Alfuzosin plasma levels were measured in BPH patients participating in various phase III studies (refer to Population Pharmacokinetics section). The plasma levels measured were classified into peak and trough concentration based on sampling time.

Table 9- Mean (SD) Peak and Trough Concentrations With Repeated Doses of Alfuzosin Extended-Release Tablets in BPH Patients

Concentration (ng/mL)	Dose	Number of Observations	Mean (SD)
Peak	7.5 mg od	38	8.8 (5.0)
	10 mg od	211	10.9 (6.9)
	15 mg od	152	17.6 (10.1)
Trough	7.5 mg od	438	5.4 (3.5)
	10 mg od	426	6.9 (4.6)
	15 mg od	219	11.0 (6.9)

Alfuzosin exposure in patients increased in dose proportional manner over the range of 7.5 to 15 mg. The peak concentrations observed in patients are similar to those observed in healthy middle aged volunteers. Trough concentrations in patients are slightly higher than those observed in healthy middle aged volunteers. However it should be noted that the plasma levels obtained in the phase III studies were based on sample collection over two windows of time (10-14 hours for peak, 20-22 hours for trough).

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?
Is there a PK/PD relationship for efficacy and safety parameters?

3. EXPOSURE-RESPONSE

a. Immediate release tablets

The effect of alfuzosin on urinary flow rate was assessed in a placebo-controlled, double blind, randomized, parallel study (#91-00087) in 93 BPH patients with a peak flow rate (PFR)<15 ml/sec following single oral administration of placebo or, 1.25 mg or 2.5 mg of alfuzosin IR tablets. The mean changes in PFR are illustrated in the following figure and table.

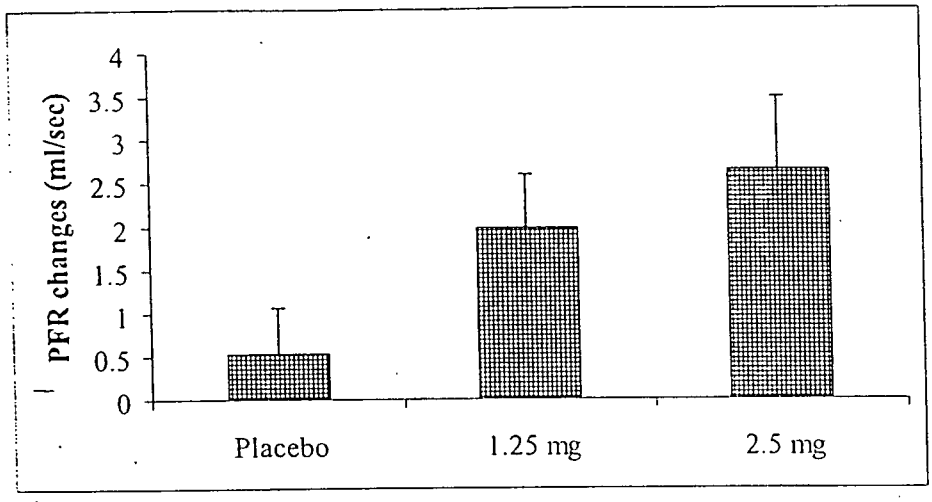


Figure 8- Mean (SEM) Absolute Change From Baseline Urinary PFR Following a Single Oral Dose of Placebo or Alfuzosin Immediate Release in 93 Patients With BPH [report no. 91-00087]

There was dose dependent increase in peak urinary flow rate and mean urinary flow rate, although not statistically significantly in case of PFR.

b. Extended release tablets

i). Efficacy

Four, double-blind, placebo controlled, randomized, multicenter phase III clinical trials have been conducted with once daily ER formulation of alfuzosin. Three doses of alfuzosin 7.5 mg, 10 mg, and 15 mg have been investigated in a total 2,008 patients. The first phase III study (ALFOD) evaluated 7.5 mg ER dose in comparison to placebo. In this study, although 7.5 mg improved some secondary endpoints, there was no significant difference between 7.5 mg dose and placebo. In subsequent studies, 10 and 15 mg doses were investigated. The effect of the different doses of alfuzosin on the primary endpoints (IPSS and PFR) from all phase III studies is illustrated in the following figures

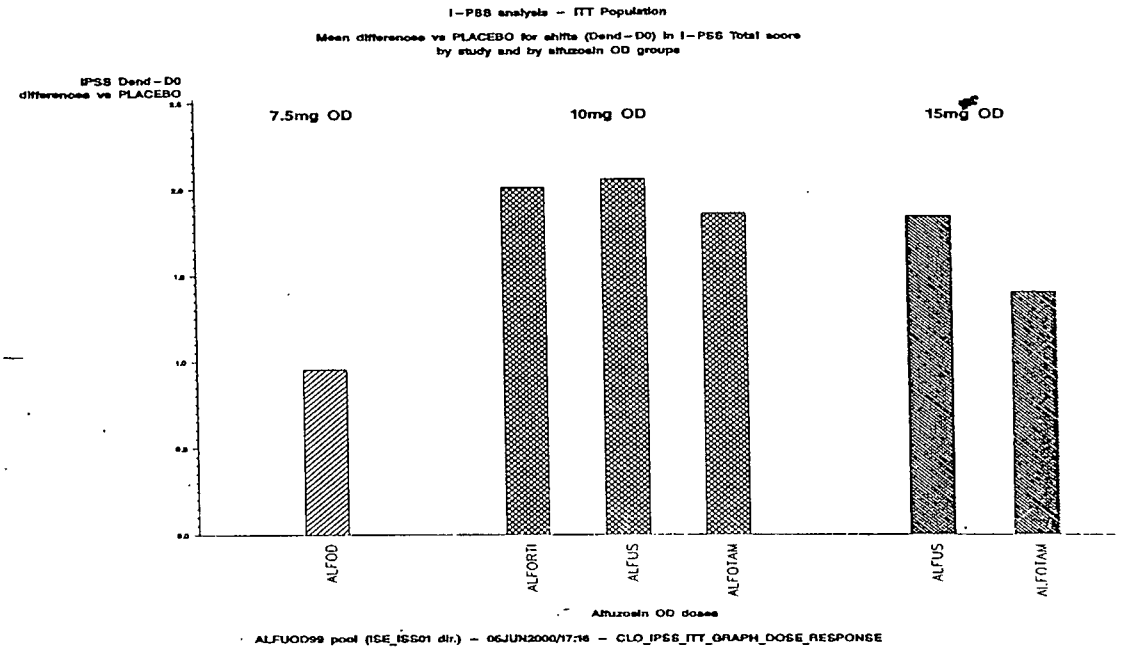
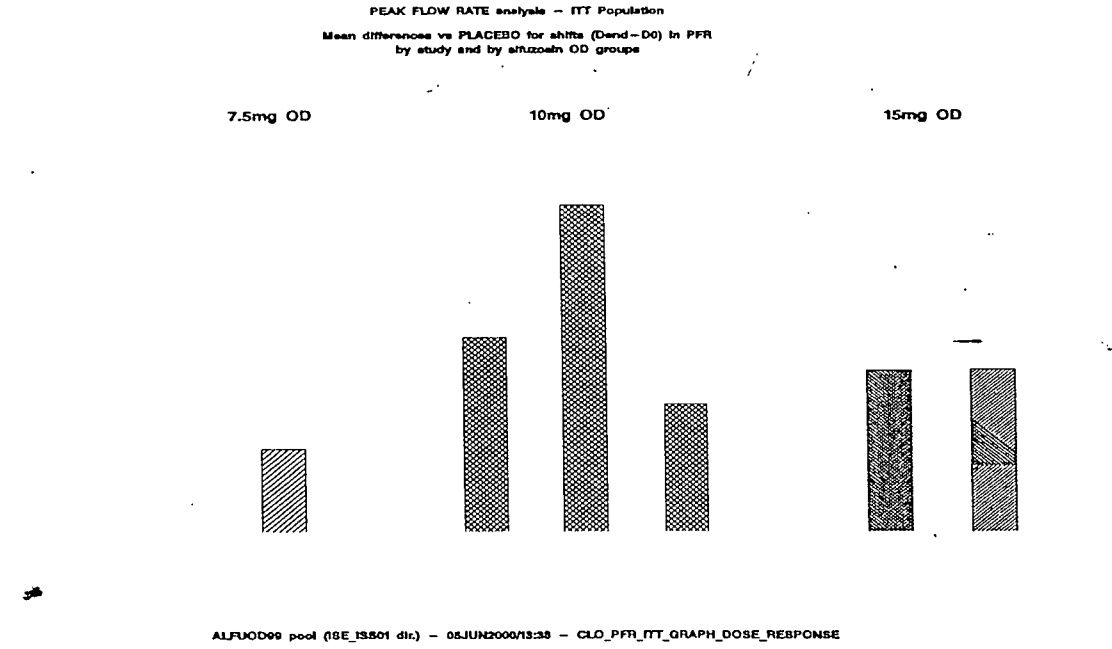


Figure 9- Mean Difference vs. Placebo for Shifts (Dend - D0) in IPSS Total Score by Study and by Alfuzosin Groups



There appears to be dose depended increases in IPSS and PFR with 7.5 and 10 mg doses. However, the dose of 7.5 mg was not found to be significantly superior to placebo, while the 10 mg dose showed significant benefit. Since the15 mg dose was not superior to 10 mg dose, sponsor proposed 10 mg dose for approval.

ii) Safety

The incidence of treatment emergent adverse events (vasodilatory) in phase III trials are summarized in the following table.

Table 10 - Vasodilatory TEAE Reported by Number (%) of Patients: Double-Blind, Placebo, and Alfuzosin ER Treatment Groups

		Alfuzosin ER		
	Placebo	7.5 mg	10 mg	15 mg
	N=678	N=204	N=473	N=335
	n (%)	n (%)	n (%)	n (%)
Count of patients with at least 1 vasodilatory TEAE	19 (2.8)	5 (2.5)	29 (6.1)	33 (9.9)
Dizziness/Malaise	19 (2.8)	4 (2.0)	27 (5.7)	30 (9.0)
Hypotension	0	0	2 (0.4)	2 (0.6)
Syncope	0	1 (0.5)	1 (0.2)	2 (0.6)
Postural hypotension	0	0	0	0
Total number of vasodilatory TEAE	19	5	30	34

NB: TEAEs are listed in descending order of frequency by alfuzosin ER 10 mg group.
The term malaise has been historically used by the Sponsor in this project as a higher-level term for events relating to "feeling faint." As per agreement with the Agency, malaise is classified as dizziness in the package insert and Section 23 of the Integrated Safety Summary.
REF: NDA Item 8.12, Integrated Safety Summary, Table (8.2) 1, V308 P39

Based on the above table, the incidence of vasodilatory AEs (dizziness) appears to be dose related consistent with the pharmacology of α_1- blockers. At 15 mg dose, higher incidence of vasodilatory adverse events are expected than at 10 mg dose. [please refer to medical review for more details on safety and efficacy evaluation.]

Hemodynamic effects of alfuzosin

The effect of alfuzosin on vital signs was evaluated in a double-blind, randomized, placebo-controlled, parallel-group, ascending design multiple dose study (#97-00725). In this study, alfuzosin doses of 7.5 mg, 15 mg, 22.5 mg, and 30 mg were assessed in sequential manner using one to four tablets of 7.5 mg ER formulation. Alfuzosin or placebo was given as single dose after evening meal on Day 1 of the study and then once daily for 5 five days (from Day 4 to Day 8 of the study). The dose-dependent effect and comparative effects of first dose and last dose on vital signs parameters are illustrated in the following figure.

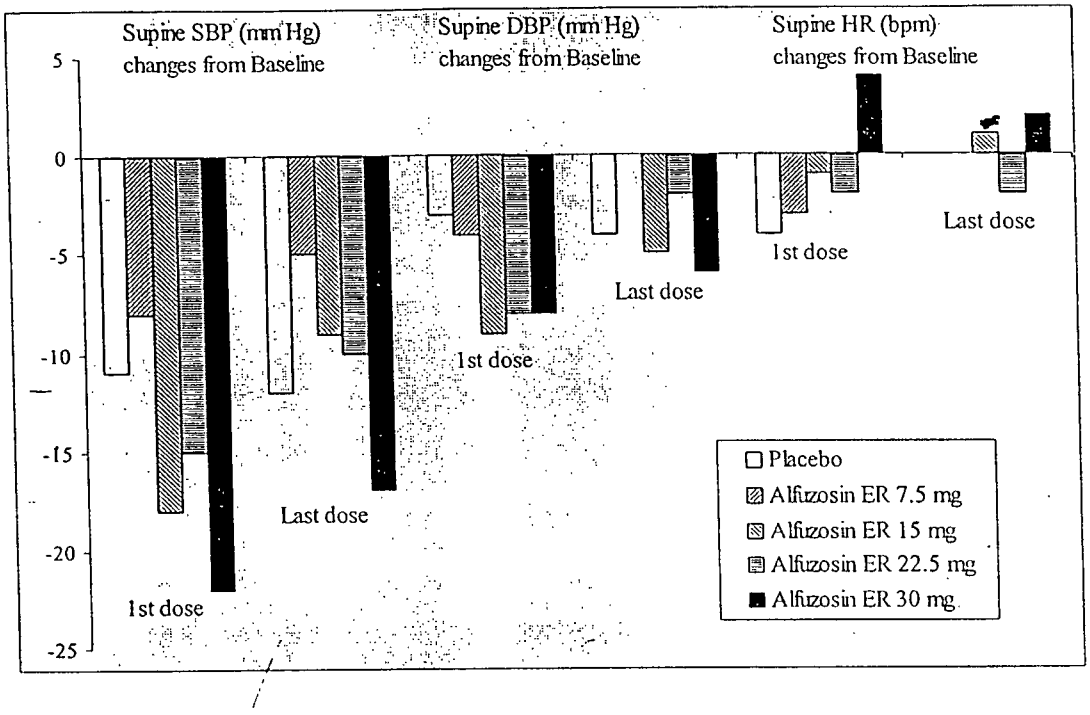


Figure 11- Mean Supine Hemodynamics Parameters Changes From Baseline to 9 Hours Following Single Dose (First Dose) and 5 Days Multiple Dose (Last Dose) of Placebo and Alfuzosin Extended-Release Tablets 7.5 mg, 15 mg, 22.5 mg and 30 mg Once Daily in 47 Healthy Middle-Aged Volunteers

Table 11- Number (%) of Subjects With at Least One Out of Range Hemodynamic Value of Clinical Significance Related to Vasodilatation any Time Following a Single Dose and Multiple Doses of Placebo and Alfuzosin 7.5 mg, 15 mg, 22.5 mg, and 30 mg Once Daily in 47 Healthy Middle-aged Volunteers

	Number of Subjects (Percentage of subjects)				
Out of Range Measure	Placebo (n=11)	Alfuzosin 7.5 mg (n=9)	Alfuzosin 15 mg (n=9)	Alfuzosin 22.5 mg (n=9)	Alfuzosin 30 mg (n=9)
supine **SBP** decreased from baseline by 20 mm Hg or more	8 (73%)	5 (56%)	4 (44%)	6 (66%)	7 (77%)
supine **DBP** decreased from baseline by 15 mm Hg or more	5 (46%)	4 (44%)	5 (56%)	4 (44%)	3 (33%)
Supine **HR** increased from baseline by 15 bpm or more	5 (46%)	5 (56%)	6 (66%)	5 (56%)	7 (77%)
Orthostatic change in **SBP** decreased by 20 mm Hg or more	5 (46%)	5 (56%)	7 (77%)	6 (66%)	7 (77%)

SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg);
HR = heart rate (bpm)

As shown in the figure above, the hemodynamic effects (decrease in blood pressure) are higher with first dose compared to last dose. Percentage of subjects with out of range values for supine SBP and DBP in active treatment groups was not worse than the placebo group. However, changes in supine HR (increase) and orthostatic change in SBP (decrease) increased in dose dependent manner.

c. PK/PD relationship (for efficacy and safety parameters)

The PK/PD relationship between alfuzosin plasma concentrations and the relevant safety and efficacy measures was analyzed retrospectively in BPH patients from four phase III studies (ALFOD, ALFORTI, ALFOTAM and ALFUS). The details of these studies are given in the following table.

Table 12. Clinical studies used for PK/PD analysis

Clinical Study	Dose range	No. of patients Per dose level	Planned PK/PD Sampling
ALFOD	7.5 mg	203 (E)* 204 (S)#	1 sample per visit for 5 visits (D0,D14, D28, D56, D84)
ALFORTI	10 mg	142 (E) 143 (S)	1 sample per visit for 4 visits (D0, D28, D56, D84)
ALFOTAM	10 mg 15 mg	154 (E & S) 159 (E & S)	1 sample per visit for 4 visits (D0, D28, D56, D84)
ALFUS	10 mg 15 mg	176 (E) 177 (S) 181 (E & S)	1 sample per visit for 4 visits (D0, D28, D56, D84)

*E: efficacy, #S; Safety

The relationship between either efficacy or safety Vs plasma concentration was assessed using a mixed effects model analysis. The interaction terms (study, visit and visit by study) were dropped if no statistical significance was determined.

i) Efficacy analysis

The effect of visit and study on the slope was assessed. All interactions with slope were found non-significant for PFR Dx-D0 (peak urine flow rate change from baseline) and therefore all interaction terms were dropped from the full model. Plasma concentrations and efficacy parameter were combined for all visits and studies to conduct the correlation analysis.

As shown in figure below, although PFR changes from baseline (Dx-D0) were significantly correlated to all and trough alfuzosin plasma concentrations, this correlation does not appear to be strong. There was no relationship between PFR and peak plasma concentration probably due to small number of peak concentrations used in the analysis.

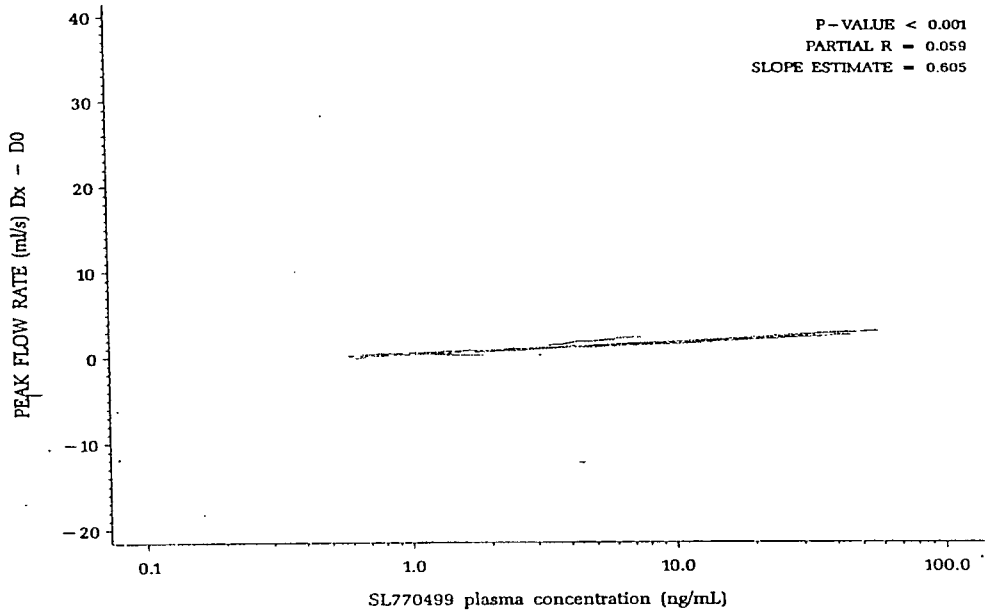


Figure 12. Relationship between plasma alfuzosin levels and peak urine flow rate

ii) Safety Analysis

The safety hemodynamic parameters selected for analysis were orthostatic changes in systolic blood pressure (OSBP) and in heart rate (OHR), supine heart rate (SUHR), supine systolic blood pressure (SUSBP). The responses obtained within ±1 hour of the plasma concentrations were correlated with all the plasma alfuzosin concentrations obtained on the same day (within 24 hour post-dose). The peak (10 –14 hour post dose) and trough (18-22 hours post dose) concentrations were analyzed as subset for secondary analysis.

From the final analysis, only SUSBP changes from baseline was inversely correlated to all and trough alfuzosin plasma log concentrations (see following figure).

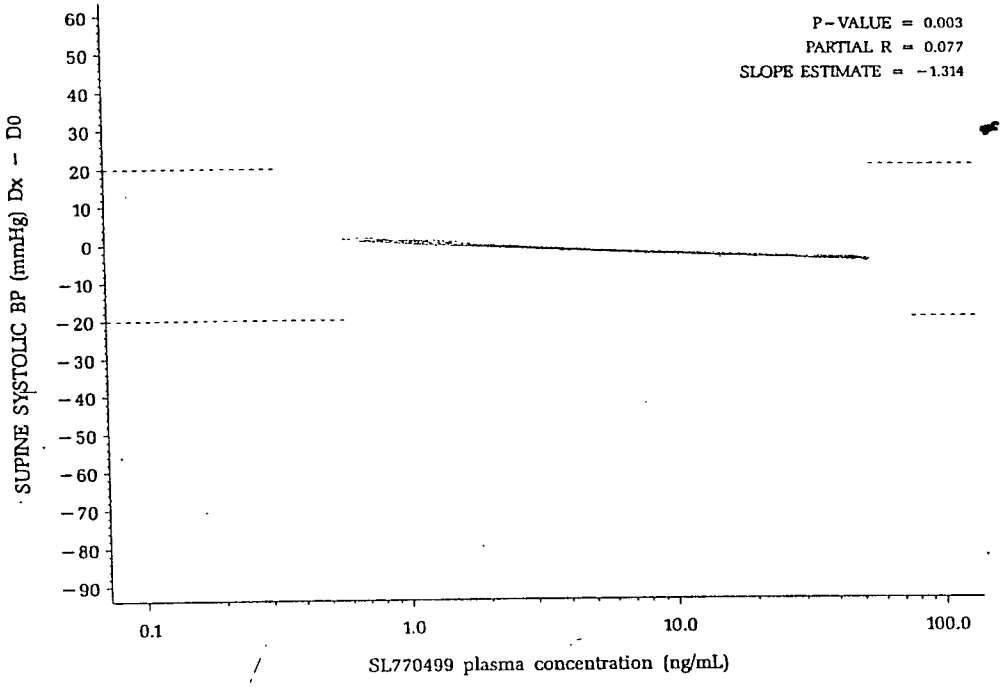


Figure 13 - SUSBP Dx-D0 Versus Log Alfuzosin Plasma Concentrations
[report no. 00-00282]

Although there was statistical significance for the regression line shown above, the relationship shown above appears to be shallow. There was no statistical relationship between SUSBP Dx-D0 and peak concentrations. Sponsor attributed this due to the small number used in the peak analysis. Orthostatic changes in heart rate and systolic blood pressure and supine heart changes from baseline were not correlated to plasma concentrations.

iii) QT effects of alfuzosin

A single center, randomized, double-blind, placebo-controlled, parallel sequentially-dose escalation study was conducted to investigate the effect of alfuzosin 7.5 mg controlled release dosage form at doses 7.5 mg, 15 mg, 22.5 mg and 30 mg on QT intervals and cardiovascular safety. Four sequential groups of 12 healthy male subjects of 50 to 70 years old (9 active and 3-placebo) participated in the study.

A single dose of alfuzosin or placebo was administered 5 minutes after evening meal on study Day 1. Starting on study Day 4, alfuzosin or placebo was administered once daily 5 minutes after the evening meal for 5 days. Blood samples were collected at the end of each dosing and for 72 hours after the last dose on Day 8 for pharmacokinetic analysis.

Electrocardiograms (12-lead ECG) were recorded at the time of screening, on Day 1 and Days 2, 5, 6, 7, 8 and 9 and as part of the exit exam on Day 11. ECG parameters recorded in the CRF included heart rate, PR, QRS, QT and QTc intervals and ST segment assessment. The ECG recordings were read by computer. QT interval was corrected for heart rate using Bazett's formula ($QTcB=QT/\sqrt{(R-R)}$, and Frediricia's formula ($QTcF=QT/\sqrt[3]{(R-R)}$ in which R-R is the interval between two successive QRS complexes). On each study day, ECG was recorded at a single time point of 15 hours after drug administration.

In the initial study report submitted with original NDA, analysis of automatic readings of ECG was provided. Subsequently, in four month safety update sponsor submitted analysis of manual readings from this study.

When QT intervals are corrected for heart rate, alfuzosin in general seems to have increased the QTc compared to placebo. The alfuzosin effect on QT prolongation on Day 1 seems to be higher than Day 8 when compared to placebo. Delta QTcB was statistically significantly higher in alfuzosin 7.5 mg group (+25 ms), 15 mg group (+29 ms) and 30 mg group (+22ms) at D1 H15 than in placebo group at D1 H15. Similar differences (although less in magnitude) were observed with QTcF values. Pharmacokinetics of afluzosin in the study was dose proportional except for the 15 mg dose that was higher than dose proportional (refer to Figure 5 in Dose proportionality section).
The relationship between peak concentrations of alfuzosin and QTc changes is given in the following figure.

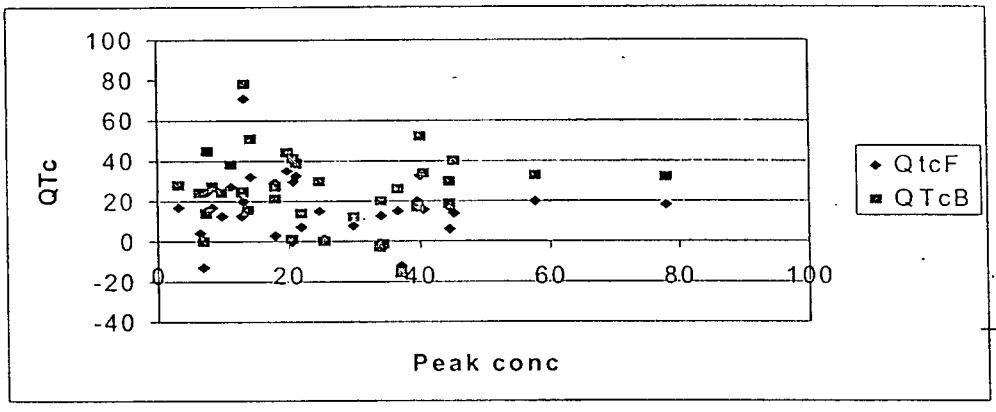


Figure 14. Relationship between peak concentrations and QTC changes

From the above figure, QTc prolongation did not increase with increase in peak concentrations. The increase in QTc also does not appear to be dose dependent. However, it should be noted that QT changes were recorded only at one time point predose and at 15 hours after drug administration.

Three subjects in placebo group, two in 7.5 mg group, five each in 15 mg and 22.5 mg dose groups and two in 30 mg group had QTcB values >450 ms while one subject each in 15 mg and 22.5 mg dose groups had QTcF >450 ms. One subject in 15 mg dose group had a prolonged QTcB with a maximal value of 515 ms observed at D1 H15 (delta QTcB = +78, delta QTcF= +71) while his heart rate remained unchanged. His QTcB returned to normal over time, even though he continued on alfuzosin.

Sponsor stated that observed QTc increases indicate a possible over correction when Bazett's and Fridericia's formula is applied in conjunction with a high HR value (>60 bpm). Cardiorenal division was consulted on QT prolongation issues of alfuzosin. For clinical significance of the QT prolongation effects of alfuzosin, please refer to the consult review from Cardiorenal division.

Another phase I study (PKD4532) was conducted to investigate the effects of alfuzosin at dose as high as 40 mg on ECG parameters. This study was submitted to the NDA with the 4-month safety update. This was a single center, placebo-controlled, double-blind, single dose, randomized, crossover study in 24 healthy young male volunteers. Single doses 10, 20 and 40 mg of alfuzosin ER formulation (10 mg strength) were studied and the drug was administered 5 minutes after high-fat breakfast. ECG recordings were performed at predose (one hour before drug administration) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, and 24 hours after drug administration. Blood samples for measurement of alfuzosin were also collected at various time intervals after drug administration.

Table 13. Mean (%CV) pharmacokinetic parameters of alfuzosin ER formulation

Dose	Cmax	Tmax	AUC_{last}	AUC	$T_{1/2z}$ (h)
10 mg	8.9 (38%)	6.5 (2.0 – 18.0)	129 (40%)	169 (27%)	13.9 (42%)
20 mg	18.3 (44%)	6.5 (3.0 – 16.0)	289 (45%)	343 (41%)	12.3 (37%)
40 mg	38.9 (40%)	8.5 (3.0 – 12.0)	664 (42%)	702 (39%)	9.5 (29%)

The pharmacokinetics of alfuzosin was dose proportional following single doses of 10mg, 20mg or 40 mg.

Table 14. Absolute ECG changes from baseline

Parameter	Pairwise comparison	p-value	Mean difference	95% CI UB
Delta HR (bpm)	10 mg vs placebo	0.1011	+0.6	+1.3
	20 mg vs placebo	0.0001	+4.6	+5.4
	40 mg vs placebo	0.0001	+5.8	+6.5
Delta QTcB (ms)	10 mg vs placebo	0.1416	+1.2	+3.0
	20 mg vs placebo	0.0001	+8.5	+10.3
	40 mg vs placebo	0.0001	+13.2	+15.0

Delta QTcF (ms)	10 mg vs placebo 20 mg vs placebo 40 mg vs placebo	0.2673 0.0001 0.0001	+0.5 +3.4 +7.1	+1.8 +4.7 +8.4

The mean corrected QT values (both QTcB and QTcF) increased in dose dependent manner from 10 mg to 40 mg dose. There was also dose dependent increase in heart rate with afluzosin treatments.

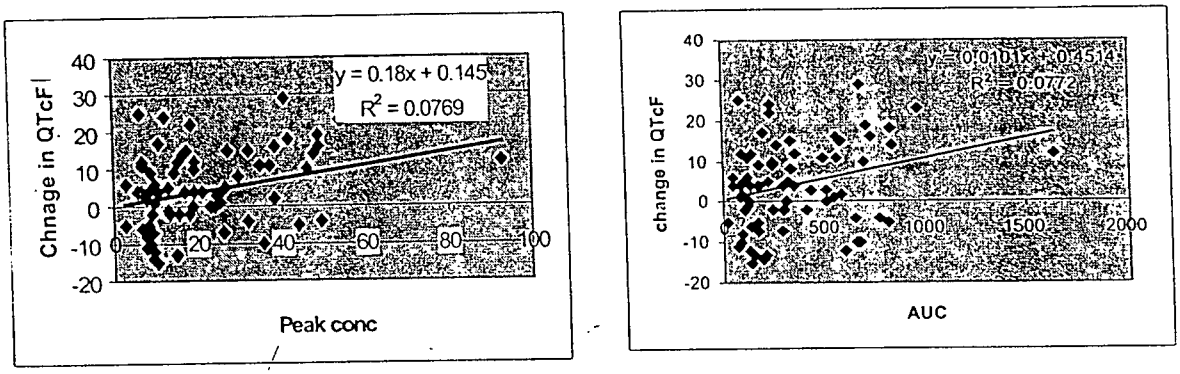


Figure 15: Relationship between pharmacokinetics and change in QTcF

As shown in the figure above, although there is a trend, there appears to be a weak correlation between QTc prolongation and peak concentrations or AUC of alfuzosin. However, as noted before, QT prolongation is dose dependent.

Sponsor stated that the increases in QTcB and QTcF were because of over correction with associated increase in HR. Sponsor measured changes in QT interval using holter monitoring technique and concluded that the mean difference in QT interval is only +2 ms. Please refer to the consult review from Cardiorenal division regarding the magnitude and clinical significance of QT changes and the appropriateness of methodology in measuring these effects.

How does the systemic exposure change with various intrinsic and extrinsic factors? Is there a need for dosage adjustment or contraindication/caution with these factors?

4. **Intrinsic Factors**

a. Population Pharmacokinetics

The effect of covariates age, body weight, and creatinine clearance on alfuzosin peak and trough concentrations were evaluated by means of population analysis of data pooled from four phase III clinical trials (ALFORTI, ALFOTAM, ALFOD, and ALFUS). The data base for this population analysis contained a total of 401 peak concentrations (sample between 10 – 14 h post-dose) and 1083 trough (samples between 18 – 22 h post-dose) obtained from 1018 male patients with age ranging from 48 to 87 years and weighing between 50 and 140 kg. Doses used in these clinical trials were 7.5 mg, 10 mg, and 15 mg ER tablets.

The relationship between the peak and trough concentrations and covariates age, body weight and the creatinine clearance was explored using mixed effect regression modeling method. There was no visit effect on alfuzosin concentrations, which were at steady state by the first visit.

i) Effect of age

The mean peak and trough plasma concentrations of alfuzosin observed in patients stratified in three age groups from four clinical trials are summarized in the following table.

Table 15- Mean (SD) Peak and Trough Concentrations Obtained in Three Age Groups After Repeated Administration of Alfuzosin Extended-Release Tablets in BPH patients

Demographic Covariate	Age Group	Dose (mg)	Peak Mean (SD) ng/mL	No. Observation	Trough Mean (SD) ng/mL	No. Observation
Age (years)	<65	7.5	8.9 (4.7)	22	4.7(2.8)	228
		10	10.9 (6.3)	144	6.4 (4.1)	212
		15	16.3 (9.4)	96	10.5 (6.7)	110
	65 - 74	7.5	8.2 (5.5)	13	5.6 (3.8)	167
		10	9.7 (7.1)	46	7.0 (4.6)	174
		15	20.1 (11.5)	48	10.8 (7.1)	84
	≥75	7.5	10.4 (7.1)	3	8.1 (3.7)	43
		10	13.4 (9.7)	21	8.7 (6.3)	40
		15	17.9 (6.0)	8	14.1 (6.2)	25

Based on the mean data from the above table, trough concentrations at each dose level appears to increase slightly with age while there is no significant effect on peak levels with increasing age. The relationship between age and afluzosin plasma concentrations was explored as part of population analysis on pooled data from the clinical trials using mixed effect regression

model. For the peak concentration, the effect of age was non-significant (p=0.69), while trough concentration was positively correlated with age (p=0.008).
Based on the population analysis, the predicted increase in trough concentration for an age increase of 10 years or 25 years is approximately 12% (95% CI: 1.03 – 1.22) or 34% (95% CI: 1.08 – 1.66), respectively.

Phase III clinical trials included large number of older patients. Based on the subgroup analysis of clinical trials patient population (reported in clinical section), there is no effect of age on the efficacy of alfuzosin. Age did not influence the incidence of vasodilatory adverse event in 7.5 mg ER, 10 mg ER and placebo treatment groups. However, the over all incidence of vasodilatory events (primarily) dizziness was reported to be higher in the elderly groups who received 15 mg dose (6.7% for <65 years; 13.5% for ≥65 years).

ii) Effect of weight

Mean peak and trough concentrations stratified in two weight classes in BPH patients from four phase III studies are summarized in the following table.

Table 16 - Mean (SD) Peak and Trough Concentrations Obtained in Two Weight Classes After Repeated Administration of Alfuzosin Extended-Release Tablet in BPH patients

Demographic Covariate	Class	Dose (mg)	Peak Mean (SD) ng/mL	No. Observation	Trough Mean (SD) ng/mL	No. Observation
Weight (kg)	60 - 100	7.5	8.8 (5.0)	38	5.3 (3.5)	408
		10	10.7 (6.4)	193	6.8 (4.5)	400
		15	18.1 (10.0)	130	10.8 (6.6)	199
	>100	7.5	NA	0	6.4 (3.3)	26
		10	13.9 (12.0)	14	7.5 (5.0)	20
		15	16.7 (10.3)	19	13.7 (8.6)	20

NA = Not applicable

Trough concentrations were slightly higher in patients of weight >100 kg. There is no consistent trend in peak concentrations. It should be noted that the number of patients in >100 kg group is very small compared to the numbers in 60-100 kg group, making it difficult to conclude the weight effect on blood levels.
The effect of weight on peak and trough concentrations was explored in population analysis of the pooled data from phase III trials. Peak and trough concentrations were positively correlated to weight (p=0.010 and p=0.0001, respectively).

Although the covariates, age and body weight have been shown to have statistically significant relationship with plasma concentrations of alfuzosin, there is high degree of variability (over one to two orders of magnitude) at any fixed covariate value.
Based on the subgroup analysis of patients from phase III trials (reported in clinical section), there is no effect of BMI on the efficacy or on the overall incidence of treatment related adverse events. Therefore, no dose adjustment is needed with covariates age and bodyweight.

b. Renal Impairment

The safety and pharmacokinetics of a single dose alfuzosin 10 mg ER tablet in patients with various degrees of renal impairment were evaluated in study # 98-00986. Twenty six male patients (26-64 years) were assigned to one of the following four groups:

Control group: CL_{CR} = > 80 ml/min/1.73 m^2 (n=8)
Mild impairment: CL_{CR} = 60 – 80 ml/min/1.73 m^2 (n=6)
Moderate impairment: CL_{CR} = 30 – 59 ml/min/1.73 m^2 (n=6)
Severe impairment: CL_{CR} = <30 ml/min/1.73 m^2 (n=6)

Table 17 - Mean (SD) Values of Pharmacokinetic Parameters of 10 mg Alfuzosin Extended-Release Tablet After a Single Administration in Patients With Various Degrees of Renal Disease

	Control N=8	Mild N=6	Moderate N=6	Severe N=6
Age (y)	58 (6)	60 (7)	57 (9)	47 (12)
CL_{CR} (mL/min/1.73m^2)	110 (19)	68 (6)	46 (3)	13 (5)
t_{max} (h)[a]	5.0	6.5	6.0	10.0
C_{max} (ng/mL)	13.1 (5.4)	16.4 (8.9)	19.6 (9.2)	17.1 (10.1)
AUC (ng.h/mL)	226.9(89.8)	323.5 (123.7)	354.1 (214.9)	344.3 (167.4)
$t_{½}$ (h)	10.3 (4.7)	11.0 (3.7)	11.0 (2.3)	15.8 (5.5)
CL/F (mL/min/kg)	10.2 (6.0)	6.4 (2.1)	6.8 (3.8)	7.6 (6.1)
CL_R (mL/min/kg)	0.98 (0.36)	0.65 (0.19)	0.47 (0.07)	0.09 (0.06)
V_Z/F (L/kg)	10.4 (12.4)	6.4 (3.0)	6.2 (2.8)	10.9 (9.7)
C(24) (ng/mL)	3.4 (1.4)	6.1 (2.2)	5.8 (4.6)	5.0 (2.2)
AE_{0-72} (%)	11.4 (6.0)	9.9 (4.1)	7.9 (3.4)	1.4 (1.0)

[a] Median

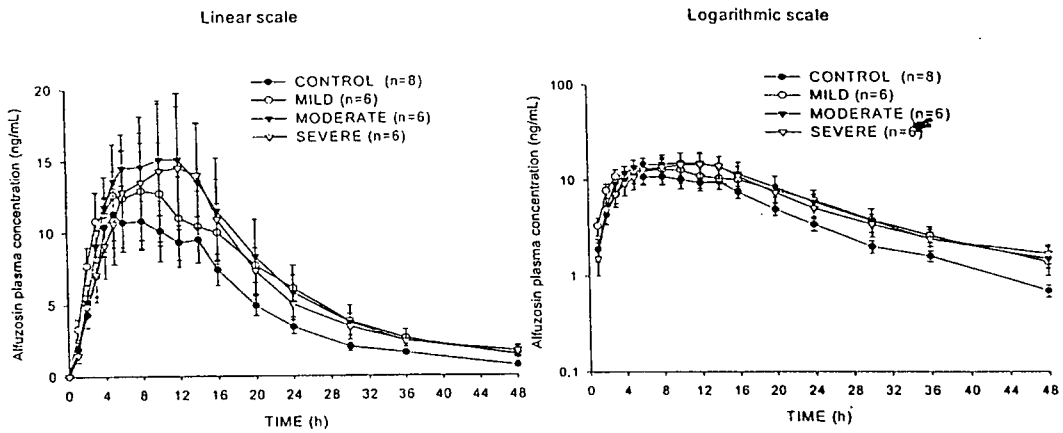


Figure 16. The effect of renal disease on mean plasma concentrations of alfuzosin

Table 18 - Estimated Ratio [90% Confidence Interval] on C_{max} and AUC Values Obtained in Patients With Mild, Moderate, and Severe Renal Impairment Versus the Control Group. [report no. 98-00986]

	Mild	Moderate	Severe
C_{max}	1.20 [0.71-2.04]	1.52 [0.89-2.57]	1.20 [0.71-2.03]
AUC	1.46 [0.89-2.39]	1.47 [0.90-2.41]	1.44 [0.88-2.36]

Peak plasma levels were increased by 20% in mild and severe impairment and by 50% in patients with moderate impairment, while AUC increased by about 50% among all degrees of impairment. The apparent elimination half-life was not affected by the renal disease. Renal clearance showed a linear correlation with creatinine clearance (CL_R =0.0663 +(0.0080 X CL_{CR}, $p<0.0001$, $R^2 = 0.5640$); however, the renal clearance accounted for only 10 % of the total clearance, which was also reduced to 60 to 75% of the normal value.

The mean peak and trough concentration measured in patients from the four phase III studies are summarized according to renal impairment class in the following table.

Table 19. Mean (SD) Peak and Trough Concentrations Obtained in Three Creatinine Clearance Classes After Repeated Administration of Alfuzosin mg Extended-Release Tablets in BPH patients

Demographic Covariate	Class	Dose (mg)	Peak Mean (SD) ng/mL	No. Observation	Trough Mean (SD) ng/mL	No. Observation
CL_{CR} (mL/min)	30 - 60	7.5	10.4 (5.4)	10	6.5 (4.6)	92
		10	15.7 (9.5)	11	6.8 (6.1)	53
		15	21.9 (14.0)	9	12.6 (6.1)	17
	60 - 80	7.5	7.9 (4.7)	19	4.9 (3.0)	184
		10	10.2 (6.6)	61	7.1 (4.5)	174
		15	16.0 (9.9)	33	10.6 (6.1)	86
	>80	7.5	8.8 (5.4)	9	5.2 (3.1)	162
		10	10.8 (6.7)	139	6.7 (4.2)	199
		15	17.8 (9.8)	110	11.2 (7.5)	116

Based on the population analysis of the above data using mixed effect regression model, peak and trough concentrations were inversely correlated to creatinine clearance (p=0.013, and 0.005 respectively). Predicted increase in peak concentration ranges from 17% to 71% in mild to severe renal impairment. These predictions are in broad agreement with renal impairment study results.

c. **Hepatic impairment**

The effect of hepatic insufficiency on the pharmacokinetics was evaluated in a study (#88-00566) of 12 patients (7females and 5 males) with hepatic insufficiency following a single administration of 2.5 mg alfuzosin IR tablet. The patients were classified retrospectively according to Child and Pugh scores (6 patients each in moderate and severe impairment groups). No control group with normal subjects was included in this study. Pharmacokinetic parameters from this study were compared with those from other studies in healthy middle aged volunteers (see table).

Table 20 - Mean (SD) Values of Pharmacokinetic Parameters of Alfuzosin in Healthy Middle-aged Volunteers and in Middle-aged Patients With Hepatic Insufficiency

Parameters	Hepatic Impaired Volunteers 2.5 mg Immediate-Release Tablet Single Dose[a]		Healthy Volunteers 10 mg Extended-Release Tablet Single Dose[b]
	Moderate n=6	Severe n=6	n=58
Age (years)	56.8 (9.1)	56.0 (9.5)	57.3 (4.6)
C_{max} (ng/mL)	22.0 (11.5)	15.9 (9.7)	13.5 (6.8)
AUC(ng.h/mL)	225 (95)	149 (40)	223 (105)
CL/F (L/h)	13.2 (6.1)[c]	18.3 (6.9)[c]	53.7 (22.2)[c]

[a] Report no. 88-00566 (V52 P18)

[b] pooled data from report nos. 98-00986, 98-00242, 00-00152, and 99-00291

[c] CL/F values were not determined in report nos. 88-00566, 00-00152 and 99-00291; however, they were calculated for this document.

The apparent clearance in moderate and severe hepatically impaired patients was 1/3 to 1/4 of that in normal subjects from other studies. Similarly, corresponding increases in exposure were also noted in hepatic impairment. These results are consistent with extensive metabolism of alfuzosin. Mild hepatic impairment subjects were not included in the study.
Sponsor's proposed labeling indicates contraindication in moderate and severe impairment and a caution in mild impairment. Since the exposure change in mild hepatic impairment is unknown and could be equal to that in moderate or severe impairment groups, labeling should indicate contraindication for all degrees of hepatic impairment.

5. **Extrinsic Factors**

a. Drug Interactions

i) Effect of ketoconazole: Study INT4285 investigated the effect of repeated oral doses ketoconazole (200 mg/d) on the single dose pharmacokinetics and safety and tolerability of alfuzosin 10 mg ER tablets in 12 healthy male volunteers aged 18 – 40 years. This was a single center, randomized, three period crossover study. The formulation used in this study is the to be marketed formulation (Batch#PDV08-02A1).

The three treatment periods are:
Period 1 and 2: single oral doses of placebo or alfuzosin 10 mg ER tablet on Day 1
Period 3: Repeated oral dose of ketoconazole (200 mg/d) from Day 1 to 6 and single oral dose of ketoconazole 200 mg co-administered with a single oral dose of alfuzosin 10 mg on Day 7.
Each period was separated by at least 4 days washout period.

Table 21: Alfuzosin mean (SD) pharmacokinetic parameters with and without ketoconazole (n=12)

Parameter	Alfuzosin	Alfuzosin + ketoconazole	Ratio estimate (90% CI)
Cmax (ng/ml)	10.86 (4.55)	21.64 (6.57)	2.11 (1.79 - 2.48)
Tmax (h)	7.11 (3.52)	8.17 (2.66)	
AUC_{0-t} (ng.h/ml)	152.5 (69.8)	367.8 (179.4)	2.46 (1.98 – 3.05)
$AUC_{0-\infty}$ (ng.h/ml)*	191.7 (60.1)[a]	419.9 (174.1)[b]	2.08 (1.64 – 2.64)[c]
$T_{1/2}$ (h)	6.68 (1.94)[a]	8.60 (3.50)[d]	

*AUC was not reported when the extrapolated fraction exceeded 30% of AUC or when t1/2 was not reported.
[a]:n=8; [b]:n=10; [c]: n=7; [d]: n=10

Based on the results noted above, repeated administration of ketoconazole led to 2.11-fold increase in Cmax and 2.46 and 2.08-fold increase in AUC_{0-t} and $AUC_{0-\infty}$ of alfuzosin., respectively.

It should be noted that ketoconazole dose used in this study was 200 mg/day and it is less than the maximum recommended dose (400 mg, once a day) in the label. So consequently, there could be greater inhibition of alfuzosin when coadministered with higher dose of ketoconazole.

Pharmacodynamic measures

Hemodynamic effects:
The maximum and mean changes in vital signs such as heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) from baseline were compared between alfuzosin alone and alfuzosin with ketoconazole arms. There was no significant overall treatment effect for either HR or SBP.

A statistically significant treatment effect was observed for maximum change from baseline in DBP (p=0.036), alfuzosin alone causing a greater decrease in DBP than placebo (-3.7 mm Hg).

As expected, the decrease of mean DBP from baseline induced by alfuzosin was greater than that by placebo at 2 hours (-5.8 mm Hg), 7 hours (-4.8 mm Hg) and 12 hours (-3.6 mmHg) post-dose. The decrease in mean DBP from baseline induced by Alfuzosin with coadministered ketoconazole was greater than the decrease with alfuzosin alone (difference of 3.3 mmHg). Sponsor stated that these mean changes in DBP were small and did not result in any symptomatology as stated by the sponsor. However, it should be noted that sample size of 12 subjects may not be adequate to detect changes in hemodynamic parameters and the study protocol was not powered for pharmacodynamic changes.

Few individual clinically significant abnormalities in vital signs were observed during the study. There were two subjects in alfuzosin + ketoconazole arm who had clinically significant

orthostatic increase in HR >30 bpm compared to none in alfuzosin alone and placebo arms. There were also two subjects with DBP<50 mmHg and decrease >15 mm HG from baseline in alfuzosin alone (two measurements) and alfozusin+ketoconazole arms (3 measurements) compared to none in placebo.

ECG recordings were done only during period 1 and 2 for placebo and alfuzosin alone arms, but not obtained during alfuzosin +ketoconazole treatment. Thus drug interaction effect on QT prolongation can't be evaluated.

It should be noted that the QT prolongation effect of alfuzosin is being reviewed by the Division of Cardiorenal Drug Products and their expert opinion would be considered by the clinical review team.

ii) Effect of Cimetidine

The influence of cimetidine on the pharmacokinetics alfuzosin 5 mg IR tablet was investigated in 10 healthy young volunteers (Study #89-00207). Pharmacokinetics of alfuzosin on day 1 was compared to that on Day 20 after repeated administration of cimetidine (1g/day: 200 mg morning, 200 mg midday, 200 mg evening and 400 mg at bed time) for 20 days.

Table 22 - Mean (SD) Values of Alfuzosin Pharmacokinetic Parameters Observed in 10 Healthy Subjects After a Single Administration of 5 mg Alfuzosin Immediate-Release Tablet Alone and With 1 Day or 20 Consecutive Days of 1 g Cimetidine

	t_{max} (h)	C_{max} (ng/mL)	$t_{½}$ (h)	AUC (ng.h/mL)
5 mg Alfuzosin IR	1.0[a]	23.2 (6.0)	5.1 (1.4)	166.6 (71.9)
5 mg Alfuzosin IR after 1 day of 1 g Cimetidine	1.0[a]	27.6 (9.5)	6.0 (1.8)	183.0 (69.4)
5 mg Alfuzosin IR after 20 days of 1 g Cimetidine	1.0[a]	28.7 (10.2)	4.4 (1.5)	199.9 (86.6)
Ratio estimate or difference estimate [90% CI]				
Day 1	NS[b]	1.16[c] [0.99-1.34]	0.89[d] [-0.09, 1.87]	1.11[c] [0.99-1.25]
Day 20		1.21[c] [1.04-1.40]	-0.77[d] [-1.75,0.21]	1.19[c] [1.06-1.34]

NS = not significant [a] Median value [b] Friedman test [c] Ratio estimate [d] Difference estimate

Single and repeated administration of cimetidine increased the Cmax and AUC of alfuzosin by up to 20%. This 20% change in exposure is considered not clinically significant based on the phase III clinical data.

iii) Interaction with Diltiazem

A double blind parallel group study conducted with 12 healthy young volunteers (6 per group) receiving either 2.5 mg alfuzosin IR tablet thrice a day or 120 mg diltiazem twice daily for 5 days followed by the combination for 5 days (Study report # 89-00220).

Table 23 - Mean (SD) Values of Alfuzosin Pharmacokinetic Parameters in 6 Healthy Young Volunteers After 2.5 mg Alfuzosin Immediate-Release Tablet Thrice Daily Alone and With 120 mg Diltiazem Twice Daily for 5 Days

	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{0-24} (ng.h/mL)
2.5 mg Alfuzosin IR tid	1.3[a]	17.2 (6.1)	3.6 (0.7)	108 (40)
2.5 mg Alfuzosin IR tid with 120 mg Diltiazem bid	0.5[a]	25.3 (7.8)	3.3 (0.4)	141 (52)
Ratio estimate or difference estimate [90% CI]	NS[b]	1.49[c] [1.26-1.77]	-0.23[d] [-0.60, 0.13]	1.30[c] [0.96-1.75]

NS = Not significant [a] median value [b] Wilcoxon's test [c] Ratio estimate [d] Difference estimate

The exposure of alfuzosin was increased (50% for Cmax and 30% for AUC) by coadministration of moderate CYP 450 3A4 inhibitor Diltiazem.

Coadministration of alfuzosin also resulted in increase of diltiazem Cmax and AUC by 40%. There was also increase in plasma levels of metabolites of dilitiazem; N-monodemethyl diltiazem (by 30 to 36%) and deacetyl diltiazem and deacetyl N-monodemethyl diltiazem (both by 10 to 15%).
In vitro inhibition studies showed alfuzosin is not an inhibitor of CYP3A4. The observed increase in diltiazem levels may be due to PgP inhibition by alfuzosin. However, the effects of alfuzosin on PgP transporter have not been evaluated.

iv) Interaction between alfuzosin and digoxin

A single center, open-label, randomized, crossover study (#INT4672) was conducted to assess the interaction between alfuzosin ER tablet formulation and digoxin at steady state conditions for both drugs. Twenty two healthy male subjects received in randomized fashion the following treatments: digoxin alone (0.25 mg/day) for 7 days or alfuzosin alone 10 mg OD) for 7days followed by coadministration of alfuzosin with digoxin for another 7 days. The two treatments were separated by 14 days of washout period.

Table 24. Steady-state mean (SD) pharmacokinetic parameters of Digoxin and Alfuzosin (n=22)

Mean Parameters	Digoxin		Alfuzosin	
	Digoxin alone (Day 7-8)	Digoxin +Alfuzosin (Day14-15)	Alfuzosin alone Day (7-8)	Digoxin +alfuzosin (Day 14-15)
C_{max} (ng/ml)	0.98 (0.21)	0.94 (0.23)	12.44 (4.02)	13.41 (4.99)
C_{min} (ng/ml)	0.31 (0.13)	0.33 (0.07)	3.46 (1.47)	3.36 (1.21)
*T_{max} (h)	2.00	2.00	5.00	9.00
AUC_{0-24h} (ng.h/ml)	12.9 (2.9)	12.9 (2.2)	189 (59)	206 (70)

*median values

Based on the above results, multiple administration of alfuzosin 10 mg ER tablets did not affect the plasma levels of digoxin. Mean plasma levels of alfuzosin were slightly higher (by 6 to 7%) with coadministration of digoxin. However, the 90% confidence intervals for geometric mean ratios of test vs reference for both Cmax and AUC were within 80 to 125%, indicating bioequivalence of alfuzosin in presence and absence of digoxin administration. The same is true for digoxin plasma levels also.

There was no evidence of pharmacodynamic interaction in terms of hemodynamic effects when digoxin and alfuzosin are coadministered. All adverse events reported were mild and there was no evidence of an increased frequency during the coadministration of both drugs compared to the administration of each drug alone.
Thus, the results of this study showed that there was no pharmacokinetic or pharmacodynamic interaction between alfuzosin and digoxin. A previous drug interaction study also showed no interaction between alfuzosin IR 2.5 mg bid and digoxin.

v) Effect of alfuzosin on warfarin

The influence of alfuzosin on the pharmacodynamics of single dose warfarin (25 mg) was evaluated in a double blind, randomized, placebo controlled, two-way crossover study in 6 healthy male volunteers aged 22 to 35 years (Study report #85-00620). In this study a single 25 mg oral dose of warfarin was administered on Day 6 of 15 days of treatment with either placebo or alfuzosin 5 mg IR tablet twice a day.

Table 25 - Values of the Coagulation Parameter Modifications Induced by Single Oral Dose of Warfarin 25 mg on Day 6 of Alfuzosin 5 mg Immediate-Release Tablet bid or Placebo 15 Days Multiple Dose Given to 6 Healthy Young Male Volunteers.

Parameter	Placebo Value Mean (SD)	Estimated Difference Placebo-Alfuzosin	p-Value From Paired t-Test	95% Confidence Interval
Emax $_{PT}$ (sec)	24.3 (6.7)	-1.62	0.0777	[-3.49, 0.26]
AUC_{PT} (sec.h)	3837.5 (448.7)	-112.4	0.0601	[-232, 7]
Emax $_{VII}$ (sec)	23.3 (3.9)	-0.65	0.3881	[-2.42, 1.12]
AUC_{VII} (sec.h)	3943.2 (385.2)	-87.3	0.0943	[-173, 22]

Emax $_{PT}$ and Emax $_{VII}$ = Prothrombin time and Factor VII clotting time maximum value; AUC $_{PT}$ and AUC_{VII} = Prothrombin time and Factor VII clotting time 0 to 240 h Area Under the Curve.

The prothrombin time (PT) and Factor VII are in general lower in alfuzosin group than in placebo group and the difference approached statistical significance. Sponsor claimed that the small difference is not clinically significant. Since PT and Factor VII are found to be lower with alfuzosin, this is not a safety concern!

Sponsor reported that one subject experienced epistaxis during treatment with alfuzosin and prothrombin time was marginally raised (19.6 seconds) at the time the adverse event.

Even though the objective of the study was to determine both pharmacodynamics and pharmacokinetics of warfarin in presence and absence of alfuzosin, sponsor claimed that since there was no change in pharmacodynamics, blood levels of warfarin were not measured.

vi) Interaction with Atenolol

A double-blind, placebo-controlled, randomized, four-way crossover study (#85-00615) was conducted to investigate the pharmacodynamic and pharmacokinetic interaction between alfuzosin and atenolol. Eight healthy (normotensive) young volunteers received the following four treatments in a randomized fashion : single dose of alfuzosin 2.5 mg capsule, placebo, atenolol 100 mg capsule, and 2.5 mg alfuzosin capsules + 100 mg atenolol capsule. The hemodynamic effects observed in the study are summarized below.

Table 26- Summary of Mean (± SEM) Supine Hemodynamic Effects (n=8)

	Baseline			+ 2 Hours			+ 4 Hours		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
Placebo	115 ± 2.5	71 ± 2.2	68 ± 4.3	123 ± 4.0	71 ± 2.2	75 ± 4.9	123 ± 5.1	71 ± 2.3	72 ± 2.5
Alfuzosin 2.5 mg IR	117 ± 3.1	76 ± 1.8	67 ± 2.0	116 ± 4.2	70 ± 2.3	73 ± 6.2	116 ± 3.7	73 ± 2.4	73 ± 2.6
Atenolol 100 mg	111 ± 2.2	74 ± 2.5	66 ± 1.7	108 ± 4.8	66 ± 3.5	59 ± 1.9	103 ± 3.7	67 ± 3.0	59 ± 2.3
Alfuzosin 2.5 mg IR + atenolol 100 mg	117 ± 5.0	71 ± 2.9	67 ± 2.9	102 ± 4.2	64 ± 2.2	58 ± 2.5	101 ± 2.3	63 ± 1.2	56 ± 3.3

SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); HR = heart rate (bpm)

The vital sign parameters (SBP< DBP and HR) were lower following atenolol alone or in combination with alfuzosin compared to placebo or alfuzosin alone.

Although Alfuzosin at the dose of 2.5 mg IR did reduce the blood pressure and increase the heart compared to baseline, the differences are not statistically significant.
Systolic and diastolic blood pressure values obtained with alfuzosin+ atenolol combination were lower than those obtained with atenolol alone or alfuzosin alone suggesting additive effects of these two drugs.

During the study, two subjects reportedly experienced feeling of faintness with significant reduction in blood pressure following the administration alfuzosin and atenolol together. One subject reported this AE at 30 minutes after taking alfuzosin + atenolol and another at 1.5 hr after the combination. Both subjects' symptoms resolved when they were brought to supine position with out medical intervention and continued in the study without further problem.

It should be noted that the sample size in this study is small (n=8) and the subjects were normotensive healthy young volunteers. Based on the results of this small study, it can be concluded that there could be additive hypotensive effects when alfuzosin is administered with atenolol. Therefore, caution should be observed when alfuzosin is to be administered together with a beta-blocker or any other antihypertensive drug.

Pharmacokinetically no significant interaction was observed except for slight increase in AUC of alfuzosin (by 18% in mean) in presence of atenolol. This increase was noted in five of eight subjects studied. However, these values were within the range observed for other studies. Furthermore, there is no common metabolic pathway to believe that these two drugs can interact pharmacokinetically. So, it can be concluded that there is no significant pharmacokinetic interaction.

vii) **Interaction with Hydrochlorthiazide**

A double-blind, randomized, placebo-controlled, four-way crossover study (#85-00757) was conducted to investigate the possibility of pharmacodynamic interaction between the diuretic, hydrochlorthiazide (25 mg) and alfuzosin (5 mg IR tablet) in 8 healthy young volunteers.
Blood levels of alfuzosin were also measured in the study and the results show that hydrochorthiazide did not affect the pharmacokinetics of alfuzosin.

Table 27- Summary of Supine Hemodynamic Effects (Mean ± SEM) Following Single Oral Doses of Placebo, Alfuzosin 5 mg Immediate-Release Tablet, Hydrochlorothiazide 25 mg, or Alfuzosin 5 mg immediate release Plus Hydrochlorothiazide 25 mg Given to 8 Healthy Young Male Volunteers

	Baseline			+ 2 Hours			+ 4 Hours		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
Placebo	129 ± 5.1	79 ± 3.5	70 ± 3.6	135 ± 5.0	82 ± 3.6	74 ± 3.0	127 ± 4.5	80 ± 2.8	72 ± 3.8
Alfuzosin 5 mg IR	126 ± 5.5	80 ± 2.9	72 ± 2.3	124 ± 7.9	76 ± 4.9	79 ± 4.0	128 ± 8.0	77 ± 4.9	75 ± 3.4
Hydrochlorothiazide 25 mg	127 ± 3.4	77 ± 2.7	71 ± 4.0	133 ± 4.5	80 ± 3.4	73 ± 3.1	129 ± 4.4	83 ± 3.6	71 ± 2.9
Alfuzosin 5 mg IR + Hydrochlorothiazide 25 mg	126 ± 6.1	73 ± 4.1	69 ± 3.8	128 ± 5.0	82 ± 3.9	75 ± 3.6	120 ± 6.0	80 ± 3.3	80 ± 2.4

SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); HR = heart rate (bpm)

Based on the mean supine hemodynamic changes noted in the above table, it appears that there is no pharmacodynamic interaction between alfuzosin and hydrochlorthaizide. However it should be noted that the study was conducted in small number (n=8) of healthy young volunteers with single dose administration of either drug. Pharmacodynamic interactions in older hypertensive patients could be different from healthy young volunteers.

C. BIOPHARMACEUTICS

What are the differences between clinical formulation and to be marketed formulation? Is to be marketed formulation bioequivalent to clinical trials formulation?

The differences between clinical trial and to be marketed formulation are summarized in the table below.

Table 2. Differences between Clinical and Commercial formulations

Batch	PDV03-01A1 (Clinical formulation)	18134 (PDV08-01A1) (To be marketed formulation)
Formulation	PDV03	PDV08
Site	SkyePharma	Tours, France
Size	pilot scale ——— tablets)	Industrial scale ; ——— tablets)
Batch size (kg) [a]	———	
——— equipment	———	
——— equipment	———	
———	———	

The main differences between the clinical trial formulation and the to be marketed formulation are in the process used for drying — site of manufacture and scale-up. SkyePharma manufactured investigational clinical batches at — Sanofi-synthelabo uses for industrial scale production for

1. Bioequivalence

In order to support the changes in manufacturing site, scale up and drying process, sponsor conducted a single dose bioequivalence study (#99-0291) between the clinical formulation (PDV03) and the to be marketed formulation (PDV08) under fed conditions. This was a single center, randomized 2-period, 2-treatment crossover single dose study in 24 healthy male volunteers comparing the pharmacokinetic profile of clinical and to be marketed formulations. The subjects were dosed with alfuzosin 5minutes after the evening meal. According to the protocol the inclusion criteria mentioned that subjects with normal diet (no vegetarians) would be enrolled. Subjects will be given standardized meals and breakfast during the study period. Before the drug administration, the evening meal was equivalent to 899 calories (57g carbohydrates, 40 g proteins, 58 g fat).

Table 28. Mean (SD) pharmacokinetic parameters of Clinical and to be marketed formulations.

Parameters	10 mg ER Tablet Clinical Batch PDV03-01A1 (A)	10 mg ER Tablet To be marketed Batch PDV08-01A1 (B)	Ratio Estimate (A/B) [90% Confidence Interval]
C_{max} (ng/mL)	14.7 (8.2)	14.2 (7.2)	0.98 [0.87-1.10]
t_{max} (h)	10.0[a]	9.0[a]	NS
AUC (ng.h/mL)	225 (114)	218 (115)	0.96 [0.88-1.04]
$t_{1/2z}$ (h)	8.0 (1.9)	8.6 (2.2)	1.07 [0.97-1.19]

[a] Median value
NS = Not significant

As shown in the table, the to be marketed formulation is bioequivalent to the clinical trial formulation when administered with high fat meal. The median Tmax is not significantly different between the two formulations.

At the end of the study a borderline QTcB of 450 ms was recorded for a 60 year old male. His baseline QTcB was 427 ms, so an increase of 27 msec was noted.

FDA BA/BE guidance recommend that the BE study be conducted under fasting conditions. However, sponsor performed this BE study under fed conditions for the following reasons:

Food increases the bioavailability of ER formulation by two fold; all phase III studies were conducted under fed conditions and the labeling recommends that the drug be taken with meals.

Fed BE study was conducted before the finalization of FDA guidance and also to satisfy the European regulations which require BE studies under the conditions of the drug use.

2. IVIVC under fasting conditions

At the time of NDA filing, sponsor was requested to provide information on IVIVC under fasting conditions and justification for not conducting a fasted BE study.

In response, sponsor submitted IVIVC using in vivo data obtained under fasting conditions from two studies (95-00961 and 95-00408).

The formulation used for the development of IVIVC under fasting conditions was KYA02. This formulation had the most similar composition and dissolution profile as compared to the one used in clinical trials. The in vivo absorption profile of the formulation was obtained by deconvolution using the data from intravenous administration as reference. The following linear correlation between in vivo absorption and in vitro dissolution was developed.

$Y= 0.3766*x-4.3258;\ r^2 = 0.9983$

Internal Predictability

Plasma concentration profile was predicted based on the dissolution rates and the linear correlation by convolution method. The observed and predicted PK parameters were compared.

Table 29. Comparison of observed vs predicted for internal predictablitiy of IVIVC.

Parameter	Observed	Predicted	%PE
Cmax (ng/ml)			
AUC (ng.h/ml)			

The prediction errors for Cmax and AUC were less than 10%.

External Predictability

Predicted values of Cmax and AUC of PDV03 (clinical formulation) are compared to the observed values in the following table

Table 30. Comparison of observed vs predicted for external predictability of IVIVC

Parameter	Observed	Predicted	%PE
Cmax (ng/ml)			
AUC (ng.h/ml)			

The prediction error for Cmax is slightly higher than 10% and for AUC under 10%. Based on internal and external validation, IVIVC under fasting conditions is acceptable.
Since the dissolution was shown to be condition independent (see Figure 19), the use of one formulation to develop IVIVC is acceptable as per the guidance on IVIVC.

Based on the IVIVC, sponsor calculated the predicted Cmax and AUC values for the clinical and the to be marketed formulation under fasted conditions. The IVIVC and the predicted plasma profiles for the clinical and to be marketed formulations are included in Appendix I.

Table 31. Predicted bioavailability of clinical and to be marketed formulations based on IVIVC.

Formulation	Cmax (ng/ml)	AUC (ng.h/ml)
PDV03(clinical)		
PDV08 (market)		
Ratio (PDV08/PDV03)		

Thus based on IVIVC and predicted PK parameters, the clinical trial formulation was predicted to be bioequivalent to the clinical trial formulation under fasted conditions.
Therefore, sponsor's justification that another BE study under fasted condition is not necessary is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

3. Effect of Food

Is there any effect of food on the pharmacokinetics of ER formulation? How is it addressed in the label?

Four studies were submitted to evaluate the effect of food on the pharmacokinetics of alfuzosin at doses of 7.5 mg, 10 mg and 15 mg. In all these studies high fat meal (58-75 g fat) was used.

Table 32. Mean (SD) Pharmacokinetic Parameters of Alfuzosin Extended Release-Tablet After a Single Administration in the Evening in Healthy middle-aged Male Volunteers Under Fed and Fasted Conditions

Parameters	Fasted (A)	High Fat Meal (B)	Standard Meal (C)	Comparison	Estimate Ratio [90% CI]
15 mg alfuzosin (n=15) [report no. 00-00149 (V82 P57)]					
t_{max} (h)	6.0 [a]	10.5 [a, d]	11.9 [a]	B-A C-A C-B	2.98h [-1.50h-5.99h] [b] 3.01h [-1.50h-5.99h] [b] ND
C_{max} (ng/mL)	12.6 (4.7)	25.7 (12.5) [d]	18.2 (9.4)	B-A C-A C-B	1.94[1.54-2.44] 1.41[1.12-1.76] 0.73 [0.58-0.91]
AUC (ng.h/mL)	256 (109)	500 (201) [d]	397 (166)	B-A C-A C-B	1.96[1.55-2.49] 1.64[1.29-2.07] 0.83 [0.65-1.05]
10 mg alfuzosin (n=18) [report no. 98-00242 (V64 P52)]					
t_{max} (h)	12.0 [a]	9.5 [a]	-	B-A	NS [c]
C_{max} (ng/mL)	10.9 (3.8)	12.3 (6.6)	-	B-A	1.09 [0.90-1.32]
AUC_{0-36} (ng.h/mL)	176 (61)	195 (101)	-	B-A	1.07 [0.94-1.22]
10 mg alfuzosin (n=8) [report no. 00-00152 (V87 P47)]					
t_{max} (h)	5.5 [a]	8.5 [a]	-	B-A	ND
C_{max} (ng/mL)	5.7 (2.7)	13.1 (3.3)	-	B-A	2.49 [2.00-3.09]
AUC_{0-24} (ng.h/mL)	89 (50)	171 (39)	-	B-A	2.13 [1.72-2.64]
7.5 mg alfuzosin (n=18) [report no. 96-00741 (V56 P41)]					
t_{max} (h)	5.0 [a]	8.5 [a]	-	B-A	NS [c]
C_{max} (ng/mL)	3.9 (1.7)	9.5 (2.8)	-	B-A	2.60 [2.09-3.25]
AUC_{0-36} (ng.h/mL)	61 (31)	133 (34)	-	B-A	2.47 [1.91-3.19]

ND = Not done

[a] Median value

[b] Estimate difference and 95% confidence interval

[c] Not significant, Friedman's test

[d] n=14

In the food-effect studies, the drug was administered in the evening at 8 pm and for the fasting group, subjects fasted for 7 hours before and 12 hours after the drug administration. Out of the four studies, three showed significant increase (about 2 to 2.5 -fold) in bioavailability of alfuzosin with food. With the 10 mg ER dose, food increased Cmax and AUC by 2.5 and 2.1 fold, respectively. The time to reach peak concentrations was delayed with presence of food. Studies with other doses (7.5 mg and 15 mg ER) also showed similar differences with high fat meal. However, one study with 10 mg ER did not show significant food effect. No explanation was given by the sponsor regarding this conflicting result. In this study, although the food effect is not significant, there was slight increase in mean Cmax and AUC values (about 10% increase) and in Tlag (1.53 h under fed vs 0.78 h under fasting). Individual data reveals that there were both increases and decreases in bioavailability with food in about same number of subjects. It should be noted that the variability in PK parameters was higher with high fat meal. The bioavailability parameters (Cmax and AUC) with food from this study are similar to those from other studies under fed conditions.

Since, there was food effect with three of these studies, overall it can be concluded that food increases the bioavailability by about two-fold. All the subsequent clinical trials, including Phase III studies, were done with food. The labeling for this drug also recommends dosing with meals.

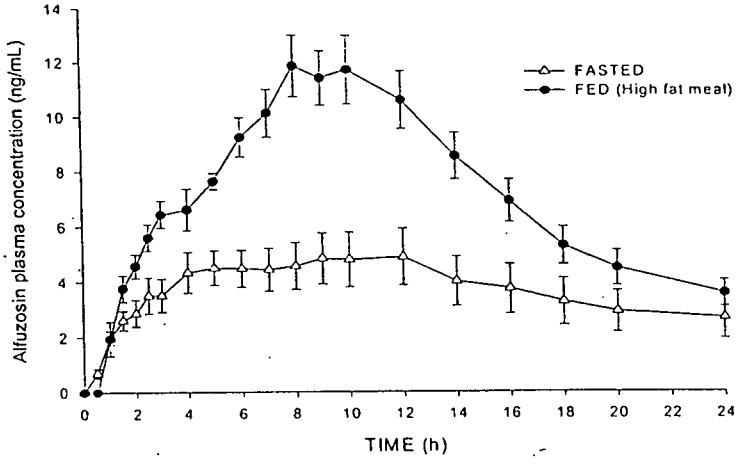


Figure 17. Mean (SEM) Alfuzosin Plasma Concentration-Time Profiles After a Single Administration of Alfuzosin 10 mg Extended-Release Tablet in 8 Healthy middle-aged Male Volunteers in Fed and Fasted States

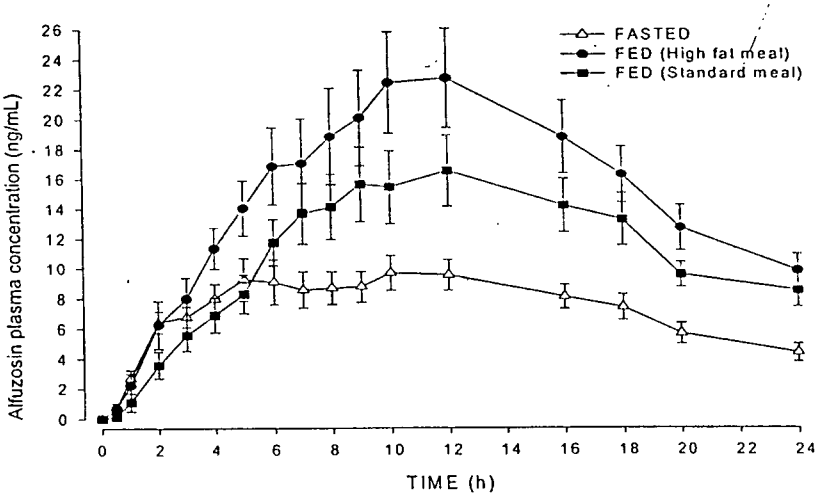


Figure 18- Mean (SEM) Alfuzosin Plasma Concentration-Time Profiles After a Single Administration of Alfuzosin 15 mg Extended-Release Tablet in 15 Healthy middle-aged Male Volunteers in Fed and Fasted States

The fat content of food also seem to affect the bioavailability. With standard meal, Cmax and AUC were 27% and 17% lower respectively when compared to administration with high fat meal.

Study 00-152 with 10 mg ER formulation assessed gastrointestinal transit and in vivo disintegration profile of Geomatrix tablet by gamma scintigraphy technique. The observed mean parameters of GI transit disintegration times under fed and fasted conditions are given in the following table.

Table 33. Transit profile (Mean ± SD) of the tablet core for fasted and fed volunteers.

	Gastric emptying (Hours post-dose)	Colon arrival (Hours post-dose)	Small intestinal transit time (hrs)	Initial tablet disintegration (Hours post-dose)	Complete tablet disintegration (Hours Post-dose)
Fasted (n=8)	0.59 (0.35)	5.82 (1.96)	5.23 (1.66)	2.98 (1.45)	18.30 (5.01)
Fed[a,b] (n=8)	5.90 (2.24)	11.70 (0.96)[a]	5.99 (5.76)[a]	2.92 (0.51)	11.57 (5.49)

[a] Data was available for only 2 subjects

[b] The timings shown are for tablet core; for the released material there was a delay (ie., 6.5 ± 1.10 hours post-dose for gastric emptying and 12.67 ± 1.51 hours post-dose for colon arrival.

Based on the gamma scintigraphy results, the gastric emptying of ER tablets was delayed significantly under fed conditions compared to fasting conditions. Initial tablet disintegration occurred at about same time for both groups. However the complete disintegration of tablets was achieved earlier for fed group (11.57 hours) compared to fasting group (18.30 hrs). It should be noted that one subject in fasting group defecated the tablet core at 12.5 hours post dose.

The higher bioavailability with food appears to be due to slower gastric emptying time allowing for more disintegration/dissolution of the tablet before it reaches small intestine where most of the drug is absorbed.

Two subjects experienced syncope (one under fasted group at 8 hours post dose, another in fed group at 4 hours and 8 hours after dosing) and hypotension and experienced loss of consciousness for less than 1 minute. Both these subjects recovered rapidly in the supine position. This second subject experienced dizziness and hypotension with fasted treatment also at 8 hours post dose and recovered rapidly by laying down.

4. Analytical Methods

The pharmacokinetic studies submitted in the NDA utilized four bioanalytical methods to measure alfuzosin concentrations in various biological fluids i.e., plasma, blood and urine. Three of these methods were using [redacted] and the fourth method was [redacted] method [redacted], which was used only for study # 00-00149. The determination of the R(+) and S(+) enantiomers of alfuzosin in plasma was accomplished with one of the [redacted] methods with [redacted] This method used a [redacted]

Table 34. Assay validation parameters

Analyte	LOQ (ng/ml)	Linearity (ng/ml)	Accuracy	Precision
plasma/ Blood		[redacted]		
Prostate Tissue		[redacted]		
Urine		[redacted]		

For the analysis of enantiomers, LOQ was [redacted] ng/ml for each enantiomer and the accuracy and precision were within 10% of nominal QC values.
Overall, the assay methods validation appears to be adequate for pharmacokinetic characterization of alfuzosin.

5. In vitro Dissolution

The details of the sponsor's proposed dissolution method are given below:

Equipment:	Rotating paddle, 100 rpm
Tablet holder:	
Dissolution medium:	0.01 M HCl at 37 °C
Volume of dissolution medium:	500 mL
Dissolution time:	20 hours
Determination:	

Sponsor provided adequate data to support the choice of medium and the dissolution conditions. During the initial development of the dissolution method, sponsor observed that the tablets tended to sink to the bottom of the vessel in the first few minuets and then become detached and float as result of swelling of outer layers of the tablet. This could be due to high amount of hydroxypropyl methylcellulose, [redacted] agent in the Geomatrix formulation. To avoid the variability associated with sticking and floating of the tablets, Sponsor used a tablet holder in the method.

Data showing the dissolution is independent of the agitation speed and the pH of the medium are shown in the following figure.

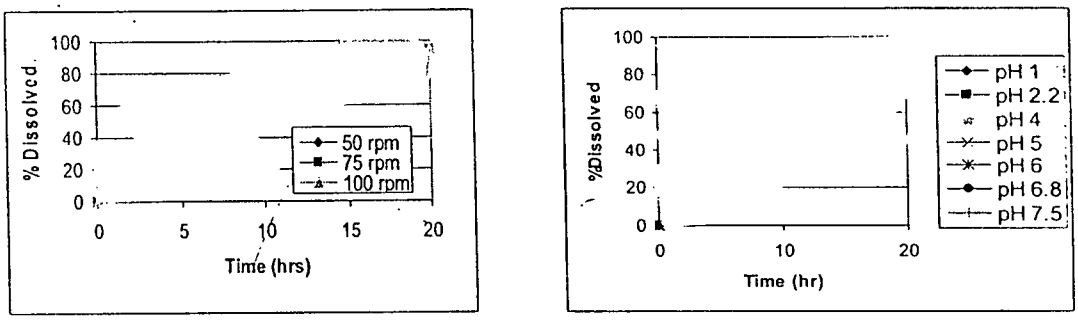


Figure 19. Effect of agitation speed and pH on dissolution.

Data showing that dissolution method discriminates between the different types of formulations was also provided. Therefore, the proposed dissolution method is acceptable.

In order to support the dissolution specifications, sponsor submitted an IVIVC using the in vivo data obtained under fed conditions. A level A (shown in Figure) was developed using the following relationship (Weibull function):

$(y = a\left[1-\exp-\left[\frac{x-x_0+b\ln 2^{1/c}}{b}\right]\right]$, a=104.1150, b=57.8058, c=2.0667, x_0=58.7005, R=0.99990).

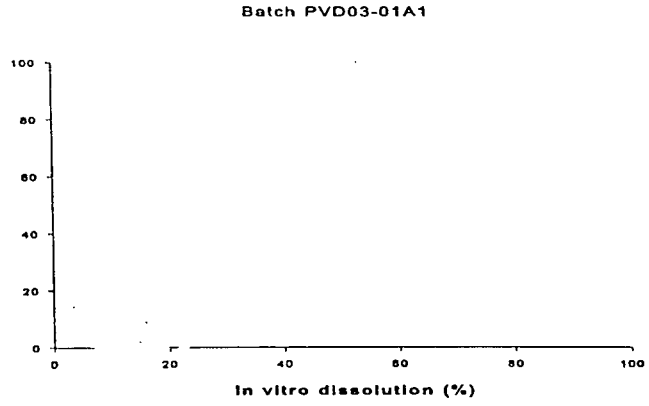


Figure 20: In vitro and In vivo correlation under fed conditions

Using the IVIVC, plasma concentration profiles were predicted for preset limits (L1 and L2) of dissolution (as shown in Table) and comparison of the predicted versus observed Cmax and AUC based on these dissolution limits is given in the following table.

Table 35- C_{max} and AUC_{0-24} Values Obtained With the Reference Batch and the Two Theoretical Lower and Upper Dissolution Profiles

	C_{max} (ng/ml)	AUC_{0-24} (ng.h/mL)
PDV03-01A1 (Ref) Predicted data Experimental data		
UPPER profile L_1 Predicted data Ratio (predicted data/ PDV03-01A1) L_2 Predicted data Ratio (predicted data/ PDV03-01A1)		
LOWER profile L_1 Predicted data Ratio (predicted data/ PDV03-01A1) L_2 Predicted data Ratio (predicted data/ PDV03-01A1)		

Based on the above table, the predictability for all dissolution limits was below 20% as recommended by IVIVC guidance except for L2 upper dissolution limit (However, based on the FDA guidance on setting specifications, the proposed specifications (L1) are within 10% of the mean dissolution of biobatch.

Table 36 - Dissolution Acceptance Criteria (%)

	Ref. (PDV03-01A1)	Limits for the Mean Dissolution Profile				L_1 Acceptance Criterion		L_2 Acceptance Criterion [a]	
Time		$L_2(-)$	$L_1(-)$	$L_1(+)$	$L_2(+)$	Minimum	Maximum	Minimum	Maximum
1 h	15.1	8	12	18	22				
6 h	45.9	35	39	53	60				
12 h	72.5	60	63	83	90				
20 h	92.3	80	85	100	100				

[a] Average for all 12 tablets complies with L_1.

- According to Sponsor's Proposed specifications, individual results for all 6 tablets should be within the L_1 limits. If one or more tablet(s) are outside the L_1 limits, then 6 more tablets will be tested. Individual results for all 12 tablets are within the following limits and the mean value for the 12 tablets is within the L_1 limits for each time point.

Based on the dissolution rates shown above for PDV03-01A1 (biobatch), the proposed L1 specifications are consistent with the guidance recommendation of mean ± 10% of the labeled content. Typically, for setting dissolution specs, it is not necessary to specify L1 and L2 criteria in the NDA. Therefore, the following specifications are recommended for approval:

Time	% dissolved
1 h	%
6 h	%
12 h	%
20h	%

Sponsor proposed debossing of tablet with letters 'X10' and submitted comparative dissolution profiles between one batch of unmarked tablets and three batches of debossed tablets (the final to be marketed). The dissolution of these batches is similar and acceptable (F_2 values are above 50).

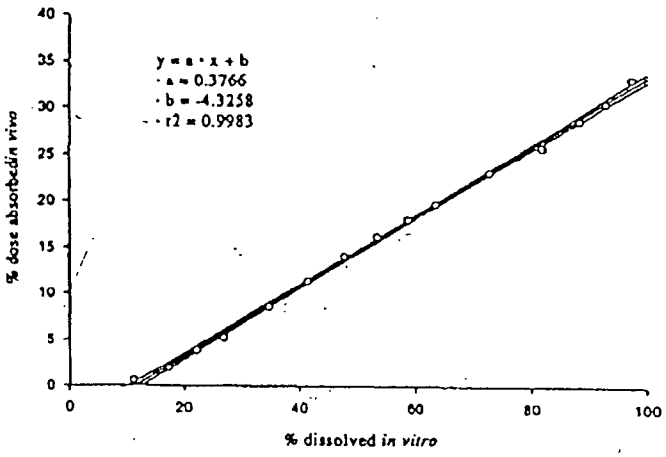
14 pages redacted from this section of the approval package consisted of draft labeling

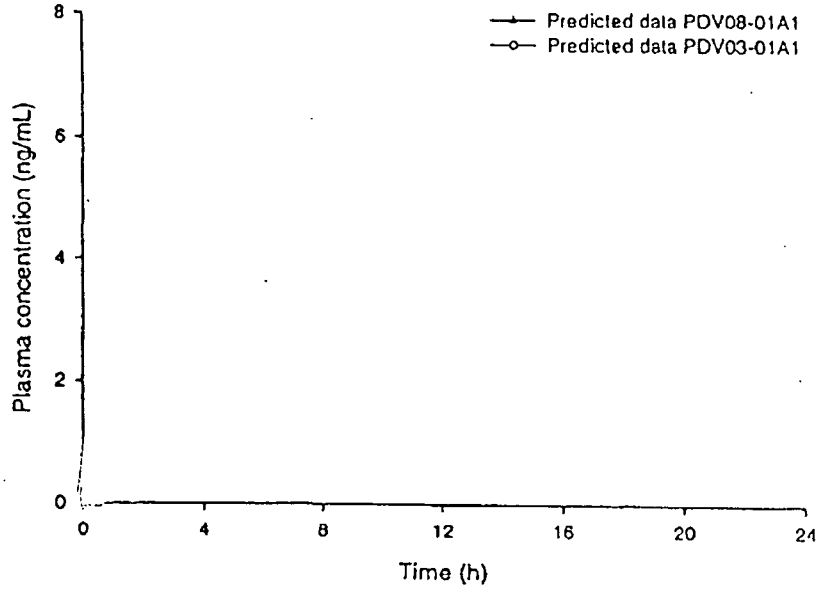
Appendix I

(IVIVC under fasting conditions and predicted plasma concentration profiles for clinical (PDV03) and to be marketed formulations (PDV08) under fasting conditions)

Figure (B) 2 - Representation of the *in vitro* correlation with the KYA02 formulation

(o Observed Data ; - Regression Line with 95% CI)





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/s/

Venkateswar Jarugula
10/4/01 02:58:55 PM
BIOPHARMACEUTICS

Ameeta Parekh
10/4/01 03:18:46 PM
BIOPHARMACEUTICS
I concur

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Controlled Substance Staff Review

Not applicable to this application.

/S/ [illegible], M.S., RD
5/15/03

NDA 21-287
Alfuzosin Hydrochloride

Abuse Liability Review

Not applicable to this application.