4 (1.1)
Deaths	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Patients permanently discontinuing treatment due to AE	3 (2.5)	4 (3.4)	0 (0)	5 (4.3)	9 (2.6)

Alfuzosin was clinically well tolerated in comparison with placebo. The numbers of patients who experienced at least 1 TEAE were similar in the 5 mg, 10 mg, and placebo treatment groups [48.7% (58/119) and 54.7% (64/117) versus 57.0% (69/121), respectively]. A slightly greater number of patients administered 15 mg alfuzosin experienced TEAEs (68.1%, 79/116). The most commonly reported TEAEs were in the infections and infestations SOC. A dose effect was observed for postural dizziness. Orthostatic hypotension was reported more frequently in the 5-, 10-, and 15-mg alfuzosin groups (5.9%, 3.4%, and 10.3%, respectively) compared with the placebo group (1.7%). Palpitation events were the only cardiac events reported, 1 in the 10-mg and 3 in the 15-mg alfuzosin groups. Anemia was reported with a high incidence in the 15-mg group (5.2%) while there were no reports of this AE in the placebo group and only one report for each of the 5- and 10-mg alfuzosin groups.

The percentage of patients who experienced at least 1 serious adverse event (SAE) was similar between groups [2.5% (3/119), 0.9% (1/117), and 0.0% (0/116) in the 5, 10, and 15 mg alfuzosin groups, respectively, and 2.5% (3/121) in the placebo group]. For 1 SAE, the Investigator considered a causal relationship with 5 mg alfuzosin to be reasonably possible (cerebral infarction of moderate intensity, 34 days after study start, hospitalization was required, corrective treatment was given, study treatment was discontinued, and the outcome at the end of follow-up was “recovering”).

Serious vasodilatory events, including syncope, were not reported. There was 1 death in the placebo group. The percentages of patients who were permanently withdrawn from the study due to an AE were higher in the 5 mg and 15 mg alfuzosin groups [3.4% (4/119) and 4.3% (5/116), respectively] than in the placebo group (2.5%, 3/121). The percentages of patients who experienced adverse drug reactions associated with the investigational product were higher in the 5, 10, and 15 mg alfuzosin groups [16.0% (19/119), 19.7% (23/117), and 31.9% (37/116), respectively] than in the placebo group (12.4%, 15/121).

The clinical laboratory safety of alfuzosin was satisfactory in comparison with placebo. For vital signs, orthostatic changes in heart rate and SBP were more frequently observed in the alfuzosin groups than in the placebo group.

Date of full report: 08 November 2006