

The number of patients with significant laboratory abnormalities is shown in Table B.9.

Table B.9. Number of patients with significant laboratory abnormalities.

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
Total bilirubin > 2 X ULN	0/142	0/122	0/132
AST > 2 X ULN	1/142	0/122	0/132
ALT > 2 X ULN	1/135	0/115	1/120
Alk. Phosphatase > 1.25 X ULN	0/143	0/123	0/134
Creatinine > 100uM and increase >30%	2/145	3/127	1/137
Neutrophils < 1500/ml	3/140	1/123	2/133
Hemoglobin Decrease > 2g/dl	2/138	3/124	4/132
Platelets <100,000/ml	0/141	0/124	1/133

One abnormal LFT was noted in the alfuzosin 10 mg OD group. This 71 year-old-man had an increased ALP and GGT both at baseline and during the study. He withdrew from the study due to the ALP increase. The investigator believed that the elevated ALP was not related to study drug but rather to excessive alcohol intake.

#### B.8.6 Special safety issues – cardiovascular (vasodilatory events) events

Cardiovascular adverse events are shown in Table B.10.

Table B.10. Cardiovascular adverse events

	Placebo N=154	Alfuzosin 10 mg OD (N=143)	Alfuzosin 2.5 mg tid N=149
Dizziness	2 (1.3%)	3 (2.1%)	7 (4.7%)
Malaise	0	2 (1.4%)	1 (0.7%)
Postural hypotension	0	0	2 (1.3%)
Hypotension	0	1 (0.7%)	0
Syncope	0	0	1 (0.7%)

Cardiovascular adverse events by age are shown in Table B.11.

Table B.11. Cardiovascular adverse events by age.

	Placebo			Alfuzosin 10 mg			Alfuzosin 2.5 mg tid		
	<65	65-75	>75	<65	65-75	>75	<65	65-75	>75
Dizziness	2(3%)			3(5%)			3(4%)	4(7%)	
Malaise				1(1%)	1(6%)		1(2%)		
Postural hypotension							1(1%)	1(2%)	
Hypotension				1(6%)					
Syncope							1(1%)		

Dizziness: The most frequently reported adverse event was dizziness. The incidence was less in the alfuzosin 10 mg OD group than in the alfuzosin 2.5 mg tid group.

Hypotension: No cases of symptomatic postural hypotension were reported in the alfuzosin 10 mg group. Two patients in the alfuzosin 2.5 mg tid group experienced postural hypotension.

Syncope: No cases of syncope were reported in the alfuzosin 10 mg group. One patient (#27740674) in the alfuzosin 2.5 mg tid group experienced syncope lasting less than 1 minute which occurred when the patient had his head laid back during eye drop instillation. No BP recordings are available.

Other cardiac events: One patient in the alfuzosin 10 mg OD group experienced palpitations.

*B.9 Reviewer's assessment of efficacy and safety:* The reviewer believes that the efficacy and safety data from the ALFORTI trial supports the approval of alfuzosin ER 10 mg for the treatment of the signs and symptoms of benign prostatic hyperplasia.

#### Appendix C:

**Clinical Trial ALFOTAM – 2440:** “Efficacy and Safety of Two Dosage Levels of Alfuzosin Geomatrix (10 mg OD and 15 mg OD) Versus Tamsulosin (0.4 mg OD) and Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia. Placebo Controlled, Double-Blind Study, Conducted in 4 Parallel Groups for Three Months Followed by an Optional 9-Month Open-Label Extension with Alfuzosin Geomatrix 15 mg OD” (Study began February 5, 1998, and ended August 25, 1999.)

**C.1 Objectives:** The primary objective of this 3-month trial was to assess, in comparison with tamsulosin 0.4 mg OD and placebo, the efficacy and safety of 2 dosage levels (10 and 15 mg) of the Geomatrix formulation of alfuzosin administered as a single daily dose in patients with symptomatic BPH.

**C.2 Design and Conduct Summary:** This trial was a multicenter, multinational, randomized, placebo-controlled, double-blind phase 3 trial with 4 parallel groups (alfuzosin 10 mg OD, alfuzosin 15 mg OD, tamsulosin 0.4 mg OD, and placebo). A 28-

day single-blind placebo run-in period was followed by a 3-month treatment period carried out on a double-blind, double-dummy basis.

The trial was composed of 2 phases. Phase A was a 28-day single-blind phase during which all patients received placebo (1 capsule matching tamsulosin 0.4 mg and 1 tablet matching alfuzosin 10 mg Geomatrix at the end of the evening meal). Phase B consisted of an 84-day (3 month) double-blind double dummy-treatment period during which patients received 1) alfuzosin 10 mg OD and placebo matching tamsulosin 2) alfuzosin 15 mg OD and placebo matching tamsulosin 3) tamsulosin 0.4 mg and placebo matching alfuzosin or 4) placebo matching tamsulosin and placebo matching alfuzosin. Six visits were planned: a screening visit (D-28), an inclusion visit (D0), 3 intermediate visits (D14, D28, and D58, and an end-point visit at the end of the double-blind period (D84). Patients were randomly allocated to treatment groups at inclusion at D0. Amendment #2 provided for 2 primary endpoints: the improvement in IPSS and the improvement in  $Q_{max}$ .

*Reviewer's comment: Tamsulosin is approved at doses of 0.4 and 0.8 mg. In this trial, the sponsor studied only the low dose.*

At D-28, hematology and chemistry (including PSA) tests, urinalysis, physical examination, IPSS and QOL index, sexual function (DAN-PSS), Urolife questionnaire, urine flow rate, residual urine, and vital signs were performed.

At D0, D28, D56, and D84, urinalysis, IPSS and QOL index, sexual function (DAN-PSS), Urolife questionnaire, urine flow rate, residual urine, and vital signs were performed. In addition, on D14, urinalysis, urine flow rate, residual urine, and vital signs were obtained. Transrectal ultrasonography was performed on D0 and alfuzosin or tamsulosin assay was performed on D0 and D84. Finally, hematology and chemistry tests and Clinical Global Impression (CGI) were performed on D84.

C.3 Study population: The study population consisted of men aged greater than 50 years with at least a 6 month history of voiding symptoms. Baseline characteristics of the study population are shown in Table C.1.

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Table C.1. Baseline characteristics of the study population:

	Placebo (N=154)	Alfuzosin 10 mg (N=154)	Alfuzosin 15 mg (N=159)	Tamsulosin 0.4 mg (N=158)
Age (mean) (yrs)	64.2	64.6	64.6	63.9
Age (range)	50-82	51-85	50-84	50-87
Age > 65 years (N) (%)	72 (47%)	73 (48%)	73 (46%)	73 (46%)
Race (N) (%)				
Caucasian	149 (97%)	150 (97%)	154 (97%)	157 (99%)
Black	3 (2%)	0	1 (1%)	0
Asian	1 (1%)	3 (2%)	3 (2%)	0
Other	0	1 (1%)	0	1 (1%)
IPSS (mean)	19.7	19.7	19.6	19.8
Q <sub>max</sub> (mean) (cc/sec)	9.0	8.9	8.7	8.8

C.4 Inclusion/exclusion criteria: Inclusion criteria included: 1) men > age 50 years 2) symptomatic BPH diagnosed clinically by digital rectal examination and a TRUS of the prostate performed within the 3 months prior to D0 3) suffering for at least 3 months from voiding disturbances which include day-time frequency, nocturia, urgency, hesitancy, poor stream, feeling of incomplete voiding, and interruption of the urinary stream 4) IPSS greater than or equal to 13 at D-28 5) nocturia greater than or equal to 2 at D-28 6) Q<sub>max</sub> between 5 and 12 cc/sec with a voided volume of at least 150 cc at D-28 and 7) residual urine volume < 350 cc at D-28.

Exclusion criteria included: 1) "bad" compliance during the screening period 2) neurogenic bladder dysfunction 3) urethral stricture 4) bladder neck disease 5) acute or chronic prostatitis 6) active urinary tract infection 7) prostate cancer 8) carcinoma of the prostate suspected following DRE and TRUS or PSA >10, unless prostate biopsies performed within the past 2 years have confirmed the absence of prostate cancer 9) gross hematuria 10) previous prostate surgery or other invasive procedures for the treatment of BPH 11) prior pelvic irradiation 12) indwelling urinary catheter 13) patients previously unimproved by alpha blocker therapy 14) Parkinson's disease 15) insulin dependent diabetes 16) multiple sclerosis 17) stroke or myocardial infarction in the 5 months before D-28 18) unstable angina or severe heart failure 19) acute liver disease (AST > 2 X ULN, ALT > 2 X ULN, alkaline phosphatase > ULN, total bilirubin > 2 X ULN 20) renal insufficiency (creatinine > 150 uM/l) 21) abnormal blood count (hemoglobin < 12 g/dl, neutrophils < 1500/ml, or platelets < 150,000/ml) 22) history of orthostatic hypotension or syncope or orthostatic hypotension demonstrated on D-28 defined as a systolic BP decrease of > 20 mmHg after 2 minutes in the a standing position 23) patients who have received alpha blockers within 1 month preceding D-28 and patients who received androgens, anti-androgens, 5-alpha reductase inhibitors, or LHRH analogues within 3 months of D-28 24) patients who had received antidepressants, anticholinergics,

sympathomimetics, antihistamines, or plant extracts for symptoms related to BPH within 1 month prior to D0.

C.5 Primary and secondary endpoints:

- The 2 primary efficacy endpoints were:
  - 1) mean change from baseline to endpoint for IPSS
  - 2) mean change from baseline to endpoint for Qmax

Secondary efficacy endpoints included: improvement in nocturia, QOL index, Urolife scale, sexual function questionnaire, Clinical Global Impression (CGI), mean urinary flow rate, and post-void residual urine measured by TRUS.

C.6 Withdrawals, compliance, and protocol violations: A total of 625 patients were randomized: 154 placebo, 154 alfuzosin 10 mg, 159 alfuzosin 15 mg and 158 tamsulosin 0.4 mg. A total of 79 centers randomized patients: 12 centers in Belgium, 7 in Germany, 5 in Denmark, 8 in Spain, 20 in France, 12 in the UK, 3 in Israel, 10 in the Netherlands, and 2 in Portugal. Forty-seven patients prematurely withdrew from the study: 12 in the placebo group, 9 in the alfuzosin 10 mg group, 17 in the alfuzosin 15 mg group, and 9 in the tamsulosin group. The reasons for premature withdrawals are listed in Table C.2.

Table C.2. Reasons for premature withdrawal – ITT group

	Placebo N=154	Alfuzosin 10 mg (N=154)	Alfuzosin 15 mg (N=159)	Tamsulosin 0.4 (N=158)
Completed	142	145	142	149
Total discontinuation	12	9	17	9
Lost to follow up	1	0	1	1
Lack of efficacy	2	0	0	0
Adverse event	5	4	14	6
Uncooperative	1	0	1	0
Recovery	0	1	0	0
Other	3	4	1	2

Thirty-nine randomized (17 placebo, 14 alfuzosin 10 mg, 6 alfuzosin 15 mg, and 6 tamsulosin) presented at least one major protocol deviation at inclusion. The most frequent deviations were either placebo being stopped for at least 5 days or Qmax > 12 cc/sec. Eighty-four randomized patients (19 placebo, 14 alfuzosin 10 mg, 30 alfuzosin 15 mg, and 21 tamsulosin) had at least one major protocol deviation during the study. The most frequent deviations were treatment stopped for at least 5 days, uroflowmetry missing, compliance <80%, and missing IPSS.

### C.7 Efficacy analysis:

The 2 primary endpoints were the mean changes from baseline to endpoint in IPSS and Qmax. The IPSS analysis in the ITT population is shown in Table C.3.

Table C.3. IPSS total score – ITT population

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
D0 (mean)	17.7	18.0	17.4	17.4
Day end (mean)	13.1	11.5	11.3	10.9
Dend-D0 (mean)	-4.6	-6.5	-6.0	-6.5
P value versus placebo		0.007	0.0503	Not reported

The results of the second primary endpoint, change from baseline in Qmax are shown in Table C.4.

Table C.4. Qmax – ITT population

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
D0 (mean)	9.3	9.5	9.3	9.3
Day end (mean)	10.2	10.9	10.9	11.7
Dend-DO (mean)	0.9	1.5	1.6	2.4
P value versus placebo		0.22	0.09	Not reported

*Reviewer's comment: For  $Q_{max}$  neither dose of alfuzosin compared with placebo reached statistical significance.*

The secondary endpoints of most clinical relevance in the opinion of the reviewer are summarized below.

The percentage of patients showing an improvement in IPSS of 3 points or greater is shown in Table C.5.

Table C.5. Percentage of patients with a greater than 3 point improvement in IPSS score.

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
N	154	154	159	158
% with > 3 point improvement	64%	80%	69%	77%
P value versus placebo		0.001	0.35	Not reported

The percentage of patients with at least a 2cc/sec improvement in Qmax is shown in Table C.6.

Table C.6. Percentage of patients with a greater than 2 cc/sec improvement in Qmax.

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
% with > 2cc/sec improvement	31.3%	41.7%	43.2%	45.2%
P value versus placebo		0.06	0.03	Not reported

No difference between groups was observed in the analysis of residual urine, QOL index, DAN-PSS scores, or Clinical Global Impression scale. No statistical comparison of alfuzosin or placebo with tamsulosin was performed.

#### C.8 Safety analysis:

C.8.1 Extent of exposure: The mean duration of exposure is shown in Table C.7.

Table C.7. Duration (mean days) of drug exposure

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
Number of patients	153	154	158	158
Mean duration of exposure (days)	84	84	81	84

#### C.8.2 Serious adverse events:

Deaths: No deaths occurred during the treatment period. One death was reported during the run-in placebo phase.

A total of 20 SAE's were reported in 19 patients. Three SAE's were reported in 3 patients in the placebo group (1 neuralgia, 1 syncope, and 1 cholecystitis).

In the alfuzosin 10 mg OD group, 4 SAE's were reported in 3 patients. In 2 cases (diverticulitis and arthrosis) a relationship with study drug was excluded by the investigator. The other 2 SAE's were peripheral edema and substernal chest pain.

Patient #30080486 (70-year-old) was hospitalized for bilateral peripheral edema on Day 51 of study drug. He recovered within 58 days and continued on the study.

Patient #15080785 (60-year-old) experienced substernal chest pain on Day 48 of study drug. Myocardial infarction was ruled out and he continued on the study.

In the alfuzosin 15 mg group, 7 SAE's occurred in 7 patients. In 4 patients, the relationship with alfuzosin was excluded by the investigator (pulmonary embolism, peritonitis, varicose vein, and knee pain leading to meniscectomy). Three of the SAE's were syncopal episodes which are discussed below in section C.8.6.

C.8.3 Premature discontinuation due to adverse event:

Study withdrawals due to adverse events occurred in 5 (3.3%) in the placebo group, 4 (2.6%) in the alfuzosin 10 mg group, 13 (8.2%) in the alfuzosin 15 mg group, and 6 (3.8%) in the tamsulosin group.

The incidence of withdrawal because of cardiovascular events was the same in the placebo and alfuzosin 10 mg groups (1 dizziness in each group). In the alfuzosin 15 mg group, withdrawals included chest pain (1), syncope (2), hypotension (1), dizziness (3), and tachycardia (1).

Two patients withdrew from the alfuzosin 15 mg group because of impotence.

C.8.4 Overall adverse events:

Adverse events reported by more than 1% of patients are shown in Table C.8.

Table C.8. Adverse events occurring in more than 1% of patients

	Placebo (N=153)	Alfuzosin 10 mg (N=154)	Alfuzosin 15 mg (N=158)	Tamsulosin (N=158)
Dizziness	6 (3.9%)	9 (5.8%)	11 (7%)	3 (1.9%)
Upper resp. inf.	0	6 (3.9%)	4 (2.5%)	4 (2.5%)
Fatigue	0	2 (1.3%)	7 (4.4%)	6 (3.8)
Influenza like symptoms	6 (3.9%)	5 (3.2%)	3 (1.9%)	5 (3.2%)
Bronchitis	1 (0.7%)	5 (3.2%)	2 (1.3%)	4 (2.5%)
Back pain	2 (1.3%)	4 (2.6%)	3 (1.9%)	2 (1.3%)
Headache	5 (3.3%)	3 (1.9%)	4 (2.5%)	7 (4.4%)
Asthenia	3 (2.0%)	2 (1.3%)	3 (1.9%)	0
Abdominal pain	1 (0.7%)	5 (3.2%)	0	4 (2.5%)
Asthma	0	2 (1.3%)	2 (1.3%)	0
Impotence	0	2 (1.3%)	2 (1.3%)	7 (4.4%)
Rhinitis	3 (2.0%)	1 (0.6%)	2 (1.3%)	1 (0.6%)
Leg pain	0	0	3 (1.9%)	0
Peripheral edema	1 (0.7%)	2 (1.3%)	1 (0.6%)	0
Tinnitus	0	2 (1.3%)	1 (0.6%)	0
Depression	1 (0.7%)	1 (0.6%)	2 (1.3%)	0
Diarrhea	6 (3.9%)	1 (0.6%)	2 (1.3%)	4 (2.5%)
Dyspepsia	2 (1.3%)	2 (1.3%)	1 (0.6%)	1 (0.6%)

Dyspnea	1 (0.7%)	2 (1.3%)	0	1 (0.6%)
Ejaculation failure	0	2 (1.3%)	0	2 (1.3%)
Syncope	0	0	2 (1.3%)	1 (0.6%)
Arthralgia	0	0	2 (1.3%)	1 (0.6%)
Migraine	0	0	2 (1.3%)	0
Insomnia	3 (2.0%)	1 (0.6%)	1 (0.6%)	0
Rash	0	1 (0.6%)	0	3 (1.9%)
Hypertension	1 (0.7%)	0	1 (0.6%)	2 (1.3%)
Arthrosis	0	1 (0.6%)	0	2 (1.3%)
Somnolence	2 (1.3%)	0	1 (0.6%)	0
Ejaculation disorder	0	0	0	3 (1.9%)
Rash erythematous	0	0	0	2 (1.3%)

#### C.8.5 Laboratory abnormalities:

The number of patients with potentially clinically significant laboratory abnormalities is shown in Table C.9.

Table C.9. Number of patients with potentially clinically significant laboratory abnormalities

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
Total bilirubin (> 2 ULN)	0/141	0/147	0/141	1/148
AST (> 2 ULN)	0/141	0/148	0/141	0/148
ALT (>2 ULN)	0/141	0/148	1/141	0/148
ALP (>1.25 ULN)	1/141	1/148	2/140	0/148
Creatinine (increase > 30%)	1/141	2/146	2/139	5/145
WBC (<3000/ml)	0/138	0/144	0/141	0/144
Neutrophils (< 1500/ml)	0/138	0/144	0/141	1/144
Eosinophils (> 500/ml)	4/138	4/143	2/141	2/144
Hemoglobin (decrease > 2g/dl)	0/137	0/141	1/137	0/142
Platelets (< 100,000/ml)	0/138	0/144	0/141	1/144

One patient (#34071633) in the alfuzosin 10 mg group had abnormal liver function tests. This 58 year-old had an isolated increase in ALP (3.17 X ULN) at Day 2. His ALP was also elevated at screening and the investigator believed that the ALP increase may be secondary to Paget's disease.

- Two patients in the alfuzosin 10 mg group had creatinine increases. Patient #15080785 (60 year-old) had a creatinine of 123 ummol/L at D1 versus 87 at baseline. He was asymptomatic and a retest on D37 showed a normal creatinine of 94 umol/L. Patient #30510344 (66-year-old) had a creatinine of 106 umol/L at D1 versus 80 at baseline. No re-test was performed.

#### C.8.6 Special safety issues – cardiovascular events:

Cardiovascular adverse events are shown in Table C.10.

Table C.10. Cardiovascular adverse events

	Placebo (N=153)	Alfuzosin 10 mg (N=154)	Alfuzosin 15 mg (N=158)	Tamsulosin (N=158)
Dizziness	6 (3.9%)	9 (5.8%)	11 (7.0%)	3 (1.9%)
Syncope	0	0	2 (1.3%)	1 (0.6%)
Hypotension	0	0	1 (0.6%)	1 (0.6%)
Malaise	0	0	1 (0.6%)	0

Three of the 9 patients in the alfuzosin 10 mg group experienced this symptom on Day 1 after the first dose. One patient reported dizziness on Day 2 to 7 and the others were symptomatic later during the trial.

Syncope: No syncope was reported in the alfuzosin 10 mg group. Two episodes were reported in the alfuzosin 15 mg group. Patient #27821056 (63-year-old) reported syncope after standing on Day 41. Hypotension was suspected but no blood pressure values were obtained. He was withdrawn from the study. Patient #30510346 (64-year-old) experienced syncope on Day 19. He had a history of angina and was taking isosorbide dinitrate, metoprolol, clonazepam, and buprenorphine. No blood pressures were obtained. He was withdrawn from the study.

Hypotension: One patient (#7440574) (55-year-old) in the alfuzosin 15 mg group experienced hypotension. He had a history of depression, diabetes, and acromegaly and reported dizziness on D2 (10 hours after taking the first dose of study drug). His blood pressure measured by the physician was 90 mmHg. He recovered within 2 days and was withdrawn from the study.

Other cardiac events: No myocardial infarction was reported in any of the treatment groups.

Other adverse events: Two patients in the alfuzosin 10 mg group reported absent or delayed ejaculation.

C.9 Reviewer's assessment of efficacy and safety: The reviewer believes that the efficacy and safety data from the ALFOTAM trial supports the approval of alfuzosin ER 10 mg for the treatment of the signs and symptoms of benign prostatic hyperplasia.

**Appendix D:**

**Clinical Trial ALFUSEXT (interim report of 9 month extension phase of ALFUS)**  
("Efficacy and safety of alfuzosin once-daily tablets at 2 dosage levels (10 mg and 15 mg) versus placebo in patients with symptomatic benign prostatic hyperplasia: A placebo-controlled double-blind study, conducted in 3 parallel groups for three months followed by two (a nine month and a twelve month) open label extensions of alfuzosin OD (15 mg).")

Design: Following the 3 month double-blind ALFUS trial, patients who continued to be eligible based on the absence of exclusion criteria were offered enrollment in the 9-month open-label extension phase. The alfuzosin 15 mg dose was selected for the open-label extension phase to obtain long-term safety information on the highest dose administered during the double-blind treatment phase. Patients who had received placebo, 10 mg alfuzosin, or 15 mg alfuzosin were all treated with 15 mg alfuzosin during the open-label extension phase. IPSS, urine flow rate, residual urine, vital signs, adverse events, and alfuzosin assay were repeated at 6, 9, and 12 months. Laboratory tests (including PSA) were repeated at 12 months.

Patient disposition: This interim report summarizes only the results available for patients who had either completed or discontinued from the 9-month extension as of October 31, 1999. Patients who received alfuzosin 15 mg during the double-blind phase and who did not enter the extension phase were also included in the safety population analysis, but are not included in the efficacy analysis. A total of 432 patients entered the 9-month extension phase. Of these, 265 had ended the extension phase as of October 31, 1999.

Efficacy: No statistical analyses were performed on efficacy variables in this open-label extension trial.

IPSS analysis: The mean IPSS total score at Dend (end of double-blind portion plus open label extension) was 14.1 versus 17.9 at D0 (beginning of double-blind portion of study). The difference in scores from D0 to Dend was similar across the three treatment groups in the double-blind phase (Table 1).

Table 1. IPSS at end of open-label phase grouped according to treatment (placebo versus 10 mg alfuzosin versus 15 mg alfuzosin) during double-blind phase. (All patients received 15 mg alfuzosin during open-label phase).

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Total
D0 (N)	80	80	72	232
Mean	17.5	18.9	17.3	17.9
Dend (N)	80	80	72	232
Mean	13.6	15.0	13.5	14.1
Dend-D0 (N)	80	80	72	232
Mean	-3.9	-3.9	-3.8	-3.9

*Reviewer's comment: Although the extension phase was not a controlled trial, these results support the concept that the efficacy of alfuzosin is maintained throughout the extension phase.*

Values for the PFR were maintained for the 9-month open-label extension. The PFR at the end of the 9-month open-label extension compared to the PFR at the end of the double-blind phase (D84) is shown in Table 2.

Table 2. PFR (cc/sec) at Day<sub>end</sub> compared to PFR at D84.

Timepoint	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg
D84 (end of double blind treatment)	9.6	11.8	11.2
Dend (end of open label extension)	10.6	11.9	10.9
Dend-D84	1.0	0.2	-0.3

#### Safety:

Safety was evaluated on 357 patients who were exposed to alfuzosin 15 mg OD, regardless of the phase of the study. Of these:

- 180 were exposed to 15 mg in the extension phase only
- 95 were exposed to 15 mg in the double-blind phase only
- 82 were exposed to 15 mg both in the double-blind and extension phases

A total of 131 patients took alfuzosin 15 mg OD for at least 9 months. The mean exposure for all 357 patients was 175 days.

At the D84 visit, 4 patients belonging to the alfuzosin 10 mg group took one dose of alfuzosin 10 mg in the morning and one dose of alfuzosin 15 mg in the evening for a total daily dose of 25 mg. None of these patients reported an adverse event.

#### Adverse events:

Adverse events with a >1% incidence are shown in Table 3.

Table 3. Adverse Events with a >1% Incidence. (Three hundred fifty-seven (357) patients exposed to study drug)

Adverse event	Alfuzosin 15 mg OD
Body as a whole	
Fatigue	17 (4.8%)
Back pain	13 (3.6%)
Influenza-like symptoms	9 (2.5%)
Peripheral edema	6 (1.7%)
Respiratory system	
Upper respiratory infection	15 (4.2%)
Rhinitis	13 (3.6%)
Sinusitis	12 (3.4%)
Dyspnea	5 (1.4%)
Vasodilatory disorders	
Dizziness	38 (10.6%)
Syncope	5 (1.4%)
Hypotension	4 (1.1%)
Gastrointestinal symptoms	
Dyspepsia	5 (1.4%)
Constipation	4 (1.1%)
Abdominal pain	4 (1.1%)
Nausea	4 (1.1%)
Nervous system disorders	
Headache	13 (3.6%)
Paraesthesia	4 (1.1%)
Urinary system disorder	
Dysuria	6 (1.7%)
Male reproductive disorder	
Impotence	10 (2.8%)
Inguinal hernia	4 (1.1%)
Psychiatric disorders	
Decreased libido	8 (2.2%)
Somnolence	6 (1.7%)
Secondary terms events	
Inflicted injury	7 (2.0%)
PSA increase	4 (1.1%)
Skin disorders	
Rash	4 (1.1%)
Cardiovascular	
Hypertension	6 (1.7%)
Musculoskeletal disorders	
Arthralgia	4 (1.1%)

Vasodilatory adverse events:

Vasodilatory adverse events are shown in Table 4.

Table 4. Vasodilatory Adverse Events

	Alfuzosin 15 mg
Vasodilatory adverse events	
Dizziness	38 (10.6%)
Syncope	5 (1.4%)
Hypotension	4 (1.1%)
Malaise	3 (0.8%)

Dizziness was the most frequently reported adverse event. Of the 38 reported cases, 29 were considered "mild" and 9 "moderate." None were classified as "severe."

Five patients experienced syncope.

One patient had syncope after undergoing spinal surgery. In another patient, syncope occurred associated with dehydration and furosemide use.

- Patient 38330734 – This 60-year-old man experienced 2 brief episodes of loss of consciousness upon awakening and 1 hour later on Day 86 following the first dose of alfuzosin 15 mg during the extension phase. He also experienced nausea. Alfuzosin therapy was discontinued.
- Patient 37470518 – This 51-year-old man experienced 2 episodes of syncope on Day 86, 13 hours after the first dose of alfuzosin 15 mg during the extension phase. The first episode was 5-10 seconds in duration and the second 3 seconds in duration. Vital signs measurements during the episode were not taken. He continued taking alfuzosin and the event resolved without sequelae.
- Patient 33120160 – This 68-year-old man experienced two episodes of syncope after standing for the first time following hip surgery. These episodes occurred on Day 160, 16 and 18 hours following the last alfuzosin 15 mg intake and 43 hours after spinal anesthesia. Treatment with alfuzosin was discontinued. The investigator believed that the events were not related to drug but rather to concomitant medication, post-surgical pain, and decreased hemoglobin.
- Patient 33010511 – This 55-year-old man experienced syncope lasting at least 3 seconds while rising from bed on Day 236 of the study, 22 hours after the last alfuzosin 15 mg intake. His BP taken that day was 115/80 mmHg. He continued on study drug and the event resolved without sequelae.
- Patient 33010163 – This 72-year-old man with a history of myocardial infarction and bypass surgery experienced nausea and dizziness followed by syncope on Day 43 of the extension phase approximately 8 hours after his last dose of alfuzosin 15 mg. He was hospitalized and received IV fluids. His BP was 120/60 mmHg. An EKG demonstrated sinus bradycardia (52 bpm) and left bundle branch block. At the time of the event he was taking furosemide. Study drug was temporarily discontinued.

Four patients reported hypotension:

- Patient 33090847 – This 74-year-old man experienced dizziness, disorientation, and slight headache 9 hours after taking his first dose of study drug. BP approximately 15

hours after the first dose of study drug was 110/64 mmHg supine (HR: 80 bpm) and 94/60 mmHg standing (HR: 84 bpm). Before taking study drug his BP was 120/76 mmHg supine and 110/70 mmHg standing. He recovered without sequelae and withdrew from the study.

- Patient 32980176 – This 73-year-old man with a history of myocardial infarction, bypass surgery, and pacemaker insertion developed hypotension and dizziness while on alfuzosin 15 mg. Concomitant medications included captopril and triamterene/HCTZ. The event occurred on Day 90, 5 days after entering the extension phase and lasted for 1 hour. His sitting BP at the time of the event was 90/50 mmHg. His BP at study inclusion was 114/76 mmHg. Study drug was discontinued and he recovered without sequelae.
- Patient 33080174 – This 65-year-old man experienced atrial fibrillation and dizziness while receiving alfuzosin 15 mg during the double-blind phase. He experienced hypotension (not further specified) and recurrence of dizziness on Day 96 of alfuzosin 15 mg (Day 7 of the extension phase). He discontinued from the study because of this event. Hypotension was observed at the time the patient experienced atrial fibrillation on Day 56 of double-blind treatment (BP 90/66 mmHg).
- Patient 33110203 – This 66-year-old man experienced hypotension and elevated heart rate while receiving alfuzosin 15 mg. His BP at the time of the event was 98/66 mmHg and heart rate 166 bpm. The patient indicated that the event occurred two to three times a week after exercising.

Three patients reported malaise:

- Patient 32970262 – This 59-year-old man experienced a mildly severe 5-day episode of malaise and fatigue that began on study Day 5. He had experienced a hypertensive episode characterized by tachycardia, dizziness, and diaphoresis (BP 150/90 mmHg) a few days earlier. The event was diagnosed as a panic attack. Study drug was stopped for 5 days.
- Patient 32980336 – This 60-year-old man with a history of hypertension experienced a moderately severe episode of malaise that began on Day 34 and persisted for 25 days. The event resolved without treatment and study drug was continued.
- Patient 33170913 – This 68-year-old man experienced general malaise on Day 71 of alfuzosin 15 mg therapy. The event subsided on Day 74.

Two patients reported myocardial infarction:

- Patient 33040229 - This 68-year-old man experienced a subendocardial myocardial infarction on Day 2 of the study, approximately 21 hours after the first intake of study drug. He underwent 2 attempts at angioplasty and then cardiac stent placement for a 100% right coronary artery occlusion. He withdrew from the study.
- Patient 33130476 – This 67-year-old man with a history of hypertension and bypass graft was hospitalized for a myocardial infarction on Day 130 of the study. A second myocardial infarction occurred one week later. Study drug was discontinued.

Two patients experienced angina pectoris:

- Patient 33010798 – This 74-year-old man with a history of angina experienced a mild exacerbation of angina pectoris on Day 2 of the double-blind treatment period while

receiving alfuzosin 15 mg.

- Patient 33050339 – This 74-year-old man with a history of myocardial infarction and hypertension experienced an attack of unstable angina on Day 87, 1 hour after the first intake of alfuzosin 15 mg during the extension phase. He underwent bypass graft and study drug was discontinued.

Three patients reported chest pain:

- Patient 33010323 – This 62-year-old man with a history of hypertension experienced chest pain diagnosed as arteriosclerosis after cardiac catheterization (not further specified). The event occurred on Day 45.
- Patient 33090433 – This 76-year-old man experienced chest pain on Day 124. The event was considered related to a pre-study motor vehicle accident.
- Patient 33120350 – This 71-year-old man with a history of cardiac bypass and hypertension experienced mild chest pain and dyspnea 10 hours after his dose of drug was changed from 10 mg/day to 15 mg/day (first day of extension phase) and lasted for 4 hours. An ECG done the next day showed no signs of ischemia. Study drug was discontinued.

Cerebrovascular disorder:

- Patient 38310584 – This 62-year-old man with hypertension was hospitalized for a cerebrovascular accident associated with headache and nausea on Day 1 of the extension study. He was receiving 15 mg alfuzosin during the double-blind phase. The study drug was discontinued.

A total of 6 (1.7%) vasodilatory events were reported on Day 1 of alfuzosin 15 mg treatment (3 dizziness, 1 syncope, and 2 hypotension). Dizziness was reported by more elderly (>65 years of age) (13.9%) than non-elderly patients (<65 years of age) (7.0 %).

There were no deaths during either the double-blind or open-label portions of the study.

Discontinuation:

The primary reason for study discontinuation was for “vasodilatory” events. Eleven patients discontinued the study due to a total of 12 vasodilatory events: 6 dizziness, 4 hypotension, and 2 syncope.

Laboratory evaluation:

Liver function studies: Five patients receiving alfuzosin 15 mg had LFT values above PCSA limits. One patient had evidence of hepatocellular damage at screening. One patient had cholestatic injury resulting from a bile duct carcinoma.

- Patient 33120629 – This 85-year-old man received alfuzosin 10 mg in the double-blind portion and 15 mg for 99 days in the open-label extension. He had elevated ALT (2.69 X ULN) and GGT (4.40 X ULN) 2 days after cessation of alfuzosin treatment. His baseline GGT was also abnormally elevated (1.98 x ULN). Other medications included ciprofloxacin (Day 98 to Day 5 post-treatment).

- Patient 32980333- This 66-year-old man had an elevated ALP (2.61 x ULN) and GGT (1.12 x ULN) at baseline. At Day 1 post-treatment the ALP was 2.66 x ULN and the GGT 2.28 x ULN. By Day 91 post treatment the GGT was 1.48 x ULN and the ALP was 2.7 x ULN. Concomitant medications included ibuprofen and ciprofloxacin.
- Patient 33020282 – This 66-year-old man had an AST elevation of 4.42 x ULN on Day 1 post-treatment compared to a normal baseline value. The AST value was 1.72 x ULN at Day 3 post-treatment and was normal by Day 20 post-treatment. The ALT followed a similar trend. A relationship to study drug could not be excluded.

Vital signs:

Mean supine heart rate and mean standing heart rate were similar to the mean values observed at baseline.

The mean variation in systolic BP versus baseline was -2.1 mmHg.

#### Appendix E:

**Clinical Trial ALFOTAMEXT** (interim report of the 9 month extension phase of ALFOTAM) (“Efficacy and safety of two dosage levels of alfuzosin Geomatrix (10 mg OD and 15 mg OD) versus tamsulosin (0.4 mg) and placebo in patients with symptomatic benign prostatic hyperplasia: Nine-month open-label extension with alfuzosin Geomatrix 15 mg”)

Design: Following the 3 month double-blind ALFOTAM trial, patients who continued to be eligible based on the absence of exclusion criteria were offered enrollment in the 9-month open-label extension phase. The alfuzosin 15 mg dose was selected for the open-label extension phase to obtain long-term safety information on the highest dose administered during the double-blind treatment phase. Patients who had received placebo, 10 mg alfuzosin, 15 mg alfuzosin or tamsulosin 0.4 mg were all treated with 15 mg alfuzosin during the open-label extension phase. IPSS, urine flow rate, residual urine, vital signs, and adverse events were repeated at 4, 6, 8, 10, and 12 months. Laboratory tests (including PSA) were repeated at 12 months.

Patient disposition: This interim report summarizes only the results available for patients who had either completed or discontinued from the 9-month extension as of October 31, 1999. Patients who received alfuzosin 15 mg during the double-blind phase and who did not enter the extension phase were also included in the safety population analysis, but are not included in the efficacy analysis. A total of 516 patients entered the 9-month extension phase. Of these, 249 had completed or prematurely discontinued the extension phase as of October 31, 1999.

Efficacy: No statistical analyses were performed on efficacy variables in this open-label extension trial.

IPSS analysis: The mean IPSS total score at Dend (end of double-blind portion plus open label extension) ranged from 10.1 to 11.3 in the 4 groups studied. At D0 (baseline – prior to the double-blind phase) the IPSS ranged from 17.2 to 18.1. (Table 1)

Table 1. IPSS at end of open-label phase grouped according to treatment (placebo, alfuzosin 10 mg, alfuzosin 15 mg, and tamsulosin 0.4 mg) during double-blind phase. (All patients received alfuzosin 15 mg during open-label phase.)

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin 0.4 mg
D0 (baseline) – Prior to double-blind phase	17.3	18.1	17.4	17.2
Dend (end of open-label phase)	10.4	11.3	10.8	10.1
Dend – D0	-6.9	-6.9	-6.6	-7.1

*Reviewer's comment: Although the extension phase was not a controlled trial, these results support the concept that the efficacy of alfuzosin is maintained throughout the extension phase.*

Values for the PFR were maintained for the 9 month open-label extension. The PFR at the end of the 9 month open-label extension compared to the PFR at the end of the double-blind phase (D84) is shown in Table 2.

Table 2. PFR (cc/sec) at Day<sub>end</sub> compared to PFR at D84

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin 0.4 mg
D84 (End of double-blind phase)	10.2	11.2	11.5	11.5
Dend (End of open-label phase)	11.4	11.3	11.1	11.4
Dend-D84	1.2	0.1	-0.3	-0.1

Safety:

Safety was evaluated on 357 patients who were exposed to alfuzosin 15 mg OD, regardless of the phase of the trial. Of these:

- 192 were exposed to 15 mg in the extension only
- 101 were exposed to 15 mg in the double-blind phase only
- 57 were exposed to 15 mg in both the double-blind and extension phases

A total of 173 patients received alfuzosin 15 mg for at least 9 months. The mean exposure for all 357 patients was 195 days.

Three patients received a maximal daily dose of greater than 15 mg/day. These patients each received 30 mg/day on 1 treatment day. No adverse events were reported for this one time 30 mg dose.

Adverse events:

Adverse events with a >1% incidence are shown in Table 3.

Table 3. Adverse Events with a >1% Incidence. (Three hundred fifty (350) patients exposed to study drug)

Adverse event	Alfuzosin 15 mg OD
Body as a whole	
Influenza-like symptoms	19 (5.4%)
Fatigue	12 (3.4 %)
Back pain	10 (2.9 %)
Peripheral edema	4 (1.1 %)
Respiratory system	
Upper respiratory infection	17 (4.9 %)
Rhinitis	8 (2.3%)
Pharyngitis	5 (1.4%)
Bronchitis	5 (1.4%)
Pneumonia	4 (1.1%)
Sinusitis	4 (1.1%)
Vasodilatory disorders	
Dizziness	27 (7.7%)
Syncope	4 (1.1 %)
Gastrointestinal symptoms	
Abdominal pain	9 (2.6%)
Diarrhea	4 (1.1%)
Urinary system disorder	
Urinary retention	6 (1.7%)
Urinary tract infection	5 (1.4%)
Male reproductive disorder	
Impotence	6 (1.7%)
Inguinal hernia	4 (1.1%)
Psychiatric disorders	5 (1.4%)
Depression	
Nervous system disorders	7 (2.0%)
Headache	
Resistance mechanism disorders	
Herpes Zoster	5 (1.4%)

Cardiac disorders Angina	5 (1.4 %)
Musculoskeletal disorders Arthralgia	4 (1.1%)
Vision disorders Conjunctivitis	4 (1.1%)
Clotting disorders Pulmonary embolism	4 (1.1%)

Vasodilatory adverse events:

Vasodilatory adverse events are shown in Table 4.

Table 4. Vasodilatory Adverse Events

	Alfuzosin 15 mg
Vasodilatory adverse events	
Dizziness	27 (7.7%)
Syncope	4 (1.1 %)
Postural Hypotension	3 (0.9%)
Malaise	3 (0.9 %)
Hypotension	2 (0.6%)

Dizziness was the most frequently reported vasodilatory adverse event. Of the 27 reported cases, 13 were considered "mild," 11 "moderate," and 3 "severe."

Four patients experienced syncope. Two occurred in the double-blind phase and 2 in the extension phase. Three of these events occurred in non-elderly men and 1 of the 4 cases occurred on Day 1 of alfuzosin 15 mg therapy.

- Patient 27821056 – This 63-year-old man reported syncope while standing up on Day 41, a few hours after last drug intake. Hypotension was suspected but no BP recordings are available. He withdrew from the trial.
- Patient 30510346 – This 64-year-old man with a history of angina and bypass surgery on multiple medications experienced syncope on Day 19, 14 hours after drug — ingestion. No BP recording is available. A Holter monitor recorded a ventricular rhythm disorder 4 days after the syncopal event. Study drug was discontinued.
- Patient 29160992 – This 57-year-old man experienced syncope 1.5 hours after his first dose of alfuzosin 15 mg in the extension phase. He was hospitalized with a systolic BP of 80 mmHg and treated. Study drug was discontinued.
- Patient 25440296 – This 69-year-old man with a history of normotensive hydrocephalus and loss of consciousness (epilepsy suspected) on Day 36 of the double-blind phase (placebo group) experienced brief loss of consciousness on Day 26 of the extension phase, 6 to 8 hours after the last dose of alfuzosin 15 mg. Study drug was discontinued.

Three patients reported postural hypotension:

These 3 patients reported postural hypotension on Days 333, 124, and 173 of therapy. BP recordings are available for one patient (140/80 supine and 120/80 standing).

Two patients experienced hypotension:

- Patient 7440574 – This 55-year-old man with depression and diabetes on multiple medications reported symptomatic hypotension on Day 2 (10 hours after first drug intake). BP was 90 mmHg. He was discontinued from the study.
- Patient 25370828 – This 67-year-old man with a history of hypertension experienced dizziness, hypotension and nausea on Day 2 of the extension 13 hours after intake of alfuzosin 15 mg. BP was 100/55 mmHg versus 150/80 mmHg at screening. The event recurred for 4 days and study drug was discontinued.

Three patients reported malaise:

One 62-year-old man reported moderate malaise on Day 2 and Day 5 associated with chest pain and asthenia. He withdrew from the trial on Day 4. Another 70-year-old man experienced a “presyncopal” episode without loss of consciousness on Day 136. Study drug was discontinued. A third patient, a 54-year-old man experienced malaise on Day 146; he continued on study drug.

One patient experienced a myocardial infarction:

- Patient 33490622 – This 86-year-old man with a history of chronic atrial fibrillation experienced chest pain about 40 days after the start of alfuzosin 15 mg. ECG showed an anterior myocardial infarction. He was discontinued from the study.

Four patients experienced angina pectoris:

Three of the four patients were withdrawn from the study.

A total of 6 vasodilatory events were reported on Day 1 of alfuzosin 15 mg treatment (4 dizziness, 1 syncope, and 1 hypotension). Dizziness, the most commonly reported vasodilatory event, was reported at a slightly higher rate by elderly versus non-elderly patients (9.6% versus 6.3%).

There were no deaths during either the double-blind or open-label portions of the study.

Discontinuation:

The main reason for discontinuation was “vasodilatory” events. Twenty patients discontinued the study due to vasodilatory events: 11 dizziness, 2 hypotension, 1 postural hypotension, 4 syncope, and 2 malaise.

Laboratory evaluation:

Liver function studies: Three patients presented with potentially clinically significant abnormalities.

- Patient 31420189 – This 57-year-old man had an isolated increase in ALP of 1.4 x ULN on Day 29. ALP was already elevated at baseline (1.6 x ULN).

- Patient 33610679 – This 55-year-old man had ALT of 1.1 x ULN, AST of 1.4 x ULN, ALP of 1.5 x ULN, and GGT of 4.8 x ULN on Day 121. His GGT was 2.2 x ULN at baseline.
- Patient 30100527 – This 62-year-old man had a history of alcohol abuse. His liver function tests were elevated at baseline and also on Day 84.

**Vital signs:**

Mean supine heart rate and mean (standing-supine) heart rate at Dend were similar to mean values at baseline. The mean variation at Dend versus baseline in elderly patients (>65 years) was 0.1 bpm versus 0.4 bpm for younger patients. At Dend, the mean variation in systolic blood pressure versus baseline was -4.9 mmHg. The mean variation in endpoint systolic blood pressure in elderly patients was -7.8 mmHg and -2.8 mmHg in younger patients.

*Reviewer's comment: The decrease in mean systolic BP of 7.8 mmHg in elderly patients with a 15 mg dose of alfuzosin is meaningful. Patients with renal failure should be treated with caution.*

**Appendix F:**

**Clinical Trial ALFORTIEXT** (“Efficacy and Safety of Alfuzosin Geomatrix 10 mg OD Versus Alfuzosin 2.5 mg TID and Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia. Placebo-Controlled, Double-Blind Study, Conducted in 3 Parallel Groups for Three Months, Followed by an Optional 9-Month Open Label Extension with Alfuzosin Geomatrix 10 mg OD”)

Design: Following the 3-month double-blind ALFORTI trial, patients who continued to be eligible based on the absence of exclusion criteria were offered enrollment in the 9-month open-label extension phase. Patients who had been treated with either placebo, alfuzosin 2.5 mg tid, or alfuzosin 10 mg were all treated with alfuzosin 10 mg during the extension phase. IPSS, uroflowmetry, vital signs, and adverse events were obtained at months 4, 6, 8, 10, and 12. Laboratory tests (including PSA) were obtained at Month 10.

Patient disposition: The 311 patients who entered the extension phase included 111 from the placebo randomized group, 94 from the alfuzosin 10 mg group, and 106 from the alfuzosin 2.5 mg tid group. Three hundred sixty patients exposed to alfuzosin 10 mg either in the double-blind phase or in the extension phase were analyzed for safety.

Efficacy: No statistical analyses were performed on efficacy variables in this open-label extension trial.

Mean IPSS and mean PFR (according to the original randomization in the double-blind phase) are shown in Tables 1 and 2.

Table 1. Mean IPSS

	Placebo	Alfuzosin 10 mg	Alfuzosin 2.5 mg tid
Baseline (D0)	17.5	17.2	16.6
End of double-blind phase (D84)	12.2	10.5	9.8
End of extension (Dend)	9.3	9.7	9.1

Table 2. Mean PFR (cc/sec)

	Placebo	Alfuzosin 10 mg	Alfuzosin 2.5 mg tid
Baseline (D0)	9.2	9.4	8.7
End of double-blind phase (D84)	10.7	11.8	12.0
End of extension (Dend)	11.4	11.2	11.3

Safety:

Safety was evaluated in 360 patients who were exposed to alfuzosin 10 mg OD regardless of the phase of the trial. Of these:

- 217 were exposed to 10 mg in the extension phase only
- 49 were exposed to 10 mg in the double-blind phase only
- 94 were exposed to 10 mg in both the double-blind and extension phases

A total of 291 patients took alfuzosin 10 mg OD for at least 6 months. Eighty patients took alfuzosin 10 mg OD for at least 11 months and 16 patients for at least 12 months.

Adverse events:

Adverse events with a >1% incidence are shown in Table 3.

Table 3. Adverse events with a >1% incidence. (Three hundred sixty patients exposed to study drug).

	Alfuzosin 10 mg OD
Body as a whole	
Flu like symptoms	15 (4.2%)
Asthenia	9 (2.5%)
Back pain	9 (2.5%)
Fatigue	4 (1.1%)
Gastrointestinal disorders	
Abdominal pain	8 (2.2%)
Diarrhea	5 (1.4%)
Dyspepsia	5 (1.4%)
Respiratory disorders	
Rhinitis	8 (2.2%)
Upper respiratory infection	6 (1.7%)

Bronchitis	6 (1.7%)
Musculoskeletal disorders	
Arthralgia	4 (1.1%)
Urinary system disorders	
Urinary tract infection	5 (1.4%)
Renal stone	4 (1.1%)
Psychiatric disorders	
Impotence	5 (1.4%)
Vasodilatory disorders	
Dizziness	9 (2.5%)
Malaise	4 (1.1%)
Cardiovascular disorders	
Hypertension	10 (2.8%)
Nervous system disorders	
Headache	5 (1.4%)
Pruritis	4 (1.1%)
Inflicted injury	4 (1.1%)

Vasodilatory adverse events:

Vasodilatory adverse events are shown in Table 4.

Table 4. Vasodilatory adverse events

	Alfuzosin 10 mg
Vasodilatory disorders	
Dizziness	9 (2.5%)
Malaise	4 (1.1%)
Hypotension	2 (0.6%)
Syncope	2 (0.6%)

Dizziness was the most frequently reported vasodilatory adverse event. Eight of 9 episodes were rated as "mild." The incidence in younger patients (2.2%) was similar to elderly patients (2.7%).

Two patients reported syncope:

- Patient 14070293 – This 66-year-old man with a history of myocardial infarction and hypertension experienced syncope on Day 141. Blood pressure measured by the patient at the time of the event was 101/70. Study drug was discontinued.
- Patient 15130153 – This 72-year-old man with a history of hypertension experienced syncope on Day 295 after his first intake of captopril 50 mg. Both alfuzosin and captopril were continued with no recurrence of syncope.

Two patients reported hypotension:

Two elderly hypertensive patients had asymptomatic hypotension. Both completed the study.

No patient experienced a myocardial infarction. Two patients experienced angina pectoris.

Two patients experienced cerebrovascular disorders (1 transient ischemic attack and 1 "arterial spasm")

Deaths: One patient died during the double-blind phase of the trial due to an ENT infection after cranial and facial trauma.

Laboratory evaluation:

Liver function studies: Three patients experienced elevations in liver function studies which exceeded the pre-determined PCSA.

- Patient 7450604 – This 63-year-old man had an ALT of 2.2 x ULN, ALP of 2 x ULN, and GGT of 5 x ULN at Day 284. Bilirubin was normal. He had experienced a "flu" syndrome on Day 276 and was taking other potentially hepatotoxic drugs.
- Patient 7760639 – This patient had ALP and GGT increases at both baseline and during therapy.
- Patient 27900439 – This patient had an elevated ALP at both baseline and end of study.

Neutrophil count: Four patients had a neutrophil count <1500/mm<sup>3</sup> during alfuzosin treatment. A relationship with treatment was excluded or unlikely in 3 of 4 cases and in the fourth case the neutropenia was mild (1300/mm<sup>3</sup>).

Vital signs:

At Dend, the mean variation in heart rate versus baseline in elderly patients (>65 years) was +0.8 bpm versus -1.4 bpm in younger patients. At Dend the mean variation in systolic blood pressure versus baseline was -2.6 mmHg.

**Appendix G:**

**120 Day Update of Integrated Summary of Safety** (received by the Division on April 6, 2001)

**NDA Final Safety Update** (received by the Division on July 11, 2001)

**QT evaluation**

The 120 Day Update of Integrated Summary of Safety (received on April 6, 2001) contained 5 study reports involving studies to determine the effect of alfuzosin on the QT interval as well as the sponsor's "Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization" (Addendum 16.1).

The following QT study reports and information were included in the 120 day safety-update:

- 4) Study report for 00-00312-EN-00 (“Effects on the action potential of piglet Purkinje fibers”)
- 5) Study report for 00-00329-EN-00 (“Effects on the hERG channel stably expressed in mammalian cell line. Comparison with tamsulosin, doxazosin, prazosin, and terazosin”)
- 6) Study report for INT4285 (“Effect of ketoconazole on alfuzosin blood levels”)
- 7) Study report for PKD4532 (“Effect of suprathreshold doses of alfuzosin on the ECG”)
- 8) Study report for PCALF96US01 (“Manual reading of QT intervals of ECG from PCALF96US01”)

These 3 studies were reviewed as well as the “Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization” included in Addendum 16.1. In PKD4532 (which studied placebo and 10, 20, and 40 mg of alfuzosin), the QTcB was prolonged greater than 60 msec in 2 of 24 placebo patients, in 3 of 24 10 mg alfuzosin patients, in 4 of 24 20 mg alfuzosin patients, and in 4 of 24 40 mg alfuzosin patients. None of the patients had QTcF prolongation of > 60 msec. The mean changes in heart rate, QT, QTcB, and QTcF for study 4532 are shown in Table 1.

Table 1. Statistical Analysis of Changes in ECG Parameters from Baseline: Mean (One-sided 95% CI, Upper Bound) Average Difference from Placebo over 0.5 to 24 Hours: Study PKD4532.

Parameter	Overall Treatment Effect	Alfuzosin 10 mg versus placebo	Alfuzosin 20 mg versus placebo	Alfuzosin 40 mg versus placebo
Heart rate	P=0.0001	0.6 (1.3)	4.6 (5.4)***	5.8 (6.5) ***
QT (ms)	P=0.0001	-1.1 (0.3)	-6.3 (-4.9)	-4.7 (-3.3)
QTcB (ms)	P=0.0001	1.2 (3)	8.5 (10.3) ***	13.2 (15.0) ***
QTcF (ms)	P=0.0001	0.5 (1.8)	3.4 (4.7) ***	7.1 (8.4) ***

\*\*\* = p-value vs. placebo = 0.001

The sponsor believes that the QTcB is “biased toward reporting normal QT as abnormally long when corrected.” The sponsor also believes that Holter monitor recording and analysis of QT/RR pairs is more accurate and this analysis showed no clinically significant difference between alfuzosin and placebo.

The sponsor’s conclusions are as follows:

“Alfuzosin belongs to the alpha<sub>1</sub>-blockers drug class, which is widely known to produce an increase in heart rate but which is not associated with ventricular arrhythmias. The information presented in this document, derived from pre-clinical and clinical development and a large post-marketing experience, indicates a lack of arrhythmogenic potential, as supported by the following conclusions:

- 1) Alfuzosin has only a slight in vitro electrophysiologic effect, and only at concentrations several hundred times the expected therapeutic levels. Alfuzosin is a very weak  $I_{kr}$  channel blocker, based on inhibition of HERG potassium current. In this model, alfuzosin is 4 to 30 times weaker than the  $\alpha_1$ -blockers doxazosin, terazosin, and prazosin.
- 2) Using the best available technique for evaluating change in repolarization independent of heart rate, alfuzosin at doses up to 40 mg appears to prolong the QT interval by only about 2 ms. This effect is not dose-related and is not clinically relevant.
- 3) Review of the large safety experience from a substantial clinical database and extensive post-marketing information provides no evidence for arrhythmia-induced risk.”

Because of the discrepancies in the QTc results depending upon which correction method was used, a consultation was requested from the Division of CardioRenal Drug Products.

The CardioRenal Division reviewed 2 preclinical (HERG channel study and the pig Purkinje fiber study) and 2 clinical QT studies (PKD4532 and PCALF96US1).

The review of the pre-clinical studies concluded: “Alfuzosin’s in vitro electrophysiologic effects suggest a low risk for repolarization abnormalities. However, while effects on HERG current suggest a low risk, alfuzosin’s potency was likely underestimated, and some drugs, e.g. sotalol, and quinolone and macrolide antibiotics weakly inhibit HERG yet prolong QT interval and induce torsade in humans. Additionally, human metabolites were not evaluated.”

The primary conclusion of the review of the clinical studies was that “the drug appears to be increasing the corrected Qt by perhaps 10 msec.”

Study PKD4532 was a single-center, double blind, placebo-controlled, single-dose, randomized, crossover study of three dose levels of alfuzosin (10, 20, and 40 mg) and placebo. Alfuzosin increased heart rate in a dose-dependent manner in comparison to placebo (+0.6, +4.6, and +5.8 bpm at the 10, 20, and 40 mg doses respectively). The 24-hour mean QTcB showed that the effect of the 40 mg dose was clearly different (and the lower doses less so) from the effect of placebo. The same findings, although to a lesser degree, were seen with QTcF (Table 1). The consultant concluded: “Heart rate, QTcB, and QTcF are significantly increased from baseline for the 20 and 40 mg doses compared to placebo.”

Study PCALF96US1 was a single-center, double-blind, placebo controlled, parallel sequentially dosed trial. Study drug doses were 7.5 mg to 30 mg. Active drug showed a greater change from baseline in the corrected QT intervals compared to placebo; the only significant differences between drug and placebo were seen on Day 1. The mean changes from baseline with the Bazett’s and Fridericias’s corrections were always higher on drug but not necessarily in a dose related manner.

In summary, the CardioRenal Division believes that alfuzosin increases the corrected QT interval by "perhaps 10 msec." They do not agree with the sponsor's argument that the analysis of the Holter monitor data is superior to the QTcB or QTcF. Finally, although the reported arrhythmia events in Europe since 1987 is small, the consultant believes that "it is hard to know how reassuring this lack of event reporting is."

#### **Other information**

Most of the new safety information included in this update is from the final results of the Phase 3 extension studies of 15 mg alfuzosin ER (ALFOTAMEXT and ALFUSEXT). These data relate to 434 patients. In addition, a second extension of ALFUS with 15 mg alfuzosin ER is currently ongoing. In addition, serious adverse events from post-marketing surveys and observational studies (primarily with the IR and SR doses) from an estimated 102,234 patients are included.

Safety information is similar to the original ISS. In the 434 patients updated, the incidence of dizziness was (19; 4.4%) and syncope was (2; 0.5%). Two hepatic serious adverse events were reported. Both of these patients had cholecystitis. No new unexpected adverse events are described.

The Final NDA Safety Update included the study report for INT4672 ("Assessment of pharmacokinetic drug interactions between alfuzosin 10 mg OD formulation and digoxin in healthy male subjects"). No new safety concerns were identified in the Final Safety Update.

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## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Consultative Clinical Review*

**NDA:** 21-287 (alfuzosin)

**Sponsor:** Sanofi-Synthelabo

**Submission:** The Division of Cardio-Renal Drug Products is asked to comment on the sponsor's QT evaluation study results.

**Review date:** December 30, 2002

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Concurrence:** DC Throckmorton, MD, Division Director

**Distribution:** NDA 21-287

HFD-580/Project Manager

HFD-580/Hirsch

HFD-580/Shames

Prior consultative reviews for alfuzosin were returned in August 2001 (Gordon) and August 2002 (Throckmorton). Alfuzosin is an alpha-adrenergic blocker. Immediate-release alfuzosin has a long marketing history in Europe for the treatment of BPH. NDA 21-287 is intended to support approval of a sustained-release formulation. The only proposed dose is 10 mg once daily in association with a meal; food doubles the bioavailability. Alfuzosin is metabolized by CYP3A4; inhibition doubles peak plasma levels. Alfuzosin has a narrow therapeutic index; dose is limited by orthostasis. The NDA approvable letter asked for an evaluation of the effects of alfuzosin on cardiac repolarization, and the sponsor has now submitted the results of study PDY5105 in response to that deficiency.

The description of study PDY5105 is based on a study report dated 6 December 2002. No protocol, data listings, or machine-readable data are provided.

This was a randomized, double-blind, placebo- and active-controlled four-way crossover study conducted between May and August 2002 at one site in France.

Subjects were normal Caucasian males age 18 to 50, screened by 12-lead and 24-hour Holter ECGs. Subjects received, in random sequence, single doses of placebo, alfuzosin 10 and 40 mg, and moxifloxacin 400 mg. The timing of moxifloxacin dosing was offset to match the timing of peak plasma levels alfuzosin. Washout was 5 to 7 days between treatments. Fifteen 12-lead ECGs were collected over the 48 hours prior to treatment, then 3 times just prior to treatment, and at 2, 4, 6, 7, 8, 9, 10, 11, 12, 24, and 30 hours after treatment. A 48-hour 3-lead Holter recording was initiated 24 hours prior to dosing. Subjects performed light exercise to achieve heart rates >80 bpm in each treatment period. Pharmacokinetic data were also obtained.

Holter ECG QT data were analyzed by 10-ms RR interval bin for a 4-hour window around peak plasma levels. Twelve-lead ECG data were analyzed by manual methods (computer assisted), with lead selection optimized by subject, and using a steepest

tangent method to determine the end of the T wave. Heart rate correction was by Bazett, Fridericia, and individualized (Malik) methods.

The study was planned for 45 subjects, three of whom withdrew (2 prior to active treatment) and were replaced. A pair of subjects received each other's planned treatments for one study period; no other significant protocol deviations are noted.

Results of Holter data analyses are shown in Table 1.

**Table 1. Placebo-subtracted changes in QT by Holter**

	Moxifloxacin N=37-43	Alfuzosin	
		10 mg N=36-42	40 mg N=35-45
1000 ms RR bin	7.0 (4.4, 9.6)	0.1 (-2.5, 2.6)	2.9 (0.3, 5.5)
Largest RR bin	6.9 (4.8, 9.1)	0.4 (-1.8, 2.6)	2.5 (0.4, 4.7)
Mean all RR bins	6.6 (4.6, 8.6)	0.1 (-1.9, 2.0)	2.0 (0.0, 3.9)

Results for 12-lead ECG analyses at C<sub>max</sub> are shown in Table 2.

**Table 2. Placebo-subtracted changes in QT by 12-lead ECG**

	Moxifloxacin N=?	Alfuzosin	
		10 mg N=?	40 mg N=?
HR	2.8 (1.3, 4.2)	5.2 (2.2, 8.3)	5.8 (3.2, 8.4)
QTcF	12.7 (8.6, 16.8)	4.9 (0.9, 8.8)	7.7 (1.9, 13.5)
QTcNi	11.1 (7.2, 15.0)	1.8 (-1.3, 5.0)	4.5 (-0.5, 9.2)

The sponsor's analyses of outliers failed to find subjects with values of interest<sup>1</sup>.

There were no notable adverse events.

The sponsor should be asked to clarify why not all subjects' data contributed to these analyses, but the answers are not likely to change the overall interpretation? a carefully designed and well-executed study is capable of demonstrating an effect of alfuzosin on cardiac repolarization, but the effect is small. At 40 mg, the effect is less than half as large as that produced with a 400-mg dose of moxifloxacin. Ten milligrams is probably also on the dose-response curve, but it would take a substantially larger study to resolve its effect. Although the 40-mg dose does not cause concern in this regard, it is reassuring that symptoms will probably prevent many patients from using doses much above 10 mg.

If the Division of Cardio-Renal Drug Products can be of further assistance, please feel free to contact us.

<sup>1</sup> QTcF > 450 or change in QTcF > 60 ms.



**From the CDER Electronic Document Room Staff**

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Re: Firm: **Sanofi-Synthelabo** Application: **NDA-21287** Letter Date: **2/5/03**

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### Memorandum

**FROM:** Douglas C. Throckmorton, M.D., Deputy Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**THROUGH:** Raymond Lipicky, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**TO:** Evelyn Farinas, Project Manager  
George Benson, M.D., Medical Officer  
Mark Hirsch, M.D. Team Leader  
Daniel Shames, M.D., Acting Division Director  
Division of Reproductive and Urologic Drug Products, HFD-580

**SUBJECT:** Assessment of potential effects of Alfuzosin on cardiac repolarization  
**NAME OF DRUG:** Alfuzosin  
**DATE COMPLETED:** 10.9.01

#### DOCUMENTS USED FOR MEMO:

1. Consultation from HFD-110 from Maryann Gordon, M.D., dated 8.29.01.
2. Meeting minutes of internal meeting to discuss effects of alfuzosin on cardiac repolarization. dated 9.7.01.
3. Fax from sponsor dated 9.24.01.
4. Study report from study PKD4532, NDA 21-287.

#### COMMENTS

In a previous consultation, the DCRDP was asked to comment on the effects of alfuzosin on cardiac repolarization. marked by changes in the QT/QTc interval, a task that is complicated by an effect of Alfuzosin to increase the heart rate. That consultation concluded that '(t)he drug appears to be increasing corrected QT by perhaps 10 msec.' This conclusion was based on Dr. Gordon's review of QT and QTc data from the NDA, including studies PKD4532 and PCALF96US1. Based on the reported data from these two studies, using the Fridericia's method of QT correction. alfuzosin causes a QTc prolongation of 8-10 msec at a dose of 30-40 mg. This effect also appears to be dose-dependent. In their letter dated 9.24.01, the sponsor asserts that this conclusion is in error. Two parts of their comments require comment today: their dismissal of Bazett's and (apparently) Fridericia's corrections, and their assertion that they have a 'more effective method' of QT correction—one that exculpates alfuzosin from any detectable effect on QTc interval.

With regard to the use of Bazett's correction, there is little issue with the assertion that its use in detecting QT effects of drugs that also increase the heart rate is problematic, especially if the drug effect is in the range of 0 to 10 msec mean prolongation. It is also true that the Fridericia's correction is imperfect in this situation; otherwise we wouldn't have 50+ alternative corrections in the literature. Fridericia's correction is, however, a more adequate correction than Bazett's; one that has not been as susceptible to the effects of changes in heart rate in other databases I've seen. In the absence of a more accurate, validated method of QT correction, it is a useful analysis tool, and one that suggests an effect of Alfuzosin on the QTc interval.

So is the sponsor's method of correction, using the Holter monitor an accurate, validated method of QT correction? The simple answer is that we don't know. Holter-based methods of QT correction have never been satisfactorily

validated, and no program submitted to the FDA has ever relied on them as the sole means of correction that I am aware of. In contrast, there are other, ECG-based, methods of correction that have been submitted and accepted as valid methods of analysis for the particular drug. I am not saying the sponsor's Holter-based methods couldn't be validated; we just don't have sufficient data on their operating characteristics. Issues that would need to be addressed in such a demonstration would be:

- Sensitivity: how well would the method detect the QT effects of other compounds known to prolong QTc in the range of 5-10 msec (e.g., moxifloxacin, cisapride)?
- Specificity: how well would the method exclude an effect of a drug we don't think affects the QT (e.g., penicillin)?
- How does this method compare with other ECG-based methods of correction, as well as the standard Fridericia's and Bazett's methods?

My recommendations would be similar to those I expressed in the previous meeting. The sponsor has conducted an apparently rigorous analysis of the QT effects of alfuzosin using a potentially valuable method. That analysis, at least with the numbers they've shown us, contradicts the findings using a more standard correction (Fridericia) that suggests a dose-dependent effect of alfuzosin on QTc interval. Their Holter-based analysis, while attractive, is unvalidated; and we can't rely on it without additional information, especially information on its sensitivity and specificity. Absent the validation, the Fridericia is the analysis we'd fall back on. To validate the use of their system, the sponsor should obtain additional information on the QT/QTc intervals from an additional study with a series of doses of alfuzosin, placebo, and appropriate controls (both positive and negative). The study should be done in parallel with the more standardized ECG corrections, and all of the analyses should be presented to the FDA. It would be quite useful for them to discuss their analysis plans before conducting the study. Without those data, my best interpretation of the available data is that there is a relevant effect of alfuzosin on cardiac repolarization.

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Doug Throckmorton  
10/14/01 10:55:58 AM  
MEDICAL OFFICER

DIVISION OF CARDIO RENAL DRUG PRODUCTS  
CONSULTATION

**To:** Susan Allen, MD, Division Director  
HFD-580 Division of Reproductive and Urologic Drug Products

**From:** Maryann Gordon, M.D., Medical Officer  
HFD-110 Division of Cardio-Renal Drug Products

**Through:** Norman Stockbridge, M.D., Ph.D., Supervisor  
HFD 110, Division of Cardio-Renal Drug Products

Raymond Lipicky, M.D., Division Director  
HFD 110, Division of Cardio-Renal Drug Products

NDA #21,287

Drug: alfuzosin

Sponsor: Sanofi-Synthelabo

Documents reviewed: part of the summary of safety of the NDA and reports for 2 completed clinical pharmacology studies.

**Conclusions**

Alfuzosin is an alpha 1 adrenergic receptor antagonist being developed for benign prostatic hypertrophy (BPH). The drug appears to be increasing corrected QT by perhaps 10 msec. The drug has been marketed in Europe since 1987 with only a small number of reports of arrhythmias. It is hard to know how reassuring this lack of event reporting is since the patient population, elderly males, is normally more at risk for sudden death. The drug increases heart rate which may or may not change the risk of provoking an arrhythmia. A strong enzyme inhibitor doubled the C<sub>max</sub> and AUC of alfuzosin (a drug metabolized by cytochrome P450 3A4); not usually acknowledged as a worrisome increase unless the drug has a very narrow therapeutic window. Dr. John Koerner who reviewed the preclinical data (attachment 1) concluded that alfuzosin had a

...low risk for repolarization abnormalities. However, while effects on HERG current suggest a low risk, alfuzosin's potency was likely underestimated, and some drugs, e.g., sotalol, and quinolone and macrolide antibiotics weakly inhibit HERG yet prolong QT interval and induce *torsade* in humans. Additionally, human metabolites were not evaluated. Further information should be provided to support a conclusion of low risk.

Although I have reviewed data from numerous drugs that affect cardiac repolarization, I find it hard to predict the size of the risk of dangerous adverse events occurring. It is especially hard when the drug increases heart rate because I believe, with no data to support this, that the risk decreases compared to drugs that lower heart rate. I am also reassured by the demonstration that a potent metabolic inhibitor increases alfuzosin only 2-2.5 fold. The one problem with this drug is the indication (symptomatic relief of BPH), because it is difficult to accept any risk for sudden death with a drug that is for symptomatic treatment. However, if the drug is effective, I believe that patients have a right to decide if they want to take any risk of something bad happening. Of course, all drugs carry a risk of causing a serious adverse event. It is the incidence rate that is critical but hard to determine.

**Introduction**

Alfuzosin is an alpha1 adrenergic receptor antagonist seeking the indication for the treatment of symptoms of benign prostatic hyperplasia. The immediate release (IR) formulation was approved in Europe in 1987 and the sustained release (SR) formulation in Europe in 1993. As of May 31, 2001, the extended release formulation was approved in 11 countries. The proposed dose of alfuzosin ER is 10mg once daily. The reviewing division

is concerned that the drug alfuzosin, is having an effect on cardiac repolarization. A cursory look through the available literature regarding alfuzosin reveals reports of orthostatic hypotension but no reports of ventricular arrhythmia.

- Alfuzosin is metabolized by cytochrome P450 3A. An *in vitro* study with alfuzosin on human hepatocytes showed that the fraction of metabolic clearance of alfuzosin inhibited by ketoconazole was 87%. The sponsor conducted an interaction study in humans with repeated oral doses of ketoconazole 200 mg and a single dose of alfuzosin 10 mg. Concomitant ketoconazole increased the C<sub>max</sub> and AUC of alfuzosin by 2-2.5 fold compared to alfuzosin alone.

The proposed dose of alfuzosin is 10 mg and the highest dose studied was 40 mg. This review concentrates on evaluating the drug's effect (if any) on cardiac repolarization.

Two studies were reviewed, both had small sample sizes and used normal volunteers. Highest dose tested was 40 mg.

#### Study #PKD4532

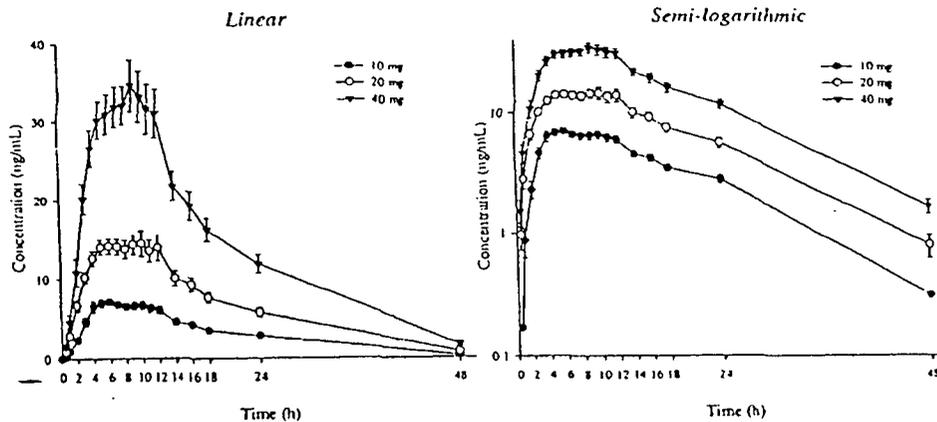
This was a single-center, double-blind, placebo-controlled, single-dose, randomized, crossover study of three dose levels of alfuzosin (10, 20 and 40 mg) and placebo. It included a screening visit performed 2 to 21 days before the first drug administration, four 1-day treatment periods separated by at least 6 days of washout, and a follow-up visit 7 days after the last dosing day. Twenty-four healthy male subjects aged 18-40 years were studied. The objective of the study was to assess the effect of single doses of alfuzosin on ECG parameters.

Over each of the treatment periods, a series of 12 lead ECGs was performed on Day 1, one hour before drug administration (baseline) as well as 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 (prior to dinner), 14 and 16 hours after drug administration. ECGs were also recorded on Day 2, 18 and 24 hours post-dose, and on Day 3, 48 hours post-dose. The baseline measurement was performed before a high fat breakfast.

A physician reviewed electrocardiographic results from the automatic reading.

The QTc interval was calculated using Bazett's formula (QTcB) and Fridericia's formula (QTcF). The RR interval used for calculations was the one preceding the measured QT interval. For any given subject, each parameter was measured by calculating, if possible, the average of three individual intervals. If three intervals were not available, the measurement was taken using the nearest number of complexes available. In all cases, a single operator always measured a given interval for all ECGs for each subject on the same ECG derivation (D2, V2-V4). A visual examination of all tracings for a given subject was carried out in order to choose a single derivation measure for a given type of interval. The intervals were measured using a digitizing tablet (SummaSketch III Professional version PC, Summagraphics) connected to a microcomputer. Any deformation of the T-wave was also noted and ranked on a scale of 0 to 2 (0=none, 1=moderate, 2=significant).

Mean plasma concentrations versus time profiles are shown below.



Mean  $T_{max}$  is between 6.5 and 8.5 hours with the range from 2 to 18 hours. The AUC of the 40 mg dose is about 5 times greater than the AUC of the 10 mg dose.

#### Heart rate

Alfuzosin increased heart rate in a dose-dependent manner in comparison to placebo (mean differences versus placebo were +0.6, +4.6, and +5.8 bpm, at 10, 20 and 40 mg, respectively). The 24-hour mean heart rate profile is shown in attachment 2. After an initial increase after dosing, heart rate decreases in all 4 treatment groups with 40 mg decreasing the least.

#### Uncorrected QT interval

The 24-hour mean uncorrected QT interval profile is shown in attachment 3. The effect of the drug at any of these dose levels is indistinguishable from the effect of placebo.

#### QT interval corrected using Fridericia's formula (QTf)

The 24-hour mean QTf interval profile is shown in attachment 4. Using this correction factor, the effect of the 40 mg dose is clearly different (and the lower doses less so) from the effect of placebo.

#### QT interval corrected using Bazett's formula (QTc)

The 24-hour mean QTc interval profile is shown in attachment 5. Using this correction factor, the effect of the 40 mg dose is clearly different (and the lower doses less so) from the effect of placebo.

The table below shows the placebo subtracted mean change from 15 minutes to 24 hours after drug administration.

Table (11.4.1) 1 - Analysis of Absolute ECG Changes from Baseline (H0.5 to H24)  
 Statistical analysis versus placebo were one-sided (upper bound).

Parameter	Fixed effect	P-value	Pairwise comparison	P-value	Mean difference	95% CI UB
Delta HR (bpm)	Treatment	0.0001	SL770499 10 mg vs PLACEBO	0.1011	+0.6	+1.3
			SL770499 20 mg vs PLACEBO	0.0001*	+4.6	+5.4
			SL770499 40 mg vs PLACEBO	0.0001*	+5.8	+6.5
Delta QT (ms)	Treatment	0.0001	SL770499 10 mg vs PLACEBO	0.8971	-1.1	+0.3
			SL770499 20 mg vs PLACEBO	1.0000	-6.3	-4.9
			SL770499 40 mg vs PLACEBO	1.0000	-4.7	-3.3
Delta QTcB (ms)	Treatment	0.0001	SL770499 10 mg vs PLACEBO	0.1416	+1.2	+3.0
			SL770499 20 mg vs PLACEBO	0.0001*	+8.5	+10.3
			SL770499 40 mg vs PLACEBO	0.0001*	+13.2	+15.0
Delta QTcF (ms)	Treatment	0.0001	SL770499 10 mg vs PLACEBO	0.2673	+0.5	+1.8
			SL770499 20 mg vs PLACEBO	0.0001*	+3.4	+4.7
			SL770499 40 mg vs PLACEBO	0.0001*	+7.1	+8.4

Ref.: Appendix 16.2.9.1.26

(\*) = Statistically significant at comparisonwise one-sided error rate of 0.05

Heart rate, QTcB and QTcF are significantly increased from baseline for the 20 and 40 mg doses compared to placebo.

The numbers of subjects with abnormal parameters are listed below, by dose group.

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Table (11.4.1) 3 - Summary of Counts and Number of Subjects with Post-Dose PCSA\* ECG Parameters (Manual Reading)

	PLACEBO		ALFUZOSIN					
			10 mg		20 mg		40 mg	
	n	s	n	s	n	s	n	s
Available	432	24	432	24	432	24	432	24
HR $\leq$ 50 bpm	27	10	31	6	17	10	18	7
PR $\geq$ 200 ms & increase $\geq$ 20 ms	.	.	10	2	11	3	2	1
QTcB > 430 ms & $\leq$ 450 ms	5	3	10	7	7	5	16	5
QTcB > 450 ms	2	2	1	1	1	1	5	2
Delta QTcB $\geq$ 30 ms & $\leq$ 60 ms	27	12	29	10	48	16	82	16
Delta QTcB > 60 ms	2	2	4	3	5	4	8	4
QTcF > 430 ms & $\leq$ 450 ms	2	2	4	3	1	1	6	3
QTcF > 450 ms	.	.	.	.	.	.	1	1
Delta QTcF $\geq$ 30 ms & $\leq$ 60 ms	8	5	15	5	15	7	21	9

Number of subjects with QTcB  $\geq$  500 ms or Delta QTcF > 60 ms = 0

Ref.: Appendix 16.2.9.1.2

n = number of observations, s = number of subjects

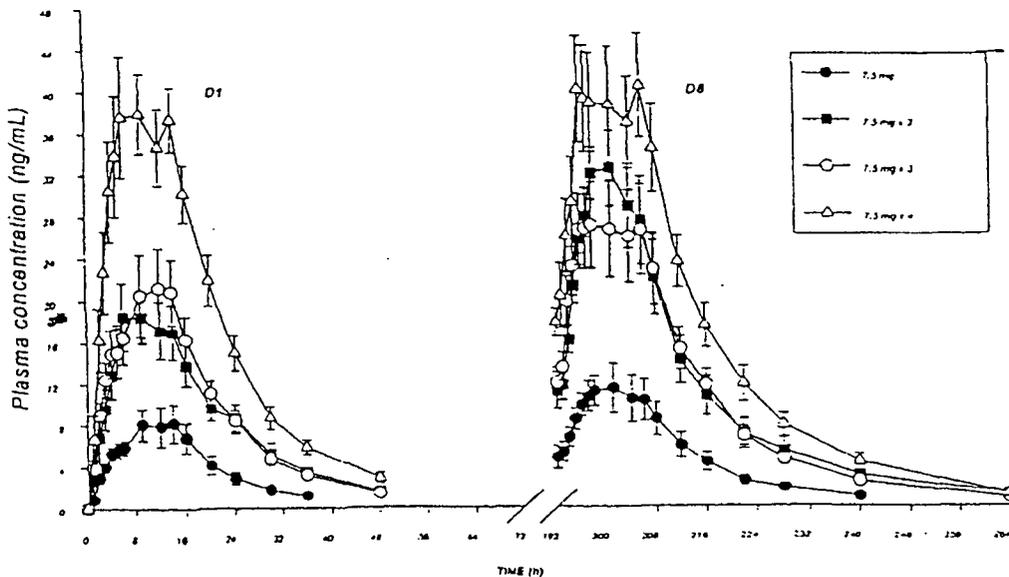
\* = a given PCSA appears in the table if at least one subject reach this PCSA

Subjects who took the 40 mg dose had a greater likelihood of having an abnormal QTcB and/or QTcF compared to those who took a lower dose or placebo.

Study PCALF96US1: Single center, double blind, placebo controlled, parallel sequentially dosed trial. Study drug doses were 7.5 mg to 30 mg qd given in the evening for 8 days. The 48 subjects were healthy males aged 50-70 years.

Plasma profiles are shown below.

FIG.13 Mean ( $\pm$ sem) plasma concentration-time profiles of alfuzosin obtained on day 1 and day 8 in 4 groups of 9 healthy middle-aged volunteers after a repeated oral administration over 5 days of 7.5 mg (group 1), 2  $\times$  7.5 mg (group 2) mg, 3  $\times$  7.5 mg (group 3) and 4  $\times$  7.5 mg (group 4) once-daily, 5 minutes after the evening meal. Representation in linear coordinates.



Mean change from baseline for corrected QT intervals for all doses of drug and placebo are shown below.

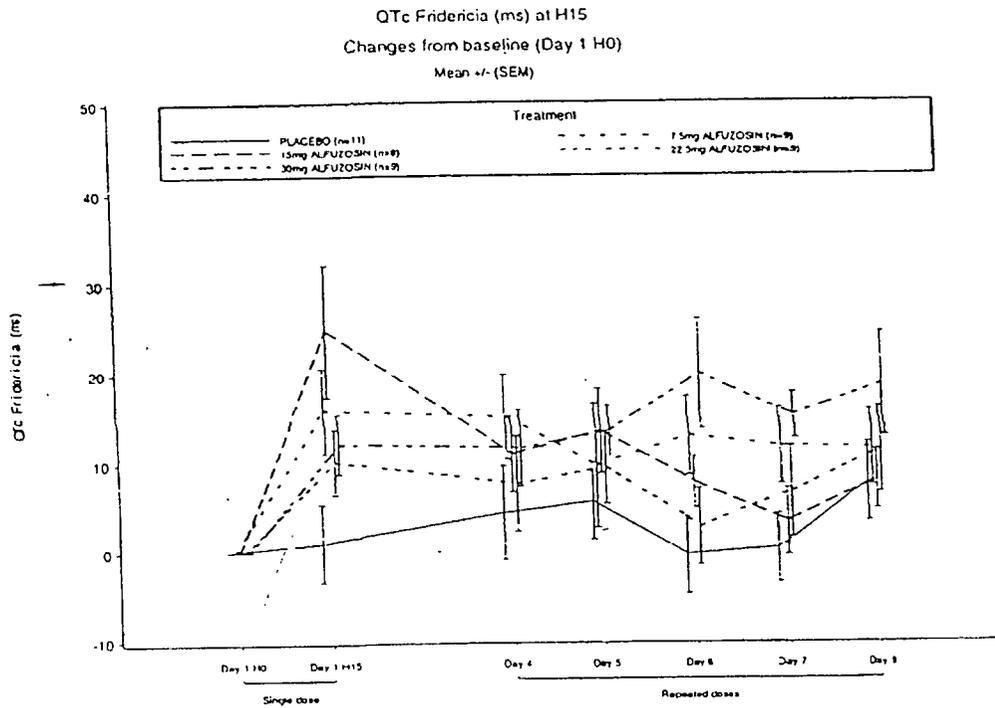


Figure (8.2.5.2) 2 - Changes from Baseline - QTc Fridericia

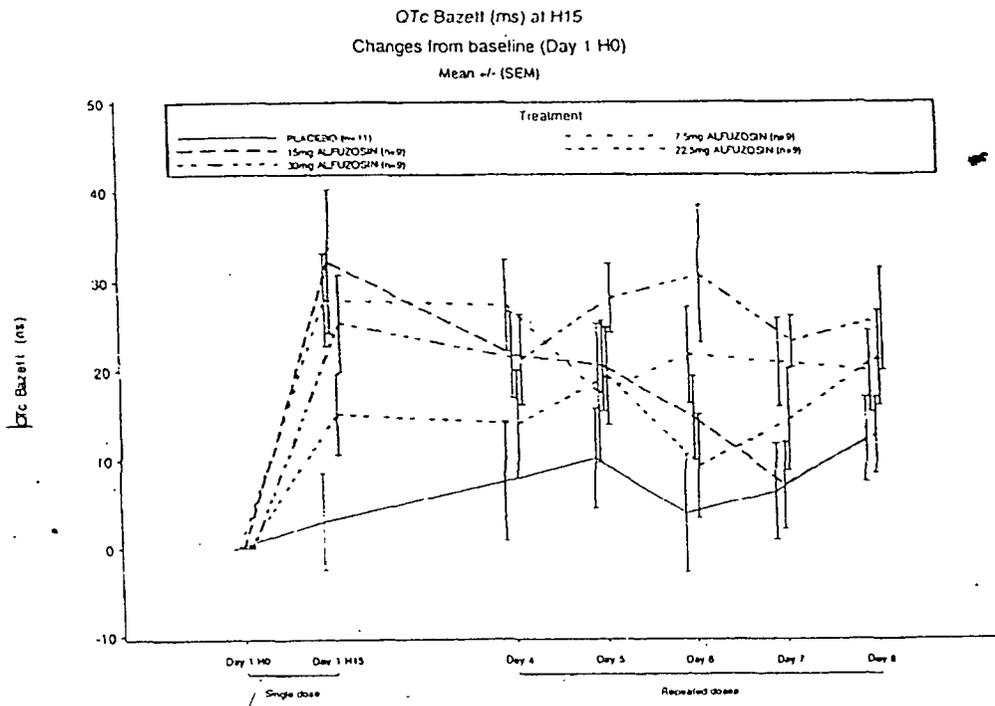


Figure (8.2.5.1) 2 - Changes from Baseline - QTc Bazett

Active drug showed a greater change from baseline in the corrected QT intervals compared to placebo.

Table (8.1) 1 - Pre-dose Abnormalities on ECG

	PLACEBO		ALFUZOSIN 7.5 mg		ALFUZOSIN 15 mg		ALFUZOSIN 22.5 mg		ALFUZOSIN 30 mg	
	N	S	N	S	N	S	N	S	N	S
Available	12	(12)	9	(9)	9	(9)	9	(9)	9	(9)
QRS>120 ms	.	.	.	.	1	(1)	.	.	.	.
QTcB>430 & ≤450 ms	2	(2)	.	.	2	(2)	1	(1)	.	.
QTcB>450 ms	1	(1)	.	.	.	.	.	.	.	.
QTcF>430 & ≤450 ms	1	(1)	.	.	2	(2)	1	(1)	.	.

N: number of data, S: number of subjects

Table (8.1) 2 - Post-dose Abnormalities on ECG

	PLACEBO		ALFUZOSIN 7.5 mg		ALFUZOSIN 15 mg		ALFUZOSIN 22.5 mg		ALFUZOSIN 30 mg	
	N	S	N	S	N	S	N	S	N	S
Available	67	(12)	54	(9)	54	(9)	54	(9)	54	(9)
PR>220 ms	.	.	1	(1)	.	.	.	.	.	.
QRS >120 ms	.	.	.	.	6	(1)	.	.	.	.
QTcB>430 & ≤450 ms	8	(5)	9	(5)	20	(7)	17	(8)	12	(5)
QTcB>450 ms	5	(3)	4	(1)	10	(5)	8	(5)	3	(2)
Delta QTcB≥30 & ≤60 ms	10	(5)	16	(7)	8	(5)	10	(6)	21	(7)
Delta QTcB>60 ms	.	.	2	(1)	1	(1)	.	.	1	(1)
QTcF>430 & ≤450 ms	7	(4)	3	(1)	11	(4)	9	(4)	3	(3)
QTcF>450 ms	.	.	.	.	3	(1)	1	(1)	.	.
Delta QTcF≥30 & ≤60 ms	2	(1)	5	(3)	6	(5)	2	(2)	5	(4)
Delta QTcF>60 ms	.	.	.	.	1	(1)	.	.	.	.

N: number of data, S: number of subjects

The mean differences from placebo and the 95% confidence interval in ECG parameters recorded day 1 hour 15 and day 8 hour 15 are shown below.

Table (8.2) 2 - Mean [95% CI] Difference from Placebo in ECG Parameters at D1 H15 and D8 H15

ECG Parameter versus Placebo	Treatment Effect versus Placebo	Treatment Group			
		ALFUZOSIN 7.5 mg versus PLACEBO	ALFUZOSIN 15 mg versus PLACEBO	ALFUZOSIN 22.5 mg versus PLACEBO	ALFUZOSIN 30 mg versus PLACEBO
<b>Day 1, H15</b>					
Mean HR	p = 0.0035	9.8 [3.4, 16.1]**	4.3 [-2.0, 10.7]	2.8 [-3.6, 9.1]	11.6 [5.2, 17.9]***
Mean QT	NS	-4.5 [-20.7, 11.7]	14.9 [-1.3, 31.2]*	3.1 [-13.2, 19.3]	-10.2 [-26.4, 6.1]
Mean QTcB	p = 0.0052	24.9 [8.6, 41.2]**	29.1 [12.9, 45.4]***	12.0 [-4.3, 28.3]	22.2 [6.0, 38.5]**
Mean QTcF	p = 0.0189	14.9 [1.3, 28.4]*	23.8 [10.2, 37.3]**	9.1 [-4.4, 22.7]	11.1 [-2.4, 24.7]
<b>Day 8, H15</b>					
Mean HR	NS	3.9 [-2.3, 10.1]	1.1 [-5.1, 7.3]	6.0 [-0.2, 12.2]	3.1 [-3.1, 9.3]
Mean QT	NS	-4.7 [-22.1, 12.7]	-0.2 [-17.6, 17.1]	-9.5 [-26.8, 7.9]	4.3 [-13.1, 21.7]
Mean QTcB	NS	7.6 [-6.2, 21.5]	0.5 [-13.3, 14.3]	9.2 [-4.7, 23.0]	13.5 [-0.3, 27.3]
Mean QTcF	NS	3.8 [-8.9, 16.5]	0.3 [-12.4, 12.9]	3.6 [-9.1, 16.3]	10.9 [-1.8, 23.6]

P-value versus placebo: \* ≤ 0.05; \*\* ≤ 0.01; \*\*\* ≤ 0.001

\* Linked to one outlier subject; see Section 8.1

According to these data, the only significant differences between drug and placebo were seen on day 1.

Changes from baseline for QTcB interval measured throughout the study are shown below.

Table (10.) 6 - Changes versus Baseline - QTc Bazett

Delta/Day1H0 QTcb (ms)			ALFUZOSIN	ALFUZOSIN	ALFUZOSIN	ALFUZOSIN		
			PLACEBO (N=11)	7.5 mg (N=9)	15 mg (N=9)	22.5 mg (N=9)	30 mg (N=9)	S
Day1	H15	Mean	3	28	32	15	25	
		SEM	5	5	8	5	6	
		SD	18	16	24	14	17	
		MIN						
		MAX						
		N	11	9	9	9	9	
Day4	H15	Mean	8	27	22	14	21	
		SEM	7	5	5	6	5	
		SD	22	15	14	10	11	
		MIN						
		MAX						
		N	11	9	9	9	9	
Day5	H15	Mean	10	17	20	19	28	
		SEM	6	8	5	5	4	
		SD	19	23	15	16	12	
		MIN						
		MAX						
		N	11	9	9	9	9	
Day6	H15	Mean	4	22	15	9	31	
		SEM	7	5	5	6	3	
		SD	22	16	14	17	21	
		MIN						
		MAX						
		N	11	9	9	9	9	
Day7	H15	Mean	6	21	7	14	23	
		SEM	5	5	5	6	3	
		SD	18	15	15	17	9	
		MIN						
		MAX						
		N	11	9	9	9	9	
Day8	H15	Mean	12	20	13	21	26	
		SEM	5	5	4	5	6	
		SD	16	14	13	16	17	
		MIN						
		MAX						
		N	11	9	9	9	9	

The mean changes from baseline with Bazett's correction were always higher on drug but not necessarily in a dose related manner. The maximum values are usually higher on drug than on placebo.

Table (10.) 8 - Changes versus Baseline - QTc Fridericia

Delta/Day1H0 QTcf (ms)			ALFUZOSIN	ALFUZOSIN	ALFUZOSIN	ALFUZOSIN	SU
			PLACEBO	7.5 mg	15 mg	22.5 mg	30 mg
			(N=11)	(N=9)	(N=9)	(N=9)	(N=9)
Day1	H15	Mean	1	16	25	10	12
		SEM	4	5	7	4	3
		SD	15	14	22	11	10
		MIN					
		MAX					
		N	11	9	9	9	9
Day4	H15	Mean	4	15	11	8	12
		SEM	5	5	4	5	4
		SD	18	14	12	16	13
		MIN					
		MAX					
		N	11	9	9	9	9
Day5	H15	Mean	6	10	13	9	13
		SEM	4	7	5	4	3
		SD	14	21	14	12	8
		MIN					
		MAX					
		N	11	9	9	9	9
Day6	H15	Mean	-1	13	6	3	20
		SEM	4	4	3	4	6
		SD	14	13	9	12	18
		MIN					
		MAX					
		N	11	9	9	8	9
Day7	H15	Mean	0	12	3	7	15
		SEM	4	4	4	5	3
		SD	13	13	12	15	8
		MIN					
		MAX					
		N	11	9	9	9	9
Day8	H15	Mean	8	11	8	11	19
		SEM	4	4	3	5	6
		SD	15	13	10	14	17
		MIN					
		MAX					
		N	11	9	9	9	9

As with the Bazett's correction, the mean changes from baseline with the Fridericia's correction were always higher on drug but not necessarily in a dose related manner. The maximum values were usually higher on drug than on placebo.

Number and percent of patients reporting selected adverse events from various sources are shown below.

Table (4.) 1 - Number (%) of Patients with Rhythm Disorder SAEs: All Alfuzosin Studies and Spontaneous Reports, ISS and ISS Update Combined

Adverse Event	Phase III, Alfuzosin ER, Completed, in BPH	Phase III, Alfuzosin ER, Ongoing, in BPII	Phase II/III, Other Formulations, in BPH	Postmarketing Surveys and Observational Studies	Phase I	Phase II/III, Non-BPH	Spontaneous Reports* (All Formulations)
	(N = 1,795)	(N = 254)	(N = 869)	(N = 120,230)	(N = 1,308)	(N = 1,167)	(N = NA)
Arrhythmia	0	0	0	3 (0.0)	0	0	1
AV block	0	0	0	0	0	0	2
Bradycardia	0	0	0	0	0	0	3
Cardiac arrest	0	0	0	3 (0.0)	0	0	1
Extrasystoles	0	0	0	0	0	0	1
Fibrillation atrial	4 (0.2)	2 (0.8)	0	2 (0.0)	0	0	6
Fibrillation ventricular	0	0	0	1 (0.0)	0	0	3
Palpitation	0	0	0	1 (0.0)	0	0	1
Sick sinus syndrome	1 (0.1)	0	0	0	0	0	0
Tachycardia	0	0	0	0	0	0	4
Tachycardia supraventricular	0	0	0	0	0	0	1
Tachycardia ventricular	0	0	0	0	0	0	2
VT, nonsustained with normal QT interval	0	0	0	0	2 (0.2) <sup>a</sup>	0	0

Abbreviations: AV, atrioventricular; BPH, benign prostatic hyperplasia; ER, extended-release formulation; VT, ventricular tachycardia

\* For the Phase III studies of the ER formulation, N = patients uniquely exposed to alfuzosin: 1,608 were described in the ISS and 187 were newly exposed in the open-label extension studies.

<sup>b</sup> Reported as first main event.

<sup>c</sup> The number of alfuzosin-treated patients cannot be estimated precisely, and no sample size is available. The number of therapy-days has been estimated at 871 million.

<sup>d</sup> Telemetric ECG monitoring. VT not associated with increase QT, relationship excluded by the investigator.

REF: NDA Item 8.12 (ISS V308 P144) and NDA Update Items 9.1 (V21 P51 and P52), 9.3.2 (V25 P1) and 9.3.3 (V25 P77)

Although the reliability of spontaneous reports can be poor, these data are reassuring in that if there is a signal, it is small.

#### QT interval prolongations

All dose groups including placebo caused a lengthening of QTcB and/or QTcF. The largest increase was reported for one subject in the 15 mg dose group (78/71 msec increase for QTcB/QTcF, respectively). The subject's values declined despite continued treatment.

## Attachment 1

### Effects on HERG

- The sponsor evaluated the effects of alfuzosin on HERG current in a stable mammalian cell line (Chinese hamster ovary cells). Effects of alfuzosin were compared to those of several other alpha-1 antagonists: doxazosin, tamsulosin, prazosin and terazosin.

HERG current was measured at room temperature (20-24 °C) using the whole cell voltage clamp configuration. HERG current was measured as the peak inward tail current elicited by voltage clamping the cell to a hyper-polarizing voltage of -120 mV after an 800 ms depolarization to +20 mV from a holding potential of -80 mV. External potassium concentration was 10 mM. Each cell was exposed to up to 5 ascending concentrations of a single drug. Current rundown appeared negligible over the duration of exposure to low drug concentrations (no rundown at 0.01 and 0.1 µM alfuzosin). Individual data provided showed low variability.

Table 1: Percentage inhibition of HERG current

	Alfuzosin	Tamsulosin	Doxazosin	Terazosin	Prazosin
0.01 µmol/L	0 (3)	-	-	4.2 ± 1.8 (3)	0 (2)
0.1 µmol/L	0 (4)	-	3.9 ± 1.6 (5)	5.7 ± 1.2 (6)	1.9 ± 0.9 (6)
1 µmol/L	3.5 ± 2 (9)	3.2 ± 1.5 (5)	31.9 ± 6.4 (5)	10.1 ± 2.4 (6)	28.9 ± 3.8 (6)
10 µmol/L	19.5 ± 2.5 (8)	15.5 ± 5.5 (5)	76.6 ± 4.2 (5)	36.6 ± 4.9 (6)	71.1 ± 4.4 (6)
100 µmol/L	57.3 ± 2.6 (8)	49.2 ± 7.2 (5)	92.7 ± 0.3 (5)	74.9 ± 4.6 (6)	90.6 ± 0.9 (6)
1000 µmol/L	77.8 ± 2.2 (5)	83.5 ± 4.4 (5)	-	-	-

Results are expressed as mean ± S.E.M (Standard Error of the Mean)

Number of cells tested is in brackets.

% of inhibition of HERG current was measured as the final current minus the control current at each concentration and divided by the control current multiplied by 100.

Table 2 - Comparison of Inhibition of HERG potassium current

Drugs	Number of cells	IC <sub>50</sub> µmol/L
Alfuzosin	3-9	83.3 ± 16.6
Doxazosin	5	2.5 ± 0.3
Prazosin	2-6	3.4 ± 0.4
Tamsulosin	5	104.8 ± 0.6
Terazosin	3-6	21.4 ± 2.9

Alfuzosin weakly inhibited HERG current in a concentration-dependent manner. However, potency on HERG was likely underestimated because of the experimental conditions utilized (high external potassium concentration, hyperpolarization, room temperature). The effects of human metabolites on HERG current were not evaluated.

### Alfuzosin's Effects on Action Potential Duration in Porcine Purkinje Fibers

The sponsor evaluated the effects of alfuzosin (SL77.0499-10) on action potential duration in porcine (piglet) Purkinje fibers stimulated at 1.0 and 0.25 Hz. Alfuzosin was evaluated at concentrations of 0.01, 0.1, 1, 10 and 30  $\mu\text{M}$ . Purkinje fibers were exposed to each concentration for 30 minutes. A 30-minute drug-free period was initiated at completion of the study to evaluate washout.

Alfuzosin shortened APD90 in Purkinje fibers when evaluated at a stimulation frequency of 1 Hz, but prolonged APD90 when evaluated at 0.25 Hz. Effects on APD90 were concentration-related. Early afterdepolarizations were not observed. Effects on APD90 indicate inverse use-dependence typical of drugs that inhibit HERG. Effects of alfuzosin were not reversed by 30 minutes of exposure to drug-free perfusate.

Fig 1: Effects of alfuzosin on the action potential of piglet Purkinje fibre stimulated at 1 Hz

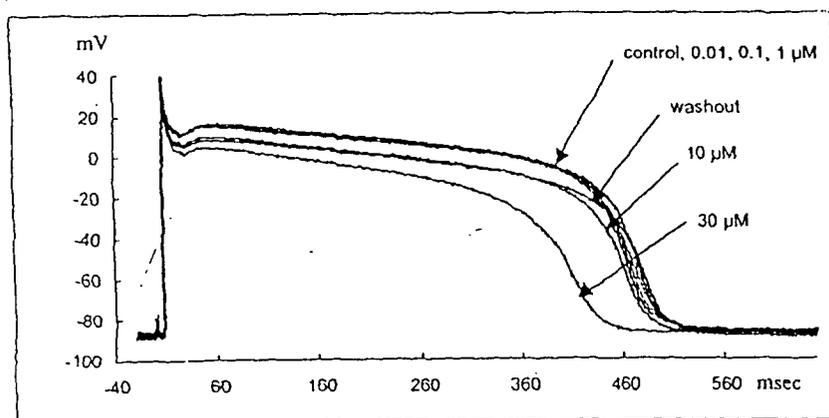
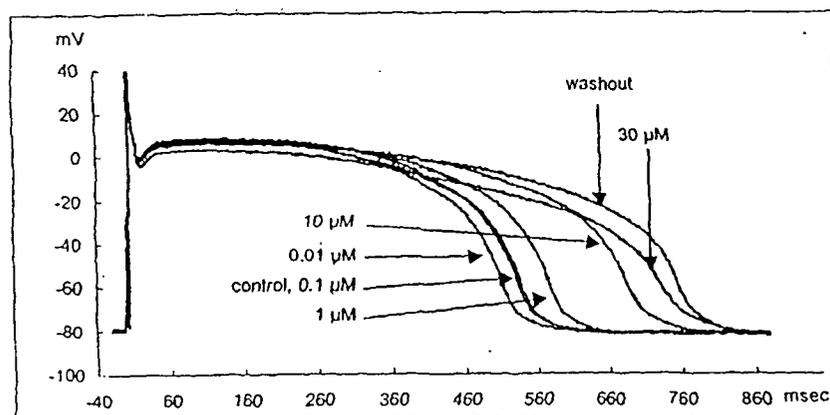


Fig 2: Effects of alfuzosin on the action potential of piglet Purkinje fibre stimulated at 0.25 Hz



Alfuzosin at concentrations  $\geq 10 \mu\text{M}$  depressed the maximal upstroke velocity ( $dV/dt_{\text{max}}$ ) of the action potential, indicative of sodium channel blockade. Therefore, alfuzosin appears to be a mixed channel blocker, with effects on both inward and outward currents.

Table 1: Effects of alfuzosin on the electrophysiological parameters of the action potential in piglet Purkinje fibres.

treatment	RP (mV)	APA (mV)	APD <sub>50</sub> (msec)	APD <sub>90</sub> (msec)	APD <sub>95</sub> (msec)	dV/dt <sub>max</sub> (V/sec)
control	-66.8 ± 0.7	132.0 ± 0.8	271.6 ± 16.5	348.6 ± 19.9	399.8 ± 17.4	906.8 ± 37.0
SL77.0499-10 0.01 $\mu\text{M}$	-67.5 ± 0.8 (-0.8 ± 0.6) NS	131.9 ± 0.9 (-0.1 ± 0.4) NS	258.2 ± 21.4 (-5.5 ± 2.2) NS	340.7 ± 22.4 (-2.5 ± 1.0) NS	391.4 ± 19.6 (-2.2 ± 0.9) NS	895.5 ± 41.1 (-1.3 ± 1.2) NS
SL77.0499-10 0.1 $\mu\text{M}$	-67.5 ± 0.5 (-0.8 ± 0.5) NS	131.6 ± 1.0 (-0.4 ± 0.6) NS	253.3 ± 21.7 (-7.2 ± 3.4) NS	342.9 ± 22.7 (-1.9 ± 1.3) NS	392.9 ± 20.1 (-1.9 ± 1.1) NS	873.8 ± 47.4 (-3.8 ± 2.6) NS
SL77.0499-10 1 $\mu\text{M}$	-67.8 ± 0.6 (-1.1 ± 0.3) NS	131.8 ± 0.6 (-0.2 ± 0.5) NS	248.8 ± 22.2 (-9.1 ± 3.1) NS	348.4 ± 23.9 (-0.4 ± 1.5) NS	401.0 ± 19.7 (+0.2 ± 1.3) NS	865.7 ± 53.3 (-4.6 ± 4.1) NS
SL77.0499-10 10 $\mu\text{M}$	-67.3 ± 0.8 (-0.5 ± 0.5) NS	130.9 ± 0.6 (-0.9 ± 0.6) NS	177.1 ± 37.3 (-35.7 ± 12.9) ***	336.1 ± 19.9 (-3.6 ± 1.9) NS	403.2 ± 17.5 (+0.9 ± 1.9) NS	822.4 ± 50.9 (-9.3 ± 4.1) *
SL77.0499-10 30 $\mu\text{M}$	-67.5 ± 0.8 (-0.8 ± 0.2) NS	128.9 ± 0.9 (-2.3 ± 0.9) ***	73.7 ± 27.1 (-74.4 ± 8.8) ***	273.0 ± 19.0 (-21.3 ± 4.6) ***	367.8 ± 13.9 (-7.8 ± 2.2) ***	749.3 ± 53.5 (-17.3 ± 5.1) ***
washout	-88.1 ± 1.4 (-1.7 ± 1.2)	130.4 ± 1.2 (-1.1 ± 1.0)	214.8 ± 21.2 (-22.0 ± 6.8)	363.2 ± 22.2 (+3.4 ± 1.9)	425.3 ± 21.7 (+4.9 ± 1.7)	803.3 ± 55.9 (-8.6 ± 4.6)

Preparations were stimulated at 1 Hz for 30 minutes in normal physiological solution at a temperature of 36°C. Data are expressed as means ± SEM (n=6/group, except washout n=5). The percentages of change with regard to the control values are given in brackets. NS: not significantly different from the control groups one-way analysis of variance with repeated measures on factor concentration (Dunnett's test). \*: significantly different from the control group (P ≤ 0.05, Dunnett's test after one-way ANOVA analysis with repeated measures on factor concentration). \*\*: significantly different from the control group (P ≤ 0.001, Dunnett's test after one-way ANOVA analysis with repeated measures on factor concentration).

### Summary/Evaluation

Alfuzosin's *in vitro* electrophysiological effects suggest a low risk for repolarization abnormalities. However, while effects on HERG current suggest a low risk, alfuzosin's potency was likely underestimated, and some drugs, e.g., sotalol and quinolone and macrolide antibiotics weakly inhibit HERG yet prolong QT interval and induce *torsade* in humans. Additionally, human metabolites were not evaluated. Further information should be provided to support a conclusion of low risk.

The sponsor should provide control data generated in their laboratory for both HERG and Purkinje fibers with standard HERG blocking drugs, e.g., cisapride, terfenadine, dofetilide and d-sotalol. Effects of human metabolites on HERG and APD90 would be useful.

The sponsor should provide *in vivo* data on QT and QTc effects of alfuzosin in experimental animals. Effects on other electrocardiographic parameters, e.g., QRS duration and PR and RR intervals should also be provided. If alfuzosin affects heart rate, pacing should be considered.

Alfuzosin should be evaluated over a wide dose range with the maximum dose evaluated showing at least minimal toxicity. The sponsor should provide a rationale for *in vivo* doses evaluated and relate doses evaluated to those which produce toxic and therapeutic effects in the same species as well as therapeutic effects in humans. QT effects should be determined at both C<sub>max</sub> and times thereafter. Both total and free plasma concentrations of alfuzosin and its human metabolites at the time of QT evaluation should be provided. Concurrent positive control data on drugs with mixed channel activity, such as terfenadine, should be provided.