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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00290030
Drug substance(s):	alfuzosin	**Study Code:**	EFC4428
		Date:	10 March 2006

Title of the study:	A double-blind randomized parallel group study of alfuzosin 10 mg once daily versus placebo in the management of acute urinary retention in patients with a first episode due to benign prostatic hyperplasia (BPH) (EFC4428)
Principal Investigator:	Claus G. Roehrborn, MD
Study centers:	Seventy-three active centers in 5 countries [Bulgaria (6), Canada (19), Mexico (4), the Ukraine (2), and the United States of America (USA) (42)]. The Principal Investigator was located at The Department of Urology, UT Southwestern Medical Center, Dallas, TX USA.
Publications:	Not applicable
Study period: **Date first patient enrolled:** 10 May 2001 **Date last patient completed**: 16 October 2004	**Phase of development:** Phase 3
Objectives: Primary**:**	The primary objective was to assess the efficacy of 10 mg alfuzosin (once daily) in the management of acute urinary retention (AUR) associated with benign prostatic hyperplasia (BPH).
Secondary**:**	The secondary objectives were to assess: • residual urine volume using transabdominal ultrasonography; • health care consumption; and • functional urinary symptoms and Quality of Life (QOL) index.
Safety:	The safety and tolerability of 10 mg alfuzosin were evaluated in all exposed patients.
Methodology:	This is an international, multicenter, randomized, double-blind, placebo-controlled, 2 parallel-group, fixed-dose (10 mg alfuzosin or placebo, once daily) study in patients with a first episode of AUR related to BPH. The acute episodes were managed with catheterization and with investigational product treatment for 2 to 3 days followed by a voiding trial to assess the patients' ability to void after catheter removal. Those patients who successfully voided continued their randomized treatment for 6 months.

Number of patients:

Summary of patient analysis populations

Number of patients	Placebo	Alfuzosin (10 mg)	Overall
Planned[a]	200	200	400
Planned (adjusted following interim analysis)	400	400	800
Randomized patients	396	410	806
Exposed patients (safety population)	393	407	800
Intent-to-treat (ITT) patients	383	393	776
ITT patients in the postcatheterization period	200	220	420

a: Adjustment to 800 patients following the interim analysis was planned in the protocol.

Diagnosis and criteria for inclusion:

- Males over the age of 50 years presenting with a first episode of painful AUR related to BPH;
- Residual urine volume between 500 and 1500 mL at the time of catheterization

Investigational product: Alfuzosin

Dose: 10 mg tablets (Geomatrix formulation) once daily

Administration: Oral administration immediately following a meal with the first dose within 36 hours after catheterization

Batch numbers: CL-03485, CL-03488, CL-04678, and CL-06287

Duration of treatment: 6 months

Duration of observation: 180 days ± 14 days

Reference therapy: Placebo matching tablet (Geomatrix formulation) once daily

Dose: Not applicable

Administration: Oral administration immediately following a meal with the first dose within 36 hours after catheterization

Batch number: CL-03486, CL-04673, and CL06285

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was success in terms of % patients meeting the following 3 criteria:

- successful voiding in the initial period (using a voiding trial) and success in spontaneous voiding after the voiding trial;
- no relapse of AUR during the 6-month treatment period; and
- no need/indication for surgery during the 6-month treatment period.

Secondary assessments included:

- residual urine volume;
- health care consumption; and
- International Prostate Symptom Score (IPSS) and QOL index.

Pharmacokinetics: Alfuzosin plasma concentrations were assessed.

Safety: Safety was assessed by spontaneously reported adverse events (AEs), vital signs assessments (blood pressure and heart rate), and clinical laboratory tests.

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were taken during the acute period at the Day 1 visit (before investigational product intake) and on Day 3/Day 4 (before the catheter was removed).

Alfuzosin plasma concentrations were determined using a validated high performance liquid chromatography method with fluorometric detection. The limit of quantification was 0.5 ng/mL.

Statistical methods:	The primary efficacy analyses were performed on the intent-to-treat (ITT) population at Month 6. The ITT population consisted of randomized patients with a successful voiding trial at the Day 4/Day 5 visit and who received at least 2 doses of investigational product. The safety population consisted of all randomized patients who were exposed to at least 1 dose of double-blind investigational product.
Efficacy:	The primary efficacy criterion was the time to failure (in days) measured as the time elapsed between the date of the Day 1 visit and the exact date of failure. Failure was defined as the earliest occurrence of 1 of the following events: failure in voiding, relapse of AUR, or the need/indication for surgery. The primary efficacy endpoint was success in terms of the percentage of patients without AUR with or without surgery [Kaplan-Meier (KM) survival analysis] at the theoretical date of Month 6 (date of the Day 1 visit + 180 days). The differences of KM survival rates are provided with 99.9% confidence intervals (CIs) and associated p-values. In addition, the estimate of the hazard ratios with 99.9% CIs and the p-values of the log-rank test comparing survival curves are provided. The same analyses were performed for the primary criterion at Month 6, the catheterization period, and for Months 1 and 3. Incidence rates of failure at each endpoint were calculated and compared between groups using a Chi-square test. This is also provided for the catheterization period analysis for failure rate at the Day 4/Day 5 visit (voiding trial failure and spontaneous voiding failure).
Safety:	All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 7.0). Treatment-emergent adverse events (TEAEs) 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. TEAEs were analyzed by system organ class (SOC) and preferred term (PT). Summary statistics of raw values at baseline and of changes from baseline, at each visit and at the endpoint, are provided by treatment group for the study period, for the catheterization period (baseline, the Day 3/Day 4 visit, and the endpoint), and for the postcatheterization period for clinical laboratory evaluations and vital signs. Counts of postbaseline potentially clinically significant abnormalities (PCSAs) are also provided.

Summary:

Efficacy results:

At 6 months, the success rate was 43.5% for alfuzosin-treated patients and 39.7% for placebo-treated patients (% patients without failure; Kaplan Meier analysis; ITT population) indicating a better, although not statistically significant, result for alfuzosin [Δ 3.8%; 99% CI (-8.0%; 15.6%)].

Summary of the percentage of patients without AUR, with or without surgery, (KM survival analysis) at Month 6 (Day 180) - ITT population

	Placebo n (%)	**Alfuzosin 10 mg n (%)**
Total number of patients	383 (100)	393 (100)
Number of patients with failure between D1 and M6	228 (59.5)	219 (55.7)
Survival rate at M6 (%)	39.7%	43.5%
Difference between survival rate [99.9% CI]	3.8% [-8.0%; 15.6%]	
Hazard ratio (Survival rate)	1.11 [0.80; 1.53]	
Hazard ratio (Log-rank test)	1.12 [0.82; 1.53]	
p-value (Survival rate)	0.28991	
p-value (Log-rank test)	0.2439	

Summary of failures during the study (Day 1 to Day 180/Month 6) - ITT population

	Placebo n (%)		**Alfuzosin (10 mg) n (%)**	
Total number of patients	383	(100)	393	(100)
Total Failures	228	(59.5)	219	(55.7)
Failure in voiding	173	(45.2)	164	(41.7)
AUR relapse only	5	(1.3)	4	(1.0)
AUR relapse following by a need for surgery	18	(4.7)	17	(4.3)
Need for surgery only	7	(1.8)	9	(2.3)
AUR relapse and need for surgery at the same time	25	(6.5)	25	(6.4)

During the different phases of the trial, the most marked difference in success rates between the treatment groups, in favor of alfuzosin, were observed for the first month of treatment {52.2% for alfuzosin-treated patients compared with 46.9% for placebo-treated patients [Δ 5.3%; 99% CI (-6.6%; 17.1%)]}. The outcome of the acute voiding trial phase was also in favor of alfuzosin with 58.3% alfuzosin-treated patients successfully treated vs 54.8% of placebo-treated patients.

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

	Placebo n (%)		Alfuzosin (10 mg) n (%)	
Total number of patients	393	(100)	407	(100)
Patients with at least 1 TEAE	94	(23.9)	96	(23.6)
Patients with at least 1 SAE	12	(3.1)	13	(3.2)
Deaths	2	(0.5)	1	(0.2)
Patients permanently discontinued due to a TEAE	13	(3.3)	21	(5.2)

Alfuzosin was clinically well tolerated. The number of patients who experienced at least 1 TEAE was similar in the alfuzosin and placebo groups. The most frequently reported AE was dizziness. The overall incidence of vasodilatory events was 4.9% (20/407) in the alfuzosin group compared to 4.3% (17/393) in the placebo group. Three patients in the alfuzosin group versus none in the placebo group experienced hypotension. Syncope events were not reported with alfuzosin, but 2 were reported in the placebo group. Cardiac events were reported infrequently in both treatment groups. No ejaculation disorders were reported with alfuzosin and the frequency of urinary tract infection was similar in both groups.

The frequency of patients who reported SAEs was similar in both the alfuzosin group [3.2% (13/407)] and the placebo group [3.1% (12/393)]. No serious vasodilatory events were reported with alfuzosin. The frequency of patients who withdrew from the study due to AEs was slightly higher in the alfuzosin group [5.2% (21/407)] in comparison with placebo [3.3% (13/393)]. Withdrawals from the study due to vasodilatory events tended to be slightly more frequent with alfuzosin [0.5% (2/407)] than with placebo [0.3% (1/393)]. One urinary tract infection led to withdrawal from the study in the alfuzosin group.
The clinical laboratory safety of alfuzosin was satisfactory in comparison with placebo. For vital signs, standing-supine changes in SBP and HR were more frequently observed in the alfuzosin group.

Date of report: 26 October 2005