Table 4. Comparison between ESRD and Healthy Control Subjects for AUC and C_{max}

Parameter	Status	Least-Squares Geometric Mean	Ratio of Geometric Mean (90% CI)
Atomoxetine			
C_{max} (ng/ml)	Healthy	86.0	
	ESRD	92.2	1.07 (0.68, 1.68)
AUC_{0-inf} (µg.hr/ml)	Healthy	0.469	
	ESRD	0.769	1.64 (0.86, 3.13)
4-Hydroxyatomoxetine			
C_{max} (ng/ml)	Healthy	1.81	
	ESRD	1.45	0.80 (0.64, 1.00)
AUC_{0-t} (µg.hr/ml)	Healthy	0.00714	
	ESRD	0.02095	2.93 (1.30, 6.60)
***N*-Desmethylatomoxetine**			
C_{max} (ng/ml)	Healthy	2.00	
	ESRD	6.19	3.09 (1.65, 5.79)
AUC_{0-t} (µg.hr/ml)	Healthy	0.00513	
	ESRD	0.09073	15.73 (3.13, 79.15)
4-Hydroxyatomoxetine –*O*-glucuronide			
C_{max} (ng/ml)	Healthy	307.7	
	ESRD	651.4	2.12 (1.71, 2.63)
AUC[a](µg.hr/ml)	Healthy	2.39	
	ESRD	20.34	8.51 (7.22, 10.02)

[a]4-hydroxyatomoxetine glucuronide AUC is AUC_{0-t} for ESRD subjects and AUC_{0-inf} for healthy subjects.

Summary

- Atomoxetine can be administered to ADHD patients with ESRD or lesser degrees of renal insufficiency without changing the normal dose-escalation sequence.
- Changes in the plasma concentrations of atomoxetine, 4-hydroxyatomoxetine , and N-desmethylatomoxetine in ESRD subjects are not sufficient to warrant a change in dose in ESRD patients.
- The plasma concentrations of 4-hydroxyatomoxetine-*O*-glucuronide, a renal excreted metabolite with no known pharmacologic action, increased as expected with a decreased in renal function.
- Plasma protein binding of atomoxetine is independent of renal function.
- The single 20-mg oral dose of atomoxetine was very well tolerated by ESRD and healthy subjects.

B4Z-LC-HFBN (Vol. 70-71): *Single Dose Pharmacokinetics of Atomoxetine Hydrochloride in Patients with Liver Disease*

The objectives of this study were to evaluate

(1) the influence of moderate and severe liver disease on the pharmacokinetics of atomoxetine and on the plasma profile of the 2 main metabolites of atomoxetine (4-hydroxyatomoxetine and N-desmethylatomoxetine),

(2) the safety of a 20-mg single oral dose of atomoxetine in patients with moderate and severe liver disease,

(3) plasma protein binding of atomoxetine in subjects with moderate and severe liver disease, and

(4) the correlation of CYP2D6 activity (Debrisoquine Metabolic Ratio) and liver blood flow (sorbitol clearance) with the clearance of atomoxetine in patients with moderate and severe liver disease and controls.

This study was an open-label, 2-period (Period 1 = Sorbitol and Debrisoquine tests; Period 2 = Atomoxetine 20-mg dose – capsule CT10230), parallel groups design. Ten patients with liver disease and 10 healthy subjects participated in this study. Debrisoquine (Delinax) was given as 10-mg tablets and Sorbitol was provided in 40% sterile solution for intravenous use.

Plasma samples for the measurement of sorbitol were taken at Period 1 at predose, and then at 165, 170, 175 and 180 minutes. Before and 30 minutes after termination of the 3-hour infusion of sorbitol, subjects were asked to completely empty their bladder, and urine samples were obtained. Urine samples for debrisoquine were collected during the interval 0-8 hours after drug intake.

Plasma samples for the measurement of atomoxetine and its metabolites were taken for healthy controls and HI patients at: predose, and then at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, and 48 hours postdose. Additional samples were collected in patients at 72, 96, and 120 hours. Urine samples were collected at period 2 over the following intervals after dosing: 0-6 hours, 6-12 hours, and 12-24 hours. One plasma sample for the measurement of plasma protein binding of atomoxetine was taken at Period 2 at predose.

Table 1. Child-Pugh Classification

	1 point	2 points	3 points	
Albumin (g/L)	>35	28-35	<28	
Total Bilirubin (µmol/l)				Child A: 5-6 points
-patients without PBC	<34	34-51	>51	Child B: 7-9 points
-patients with PBC	<68	68-170	>170	Child C: 10-15 points
Prothrombin Time (%) (or INR)	>70%	40-70%	<40%	
Ascites	Absent	Slight	Moderate	
Encephalopathy	None	1-2	3-4	

PBC: Primary biliary cirrhosis, INR=International Normalized Ratio©patient prothrombin time/normal plasma pool prothrombin time)^{ISI}. ISI=International Sensitivity Index (provided by the laboratory).

CYP2D6 Genotyping

Procedure - A 10-ml whole blood sample was collected from each subject at screening for CYP2D6 genotyping. CYP2D6 genotype was determined by allele-specific polymerase chain reaction (PCR) amplification using a method derived from the method (Heim and Meyer 1991). Two laboratories were successively used to perform this analysis, Regipharm S.A., Belgium, and PPGX, UK. The wild type (wt) and the mutant alleles A (*3), B (*4), D (*5) and E (*7) were identified in genomic DNA of human peripheral lymphocytes by both laboratories. Additionally, the mutant alleles T (*6) and G (*8) were also identified by PPGX (Daly et al. 1996).

Table 2. Individual Mean Atomoxetine Plasma Protein Binding Results

Healthy Controls					Hepatic patients				
Subject ID	Age (yrs)	Gender	Origin	% Protein Binding (SEM)	Subject ID	Age (yrs)	Gender	Origin	% Protein Binding (SEM)
011	47	M	Caucasian		001	62	M		98.1 (0.09)
012	57	M	Caucasian		002	43	M		97.4 (0.03)
013	55	F	Caucasian		003	58	F		97.3 (0.00)
014	48	M	Caucasian		004	59	M		93.0 (0.06)
015	59	M	Caucasian		006	63	M		95.8 (0.03)
016	34	M	Caucasian		007	53	M		95.7 (0.06)
017	52	M	Caucasian		008	48	M		97.4 (0.06)
018	62	M	Caucasian		009	52	F		96.2 (0.17)
020	49	F	Caucasian		010	54	F		95.3 (0.10)
906	52	F	Caucasian		901	35	M		98.0 (0.07)
Mean±SD				**98.7±0.07**	p-Value 0.0008				**96.4±1.56**

Table 3. Values of Atomoxetine Pharmacokinetic Parameters (Mean with CV%)

Group	C_{max} (ng/ml)	C_{max} (ng/ml)/(mg/kg)	AUC_{0-t} (µg.hr/ml)	AUC_{0-inf} (µg.hr/ml)	V_z/F (L/kg)
Healthy Controls (n=10)	142.2 (36)	560.4 (35)	0.692 (69)	0.706 (68)	2.66 (41)
Child-Pugh B (n=6)	115.8 (55)	431.9 (48)	1.16 (37)	1.17 (37)	3.26 (35)
Child-Pugh C (n=4)	125.8 (45)	431.9 (48)	2.54 (56)	2.73 (63)	2.72 (22)
	T_{max} (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)	CL/F (L/hr/kg)	
Healthy Controls (n=10)	1.0 (0.5-1.6)	4.3 (2.4-8.0)	41.5 (63)	0.506 (54)	
Child-Pugh B (n=6)	3.3 (0.5-6.0)	11.0 (7.9-17.9)	20.0 (52)	0.208 (28)	
Child-Pugh C (n=4)	6.0 (0.5-12.0)	16.0 (7.2-26.3)	10.8 (80)	0.155 (79)	

Median with range for T_{max} and mean with range for $t_{1/2}$.

Table 4. Values of Pharmacokinetic Parameters for Metabolites of Atomoxetine (Mean with CV%)

Parameter	C_{max} (ng/ml)	AUC_{0-t} (µg.hr/ml)	$AUC_{0-\infty}$ (µg.hr/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
4-Hydroxyatomoxetine					
Healthy (n=9)	1.9 (37)	0.0046 (97)	--	1.2 (1.0-2.1)	--
C-P B (n=6)	3.3 (33)	0.0263 (37)	--	1.8 (1.0-8.0)	--
C-P C (n=3)	2.9 (41)	0.0334 (77)	--	2.0 (1.0-12.0)	--
N-Desmethylatomoxetine					
Healthy (n=10)	4.1 (75)	0.0385 (145)	--	2.0 (1.0-8.0)	--
C-P B (n=3)	1.9 (18)	0.0124 (45)	--	6.0 (0.5-8.1)	--
C-P C (n=3)	1.7 (19)	0.0493 (109)	--	12.0 (6.0-96.3)	--
4-Hydroxyatomoxetine-*O*-Glucuronide					
Healthy (n=10)	355.9 (45)	2.20 (16)	2.28 (16)	2.0 (1.2-4.1)	5.7 (3.8-8.8)
C-P B (n=6)	104.5 (36)	1.46 (41)	1.56 (38)	3.0 (1.0-8.0)	9.4 (7.2-10.5)
C-P C (n=4)	92.2 (47)	2.79 (40)	2.94 (35)	9.0 (2.0-18.0)	21.3 (9.7-38.6)

Median with range for T_{max} and mean with range for $t_{1/2}$.

Table 5. Parameter Comparison between Hepatic Impairment and Healthy Control Subjects

Parameter	Status	Least-Squares Geometric Mean	Ratio of Geometric Mean (90% CI)
Atomoxetine			
C_{max} (ng/ml)	Healthy	136.9	
	Hepatic	107.1	0.78 (0.54, 1.12)
$AUC_{0\text{-}inf}$ (µg.hr/ml)	Healthy	0.849	
	Hepatic	1.585	1.87 (1.17, 2.98)
4-Hydroxyatomoxetine			
C_{max} (ng/ml)	Healthy	1.681	
	Hepatic	2.904	1.73 (1.28, 2.34)
$AUC_{0\text{-}t}$ (µg.hr/ml)	Healthy	0.003	
	hepatic	0.025	7.88 (4.05, 15.3)
4-Hydroxyatomoxetine-O-glucuronide			
C_{max} (ng/ml)	Healthy	276.2	
	Hepatic	86.9	0.31 (0.22, 0.45)
$AUC_{0\text{-}inf}$ (µg.hr/ml)	Healthy	3.034	
	hepatic	2.003	0.66 (0.54, 0.81)

Table 6. Cumulative Amounts of Total (after Hydrolysis) Atomoxetine and Metabolites Excreted in Urine from 0-24 hours following a 20-mg Dose

Compound (µg)	Healthy (n=9)	Child-Pugh B (n=5)	Child-Pugh C (n=4)
Atomoxetine	19.9 (112)	45.8 (48)	116 (64)
(% of Dose)	0.10	0.23	0.58
N-Desmethylatomoxetine	2.8 (143)	0.31 (190)	1.7 (76)
(% of Dose)	0.015	0.0017	0.009
4-Hydroxyatomoxetine	6830 (30)	5430 (37)	3750 (80)
(% of Dose)	32.1	25.6	17.6
Total (% of Dose)	**32.3 (30)**	**25.8 (37)**	**18.2 (76)**

Table 7. Individual and Mean Clearance Values

Group	Subject	*Sorbitol* CL^{ss}_{hep} (ml/min)	*Debrisoquine* Molar Metabolic Ratio in Urine	*Atomoxetine* CL/F (L/hr)
Healthy				
	0011			
	0012			
	0013			
	0014			
	0015			
	0016			
	0017			
	0018			
	0020			
	0906			
Mean (%CV)		**1380 (20)**	**1.73 (188)**	**41.5 (63)**
Child-Pugh B				
	0001			
	0002			
	0003			
	0007			
	0008			
	0901			
Mean (%CV)		**736 (36)**	**7.68 (111)**	**20.0 (52)**

Group Subject Healthy	*Sorbitol* CL^{ss}_{bcp} (ml/min)	*Debrisoquine* Molar Metabolic Ratio in Urine	*Atomoxetine* CL/F (L/hr)
Child-Pugh C			
0004	[redacted]		
0006			
0009			
0010			
Mean (%CV)	**540 (32)**	**18.7 (78)**	**10.8 (80)**

[a] Debrisoquine PM phenotype (>12.6)

Table 8. Relationships between Atomoxetine Parameters and Sorbitol or Debrisoquine Parameters

Parameter	Correlation	Population
CL_{atomox} and CL_{sorb}	0.8037	Hepatic
CL_{atomox} and Debrisoquine MR (Log-log)	-0.9248	All
Atomoxetine Urine Ratio and Debrisoquine MR	0.9435	All
Atomoxetine MR and Debrisoquine MR	-0.1164	All

Summary

- Single doses of 20-mg atomoxetine were well tolerated by healthy subjects and hepatic impairment (HI) patients with moderate to severe liver disease (Child-Pugh B and C) and genotyped as CYP2D6 extensive metabolizers.
- Moderate to severe hepatic impairment (Child-Pugh Class B and C) is associated with a decrease in mean atomoxetine plasma protein binding (96.5 vs. 98.7% in healthy controls).
- Moderate to severe liver hepatic impairment (Child-Pugh B and C) results in a reduced atomoxetine clearance (41% and 31% of the normal, respectively), increased atomoxetine exposure (AUC, 166% and 387% of the normal, respectively), and a prolonged half-life of the parent drug (from 4.3 to 11 and 16 hours, respectively) compared to healthy controls with the same CYP2D6 EM genotype.
- Compared to healthy controls with the same CYP2D6 EM genotype, the following changes in the metabolites of atomoxetine were observed in HI patients:
  - *N*-desmethylatomoxetine mean C_{max} decreased, median T_{max} was delayed,
  - 4-hydroxyatomoxetine mean Cmax and mean AUC_{0-t} increased,
  - for the glucuronide conjugate of 4-hydroxyatomoxetine, the mean half-life was longer and mean AUC_{0-inf} and C_{max} were lower.
- The sponsor claims that the atomoxetine pharmacokinetic and cardiovascular changes noted in hepatic impairment (HI) patients are less than those exhibited by healthy subjects with poor metabolizer CYP2D6 genotypes; therefore, dosing with ADHD to those who also have identified liver disease of Child Pugh B or C is not likely to result in higher plasma concentrations of atomoxetine than PM subjects.

B4Z-LE-LYAN (Vol. 72, Amendment Vol. 1-6): ***Phase I Study of LY139603 in Healthy Adult Male Subjects: Single Dose Oral Administration Study (Dose Escalation), Multiple Oral Administration Study***

Study Design

The objectives of this study were to evaluate (1) the safety of atomoxetine administered as single oral doses (10, 40, 90 and 120 mg), the single dose pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and *N*-desmethylatomoxetine, and dose proportionality of atomoxetine in healthy Japanese adult men, and (2) the safety of atomoxetine administered as multiple oral doses (placebo, 40 mg or 60 mg, twice daily), and the multiple dose pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylatomoxetine in healthy Japanese adult men.

Twenty-three male volunteers (CYP2D6 EM) in the Part A of the study (placebo-controlled, single-dose escalation) received a single doses of 10 mg, 30 mg 60 mg, 90 mg and 120 mg atomoxetine capsules with a minimum washout of 4 days between dosing. Twenty male subjects (all CYP2D6 EM) in the Part B of the study (multiple doses) received 40 mg or 60 mg of atomoxetine capsules, twice daily for up to 7 days. Placebo capsules (CT13981/CT17087), 10-mg and 20-mg atomoxetine capsules (CT15498/CT17086 and CT15499/CT17083) were used in this study. Blood and urine samples for drug concentration determination were collected after dosing and analyzed using a validated method.

Pharmacokinetic Results

Atomoxetine

Table 1. Values of Single-Dose Atomoxetine Pharmacokinetic Parameters (Mean with CV%)

Parameter	10 mg (n=22)	40 mg (n=21)	90 mg (n=20)	120 mg (n=19)
C_{max} (ng/ml)	110.5 (33)	478.4 (34)	920.0 (33)	1086.2 (31)
AUC_{0-t} (μg.hr/ml)	0.567 (71)	2.50 (69)	5.29 (54)	6.42 (37)
$AUC_{0-\infty}$ (μg.hr/ml)	0.574 (70)	2.51 (69)	5.30 (54)	6.43 (38)
T_{max} (hr)	1.25 (0.5-2.0)	1.0 (0.5-4.0)	1.75 (0.5-6.0)	1.0 (0.5-4.0)
$T_{1/2}$ (hr)	3.5 (1.9-6.6)	4.1 (2.1-7.1)	4.0 (2.2-7.0)	4.3 (2.9-6.2)
CL/F (L/hr/kg)	0.377 (43)	0.347 (47)	0.337 (40)	0.348 (39)
V_Z/F (L/kg)	1.64 (26)	1.83 (34)	1.79 (31)	2.06 (32)

Median with range for T_{max} and mean with range for $t_{1/2}$.

Table 2. Dose Proportionality Assessment from Power Model for Atomoxetine

Parameter	Dose (mg)	Predicted GM	Ratio of Dose Normalized GM	90% CI of Ratio	DP[a] (10-120 mg)	DP
AUC_{0-t}	10	0.483				
(μg.hr/ml)	120 mg	0.677	1.17	(1.22, 1.23)	16.59	Yes
AUC[b]	10 mg	0.489				
(μg.hr/ml)	120 mg	6.80	1.16	(1.10, 1.22)	19.33	Yes
C_{max}	10 mg	105.5				
(ng/ml)	120 mg	1067.2	0.84	(0.75, 0.95)	11.10	Unsure

[a] Dose proportionality (DP) could be theoretically concluded for any dose ratio less than this value. [b] Since the clearances were similar in the single- and multiple-dose parts of the study, multiple dose information ($AUC_{0-\tau}$ was combined with the single-dose information ($AUC_{0-\infty}$).

C_{max} and AUC values in Table 1 generally increased proportionally with dose with CL/F remaining relatively constant. Dose proportionality was concluded over the dosing range of 10 to 120 mg (12-fold range) for AUC but conclusion was uncertain for C_{max} based on the results of the power model analysis. The proportional increase of AUC with dose as

well as remaining relative constant of clearance with dose in EM subjects supports the hypothesis of linear pharmacokinetics.

Table 3. Comparison of *10/*10 Subjects versus Other EM Subjects for C_{max} and AUC

Parameter	Dose (mg)	Genotype	Predicted GM	Ratio	90% CI of Ratio	p-Value
$AUC_{0-\tau}$ (μg.hr/ml)	10	*10/*10 (n=4)	0.713	1.61	(1.01, 2.57)	0.092
		Other EMs (n=18)	0.442			
$AUC_{0-\infty}$ (μg.hr/ml)		*10/*10 (n=4)	0.727	1.62	(1.02, 2.58)	0.087
		Other EMs (n=18)	0.448			
C_{max} (ng/ml)		*10/*10 (n=4)	125.1	1.23	(0.94, 1.62)	0.205
		Other EMs (n=18)	101.6			
$AUC_{0-\tau}$ (μg.hr/ml)	120	*10/*10 (n=4)	9.80	1.86	(1.43, 2.44)	0.001
		Other EMs (n=14)	5.26			
$AUC_{0-\infty}$ (μg.hr/ml)		*10/*10 (n=4)	9.83	1.87	(143, 2.44)	0.001
		Other EMs (n=14)	5.27			
C_{max} (ng/ml)		*10/*10 (n=4)	1270.8	1.30	(0.96, 1.76)	0.150
		Other EMs (n=14)	977.8			

The comparison of AUC and C_{max} between *10/*10 homozygous and other EM subjects shows that there is evidence of a difference in mean concentrations between these two groups. It should be noted, however, that the concentration for *10/*10 subjects falls in the range of concentrations for other EM subjects.

Table 4. Values of Atomoxetine Pharmacokinetic Parameters after Multiple-Dose (Mean with CV%)

Dose (mg)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12} (μg.hr/ml)	$AUC_{0-\tau}$ (μg.hr/ml)	Accumulation Ratio
	First Dose			***Steady-State***	
40 BID	427 (34)	1.25 (0.5-2.0)	1.95 (38)	2.47 (42)	1.26 (9)
60 BID	616 (32)	1.00 (1.0-2.0)	3.14 (42)	3.73 (42)	1.28 (8)
	C^{SS}_{max} (ng/ml)	C^{SS}_{min} (ng/ml)	C^{SS}_{avg} (ng/ml)	Flux (%)	CL^{SS}/F (L/hr/kg)
40 BID	604 (35)	34.6 (95)	205.9 (42)	292 (21)	0.321 (50)
60 BID	874 (26)	59.1 (87)	310.7 (42)	291 (38)	0.292 (41)

Median with range for T_{max} and mean with range for $t_{1/2}$.

N-Desmethylatomoxetine

Table 5. Values of Single-Dose *N*-Desmethylatomoxetine Pharmacokinetic Parameters

Parameter	10 mg (n=16)	40 mg (n=21)	90 mg (n=20)	120 mg (n=19)
C_{max} (ng/ml)	3.9 (57)	12.9 (86)	24.2 (76)	28.0 (72)
$AUC_{0-\tau}$ (μg.hr/ml)	0.046 (141)	0.182 (155)	0.334 (130)	0.345 (118)
$AUC_{0-\infty}$ (μg.hr/ml)	0.063 (116)	0.197 (147)	0.350 (126)	0.360 (114)
T_{max} (hr)	2.0 (1.0-8.0)	2.0 (1.0-12.0)	2.0 (1.0-8.0)	2.0 (1.0-6.0)
$T_{1/2}$ (hr)	7.6 (2.2-15.4)	6.3 (2.4-13.4)	5.8 (2.7-10.8)	5.8 (2.8-10.4)

Data presented as Arithmetic Mean (CV%), T_{max}: Median (range), $t_{1/2}$: Arithmetic Mean (range).

Table 6. Values of Desmethylatomoxetine Pharmacokinetic Parameters after Multiple-Dose

Dose (mg)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12} (μg.hr/ml)	$AUC_{0-\tau}$ (μg.hr/ml)	T_{max} (hr)
	First Dose			***Steady-State***	
40 BID (n=10)	11.6 (85)	3.0 (1.0-6.0)	0.108 (74)	0.194 (80)	1.5 (1.0-4.0)
60 BID (n=10)	13.4 (60)	4.0 (1.5-12.0)	0.128 (64)	0.227 (83)	1.5 (1.0-4.0)
	C^{SS}_{max} (ng/ml)	C^{SS}_{min} (ng/ml)	C^{SS}_{avg} (ng/ml)	Flux (%)	
40 BID	20.2 (87)	6.4 (123)	16.2 (80)	119 (29)	
60 BID	27.3 (75)	9.0 (115)	18.9 (83)	132 (40)	

Data presented as Arithmetic Mean (CV%), T_{max}: Median (range), $t_{1/2}$: Arithmetic Mean (range)

4-Hydroxyatomoxetine

Table 7. Values of Single-Dose 4-Hydroxyatomoxetine Pharmacokinetic Parameters

Parameter	10 mg (n=18)	40 mg (n=21)	90 mg (n=20)	120 mg (n=19)
C_{max} (ng/ml)	1.5 (28)	4.7 (36)	9.1 (38)	11.2 (35)
AUC_{0-t} (μg.hr/ml)	0.002 (131)	0.025 (52)	0.065 (35)	0.921 (37)
$AUC_{0-\infty}$ (μg.hr/ml)	--	0.036 (45)	0.076 (30)	0.103 (34)
T_{max} (hr)	1.5 (1.0-2.0)	1.5 (1.0-4.0)	2.0 (1.0-6.0)	2.0 (1.0-6.0)
$T_{1/2}$ (hr)	--	5.1 (1.7-13.0)	4.7 (3.1-8.0)	4.7 (3.3-6.6)

Data presented as Arithmetic Mean (CV%), T_{max}: Median (range), $t_{1/2}$: Arithmetic Mean (range)

Table 8. Values of 4-Hydroxyatomoxetine Pharmacokinetic Parameters after Multiple-Dose

Dose (mg)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12} (μg.hr/ml)	$AUC_{0-\tau}$ (μg.hr/ml)	T_{max} (hr)
	First Dose			***Steady-State***	
40 BID (n=10)	4.5 (44)	1.5 (1.0-4.0)	--	0.037 (27)	1.5 (1.0-4.0)
60 BID (n=10)	5.6 (37)	1.5 (1.0-4.0)	0.037 (24)	0.057 (23)	1.5 (1.0-4.0)
	C^{SS}_{max} (ng/ml)	C^{SS}_{min} (ng/ml)	C^{SS}_{avg} (ng/ml)	Flux (%)	
40 BID	6.1 (37)	1.3 (23)	3.1 (27)	152 (27)	
60 BID	10.1 (35)	1.9 (29)	4.7 (23)	171 (29)	

Data presented as Arithmetic Mean (CV%), T_{max}: Median (range), $t_{1/2}$: Arithmetic Mean (range)

Urine Excretion

Table 9. Cumulative Amounts of Atomoxetine and Metabolites Excreted in Urine in 24 Hours (Single-Dose)

Compound	10 mg (n=22)	40 mg (n=21)	90 mg (n=20)	120 mg (n=19)
Atomoxetine (μg)	27.2 (83)	78.3 (87)	153 (143)	178 (92)
% of Dose	0.27 (83)	0.20 (88)	0.17 (143)	0.15 (92)
N-Desmethylatomoxetine (μg)	0.85 (187)	3.43 (148)	7.43 (195)	5.68 (89)
% of Dose	0.009 (187)	0.009 (148)	0.009 (195)	0.005 (89)
4-Hydroxyatomoxetine ((μg)	196 (36)	801 (28)	1609 (20)	2274 (18)
% of Dose	1.84 (36)	1.88 (28)	1.68 (20)	1.78 (18)
4-Hydroxyatomoxetine-O-Gluc (μg)	3904 (27)	17072 (29)	40021 (21)	49757 (28)
% of Dose	36.7 (27)	40.2 (29)	41.8 (21)	39.0 (28)
Total (% of Dose)	**38.9 (26)**	**42.3 (28)**	**43.7 (20)**	**41.0 (27)**

Pharmacodynamic Evaluation

CYP2D6 EM subjects experienced atomoxetine dose-related increases in their mean standing heart rate (HR) following single doses of atomoxetine, 10- to 120-mg. A maximum mean HR increase to about 115 bpm was associated with the 90-mg dose. This represents a maximum increase of approximately 23 bpm above the placebo mean HR at the same time of day. A rise in HR began at 3 hours following a 10-mg dose, at 1 hour following a 40-mg dose and at 0.5 hour following a 90- or 120-mg dose.

Table 10. Effects of Single Doses of Atomoxetine on Pharmacodynamics

Variable	10 mg	40 mg	90 mg	120 mg
Standing HR (bpm)	91.4	100.1	104.6	104.9
Orthostatic HR Change (bpm)	29.9	35.4	36.6	34.6
Orthostatic SBP Change (mm Hg)	-3.7	-6.7	-11.9	-13.3

Data represent Least Squares Means

After multiple doses, statistical increases in mean standing HR were first seen in the 40- and 60-mg dose group 1 hour after on the 1st dosing day. For the remaining days, increases in mean standing HRs compared to placebo group were significant for all subjects in the 40 mg dose group but not for 60 mg dose group. EM subject mean standing HR increases appeared to reach a plateau at 47.5 hrs post first dose at about 90 bpm in the 40-mg dose group, and at 23.5 hrs post first dose at about 81 bpm in the 60-mg dose group through to 143.5 hrs post first dose. Similarly, statistically significant increases in mean orthostatic HR were first seen in the 40- and 60-mg dose groups 1 hr after dosing, but were insignificant by the 2nd and 3rd hr following dosing. There were no significant changes in the mean orthostatic systolic blood pressure over the observation period.

Summary

Pharmacokinetics

- C_{max} and AUC generally increased proportionally with dose with clearance remaining relatively constant over the dose range studied.
- Accumulation at steady state in EM subjects was minimal and averaged 1.3-fold increase. There was no difference in apparent clearance between multiple dosing and single doses.
- Plasma concentrations of atomoxetine are substantially higher than *N*-desmethylatomoxetine and 4-hydroxyatomoxetine concentrations.
- 4-Hydroxyatomoxetine-*O*-glucuronide was the predominant metabolite observed in the urine. Over a 24 hour period, the measured analytes in the urine across all doses accounted for approximately 40% of the total dose in EM subjects.
- The *10/*10 homozygous EM subjects had higher mean exposure (C_{max} and AUC) than other EM subjects, however, their concentrations fall in the range of concentrations for other EM subjects.

Safety

- At a quantitative level, the frequency, severity and type of adverse events reported by *10/*10 homozygous Japanese subjects are indistinguishable from those reported by participants with other EM CYP2D6 genotypes.

- All doses of atomoxetine were well tolerated. Two subjects in Part A and one subject in Part B were discontinued due to adverse events (nausea and dizziness after a 90 mg dose, nausea, orthostatic hypotension, and a mild pale bloodless feeling after a 40 mg dose, and urinary incontinence after a 60 mg dose of study drug), although considered slight (mild) in intensity.
- Single doses of atomoxetine between 10 and 120 mg resulted in increases in standing heart rate in CYP2D6 EM subjects. The magnitude of heart rate increase was not proportional to the atomoxetine dose increase.
- Multiple doses of 40-mg of atomoxetine, taken twice daily for 7 days, resulted in mean standing heart rate increases in CYP2D6 EM subjects.
- CYP2D6 EM subjects reached a plateau to the increases in standing heart rate during atomoxetine twice-daily dosing.
- Orthostatic changes in systolic blood pressure and heart rate were not clinically significant in CYP2D6 EM subjects.
- According to the sponsor, there was no evidence of a positive relationship between QT_c interval length and dose, and none of the mean changes in QT_c interval during atomoxetine treatment resulted in a QT_c interval measurement above the normal limit for adult men (450 msec).

Ethnic Comparison Report: Japanese Study LYAN and US Study HFBJ

This report is for comparison of the study results for healthy Japanese subjects in Study LYAN with the results for healthy subjects in the US, Study HFBJ. The objectives are

- describe the relationship, if any, between known extensive metabolizer CYP2D6 alleles and the pharmacokinetics of atomoxetine and the 4-hydroxyatomoxetine metabolite following single- and multiple-dose regimens of atomoxetine;
- dose proportionality of atomoxetine C_{max} and AUC;
- safety and tolerability following single- and multiple-dose regimens of atomoxetine;
- effect of single and multiple oral doses of atomoxetine on the pharmacodynamics of atomoxetine through repeated vital signs and orthostatic change measurements.

Demographic Comparison

Table 1. Demographic Comparison of Japanese (Study LYAN) and US (Study HFBJ) Subjects

Demographic	HFBJ		LYAN	
	Part A	Part B	Part A	Part B
# Subjects Enrolled	27	21	23	26
Completed	25	20	19	25
Age (yrs)	28.5 (19-40)	27.7 (19-40)	23.7 (20-31)	22.0 (20-26)
Weight (kg)	76.7 (55.8-107.5)	76.4 (55.8-107.5)	61.4 (49.9-82.8)	61.7 (49.7-81.8)
Gender (Male/Female)	14/13	11/10	23/0	26/0
Ethnic Origin	22 Caucasian	17 Caucasian	23 Japanese	26 Japanese
	4 Hispanic	3 Hispanic		
	1 Native American	1 Native American		
CYP2D6 genotype (EM/PM)	16/11	14/7	23/0	23/0
*10 Homozygous			4	5

The primary differences (other than ethnic background) were the use of exclusively male subjects in Japan who also had relatively smaller body weight and a younger mean age

than the largely Caucasian subjects in Study HFBJ. However, no gender differences were found in the Caucasian population thus all EM subjects for Study HFBJ were included in the analysis. No PM subjects were identified in Study LYAN due to the extremely low frequency in the Japanese population.

Table 2. CYP2D6 Classification Based on Genotype and Gene Duplication

CYP2D6 Phenotype	CYP2D6 Genotype (allele / allele)	Duplication Result	CYP2D6 Phenotype Subpopulations
Poor Metabolizer	defective[a] / defective	Irrelevant	PM
Extensive metabolizer	wild type / wild type	Yes (*2xN)	UM
	Wild type / wild type	No	homozygous EM
	Defective / wild type	Irrelevant	heterozygous EM
	*2 e or 10 e / defective	Irrelevant	IM
	*2 or *10 / *2 or *10	Irrelevant	IM

EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer; UM = ultrarapid metabolizer. [a] Indicates any defective allele, which includes the following alleles: *3, *4, *5, *6, 7, 8. Gene duplication results in CYP2D6 UM. Gene duplication results (2xN) were not available for Study B4Z-LC HFBJ. Determinations of *2 and *10 alleles were not performed in Study HFBJ.

Pharmacokinetic Results Comparison

Table 1. Comparison of Pharmacokinetics between EM Subjects from Japan (Study LYAN) and the US (Study HFBJ)

Parameter	Dose	Group	Geometric Mean	Ratio (90% CI)	P-Value
			Atomoxetine		
C_{max} (ng/ml)	0.157 (mg/kg)	US	95.33	1.12 (0.94, 1.33)	0.2707
		Japanese	106.78		
	1.88 (mg/kg)	US	1211.19	0.92 (0.79, 1.09)	0.4224
		Japanese	1120.01		
AUC (µg.hr/ml)	0.157 (mg/kg)	US	0.52	0.94 (0.73, 1.20)	0.6621
		Japanese	0.49		
	1.88 (mg/kg)	US	7.52	0.91 (0.70, 1.17)	0.5169
		Japanese	6.82		
			4-Hydroxyatomoxetine		
C_{max} (ng/ml)	0.631 (mg/kg)	US	3.93	1.05 (0.86, 1.29)	0.6713
		Japanese	4.14		
	1.88 (mg/kg)	US	9.98	0.98 (0.80, 1.19)	0.8343
		Japanese	9.74		
AUC (µg.hr/ml)	0.631 (mg/kg)	US	0.024	0.87 (0.71, 1.06)	0.2391
		Japanese	0.021		
	1.88 (mg/kg)	US	0.11	0.76 (0.63, 0.93)	0.0258
		Japanese	0.08		

None of the differences in geometric means (C_{max} 8% to 12% and AUC 6% to 9%) tested statistically significant. Furthermore, the 90% confidence intervals indicate no differences that could be considered clinically relevant. The figure below shows the proportionality of C_{max} and AUC to dose is similar in both groups of subjects. This data is also consistent with the proportionality data obtained in the integrated analysis of all US clinical pharmacology data.

Table 2. Cumulative Amounts of Atomoxetine and Metabolites Excreted in Urine from 0 to 24 hours following a Single 90-mg Dose for EM Subjects from Japan (Study LYAN) and the US (Study HFBJ)

Compound	A	*N*-Desmethyl-A	4-Hydroxy-A	4-Hydroxy-A-*O*-Glucuronide
Study HFBJ (n=15) (μg)	151 (74)	30 (98)	1150 (34)	56500 (27)
(% of dose)	0.17	0.035	1.20	59.0
Study LYAN (n=20) (μg)	153 (143)	7.4 (195)	1609 (20)	40021 (21)
(% of dose)	0.17	0.009	1.68	41.8

Table 3. Atomoxetine Clearance Comparison among Different Metabolizers

Study	Homozygous EM	Heterozygous EM	Intermediate Metabolizer	Poor Metabolizer
HFJB	28.5±7.9 (N=7, n=22)	19.3±10.2 (N=9, n=32)	ND	2.4±0.5 (N=11, n=37)
LYAN	26.4±8.2 (N=20, n=44)	21.1±2.8 (N=5, n=20)	14.7±7.2 (N=16, n=37)	NA
			12.5±2.7 (N=8, n=20, *10/*10 only)	

Homozygous EM included *10/wild type, *2/wild type, or wild type/wild type (allele/allele).
Heterozygous EM included *3/wild type, *4/wild type, *5/wild type, or *6/wild type (allele/allele).
IM included *10/*10, *2/*10, or *5/*2 (allele/allele).
PM included *4/*4, or *4/*5 (allele/allele).

Summary

- There is no clinically meaningful difference in the pharmacokinetics of atomoxetine and 4-hydroxyatomoxetine in Japanese and US population.
- The distribution of CL/F in EM subjects was similar after single- and multiple- dose regimens of atomoxetine in the Japanese and US populations.
- The dose proportionality of atomoxetine was similar in both populations.
- The similar amount of unchanged atomoxetine and its primary metabolites excreted in the urine indicates that the metabolism and excretion of atomoxetine is the same in both Japanese and US subjects.
- CL/F in PM subjects of Study HFBJ was clearly distinct from the CL/F in EM subjects. The variability of CL/F in EM subjects is higher as shown by the wide width of the distribution. The data from LYAN *10/*10 homozygous EM subjects are distinguishable from other EM subjects.
- The safety and tolerance of atomoxetine administered as single oral doses (ranging from 10 mg to 120 mg) and multiple doses of 40 mg twice daily, were not different between Japanese (n=49 men) and US (n=27 predominantly Caucasian men and women) populations.
- The expected pharmacological effects of atomoxetine on the cardiovascular system, as measured by positional changes in vital signs, were not different between the Japanese and US populations.
- There was no evidence of QT_c interval prolongation with the administration of atomoxetine in either the Japanese and US populations.

Evaluation of Effects of Extrinsic Factors (DDI, Food)

B4Z-LC-HFBP (Vol. 73-74): ***Safety and Pharmacokinetic Interaction of Coadministered Atomoxetine and Desipramine in Healthy Subjects***

The objectives of this study were to evaluate
(1) the PK of desipramine (CYP2D6 inhibitor) and atomoxetine when coadministration of these two drugs to healthy adults,
(2) the safety of atomoxetine-desipramine coadministration when desipramine is given as a single dose,
(3) the pharmacodynamic interaction of atomoxetine and desipramine by repeated measures of postural changes in blood pressure and heart rate, and
(4) the tolerability of 60-mg twice-daily atomoxetine therapy.

Twenty-two healthy subjects (11 males and 11 females) with CYP2D6 EM genotype participated in this open-label, sequential, 2-period, drug interaction study. The study medications were atomoxetine capsules 30-, 40- and 60-mg oral dose twice-daily (10-mg, CT15503 and 20-mg, CT15502) for 13 consecutive days, desipramine 50-mg single oral dose (50-mg tablet, Lot 3000251) taken alone followed by a washout period of up to 14 days and given on the 4th atomoxetine dosing day. Morning doses of atomoxetine and desipramine were given after an overnight fast of at least 7 hours.

Blood samples for desipramine were obtained prior to dosing, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdose in Period 1, and prior to dosing, then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours postdose in Period 2.
Blood samples for atomoxetine and its metabolites were taken on Study Day 3 and Day 4 prior to dosing, then 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose.

Table 1. Values of Desipramine Pharmacokinetic Parameters (Mean with CV%)

N=21	C_{max} (ng /ml)	LS Mean C_{max}	$AUC_{0-\tau}$ (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	LS Mean $AUC_{0-\infty}$
Alone	18.3 (45)	17.6	639 (88)	698 (95)	569
+Atomoxetine	19.2 (50)	18.1	699 (102)	740 (106)	591
Ratio of LS Mean (90% CI)		0.97 (0.87, 1.08)			0.96 (0.89, 1.04)
	T_{max}(hr)	$t_{1/2}$(hr)	CL/F (L/hr/kg)	V_z/F (L)	
Alone	6.0 (2.0-12.00	23.5 (7.9-52.5)	142 (95)	3340 (46)	
+Atomoxetine	6.0 (2.0-12.0)	24.5 (9.4-58.3)	144 (117)	3490 (61)	

Table 2. Values of Atomoxetine Pharmacokinetic Parameters (Mean with CV%)

N=21	T_{max} (hr)	C^{ss}_{max} (ng /ml)	C^{ss}_{min} (ng /ml)	C^{ss}_{avg} (ng/ml)	$AUC_{0-\tau}$ (µg.hr/ml)
A alone (n=6)	1.0 (0.5-4.0)	552 (45)	105 (138)	265 (85)	3.18 (85)
A+D (n=6)	1.0 (0.5-4.0)	557 (48)	110 (124)	289 (76)	3.47 (76)
A alone (n=15)	1.0 (0.5-2.0)	591 (46)	57 (97)	224 (57)	2.69 (57)
A+D (n=15)	1.0 (0.5-2.0)	647 (35)	64 (99)	251 (52)	3.01 (52)
Ratio of LS Mean (90% CI)		0.95 (0.86, 104)			0.87 (0.84, 0.91)

	CL/F (L/hr)	CL/F (L/hr/kg)	V_z/F (L)	V_z/F (L/kg)
A alone (n=6)	20.4 (61)	0.327 (73)	94.8 (41)	1.48 (55)
A+D (n=6)	17.2 (57)	0.270 (67)	82.2 (29)	1.25 (45)
A alone (n=15)	29.4 (55)	0.399 (62)	132 (42)	1.76 (45)
A+D (n=15)	25.2 (50)	0.343 (58)	115 (45)	1.57 (53)

Each individual's atomoxetine and desipramine parameters are highly correlated (C_{max}, r^2=0.537, AUC, r^2=0.950). The high correlation can be explained by the fact that both of these compounds are primarily biotransformed by the same metabolic pathway, CYP2D6. This, in turn, suggests that the high intersubject variability seen for these CYP2D6 substrate results from intrinsic differences in CYP2D6 activity.

PK Summary

Coadministration of atomoxetine and desipramine, a selective CYP2D6 probe drug, was used to assess atomoxetine's ability to inhibit metabolism of CYP2D6 substrates in EM subjects:

- Comparison of desipramine C_{max} and AUC following desipramine administration vs. desipramine-atomoxetine coadministration revealed no clinically or statistically significant changes (90% CI, [0.869, 1.084] and [0.893, 1.039], respectively). Thus, atomoxetine, at steady-state conditions, does not inhibit CYP2D6-mediated metabolism in EM subjects.
- Similarly, atomoxetine PK parameters showed no clinically important changes following a single dose of desipramine with 90% CI for Cmax (0.858, 1.040) and AUC (0.836, 0.911) falling within the 0.80 to 1.25 region.

PD and Safety

Table 3. Least-Squares Mean Vital Signs

Variable	Time (hr)	A LS Mean	D LS Mean	C LS Mean	A-D	C-D	C-A
Standing HR	1	90.8	75.9	96.3	0.0001	0.0001	0.083
(bpm)	24	93.0	97.2	102.1	0.083	0.057	0.0015
Orthostatic HR	1	22.4	8.5	26.0	0.0017	0.0003	0.28
(bpm)	24	21.1	20.1	25.8	0.60	0.0094	0.072
Orthostatic SBP	1	-11.5	-2.1	-14.1	0.103	0.0002	0.58
(mm Hg)	24	-18.4	-10.9	-21.1	0.0056	0.017	0.25

A=atomoxetine, D=desipramine, C=combination.

PD Summary

- The addition of a small dose of desipramine to atomoxetine resulted in minimal effect as evidenced by the p-values (0.083, 0.28, and 0.58 respectively for standing HR, orthostatic HR, and orthostatic SBP) for the difference in the combination treatment versus atomoxetine alone at 1 hour postdose.
- The 24-hour results are difficult to interpret. Standing HR is more greatly affected by the combination treatment than atomoxetine alone (p=0.0015). The orthostatic HR

increase of desipramine and atomoxetine is modestly enlarged (p=0.072) with the combination. Adding desipramine to atomoxetine seems to have little change on orthostatic SBP.

Five subjects had at least 1 of the following 3 adverse events after the combination treatment: dizziness, vasodilatation, and palpitations. These events are clinically associated with the pharmacodynamic effects of both drugs on BP and HR. In order to explore a relationship between drug concentration and/or exposure with these events, graphics of individual C_{max} and AUC of atomoxetine and desipramine are plotted for these 5 subjects versus the remaining subjects in the study. These 5 subjects display a wide range of atomoxetine and desipramine AUC and C_{max}, from lowest to highest. It is not possible to identify relationship in this study.

Possible modification of the known mild orthostatic tachycardia and hypotension resulting from atomoxetine therapy was examined following the addition of a single small dose of desipramine. Desipramine is a norepinephrine reuptake inhibitor with similar effects as atomoxetine on HR and BP. A full examination of the PD interaction and safety of these 2 drugs requires the testing of steady-state concentrations of both. In clinical practice, 200-mg doses of desipramine daily are common. Instead, a subtherapeutic dose of desipramine (50 mg) was administered to subjects at therapeutic steady-state atomoxetine concentrations. This conservative desipramine dose was used since elevated desipramine concentrations could have resulted if atomoxetine inhibition of CYP2D6 had occurred during combination therapy.

Since there was no PK interaction and the desipramine dose was small, as expected, the combination therapy did not result in clinically relevant orthostatic changes compared to atomoxetine therapy alone.

Summary

- In EM subjects, single-dose PK parameters of desipramine, a CYP2D6 probe substrate, were not altered when coadministered with atomoxetine, demonstrating that atomoxetine does not inhibit CYP2D6-mediated metabolism.
- Steady-state PK of atomoxetine in EM subjects was not significantly influenced by a single-dose of desipramine.
- Multiple twice-daily doses of 60-mg atomoxetine were safe and well-tolerated by EM subjects when administered alone and in combination with single doses of 50-mg desipramine.
- Pharmacodynamic effects of the combination of steady-state atomoxetine and single-dose desipramine did not show clinically relevant orthostatic changes in blood pressure or heart rate.
- No mean QT_c interval prolongation or individual prolongation greater than 30 msec were observed.
- The potential safety and tolerance of multiple desipramine dosing with chronic atomoxetine dosing cannot be determined from this study.

B4Z-LC-LYAJ (Vol. 74-75): ***Safety and Pharmacokinetic Interaction of Atomoxetine and Midazolam in CYP2D6 PM Healthy Adults***

The objectives of this study were to evaluate

(1) the ability of atomoxetine to act as an inhibitor of the cytochrome P450 3A (CYP3A) metabolic pathway using midazolam as a probe drug by evaluation of the pharmacokinetics of oral midazolam during coadministration of atomoxetine in healthy PM adults,

(2) the safety of atomoxetine-midazolam coadministration when midazolam is given as a single, oral 5-mg dose to healthy PM adults, and

(3) the change, if any occurs, on the length of QT_c intervals of ECG tracings, done before and after atomoxetine in healthy PM adults.

A total of eight PM healthy young subjects (4 males and 4 females) participated in this study. Five subjects completed the study (all Caucasians, 1 female and 4 males). Dosing schedule is as following:

	Midazolam (5 mg/day) (Versed oral syrup, Lot 0004)	Atomoxetine 60 mg twice daily (Capsules: 40-mg, Lot CT16877, 10-mg, Lot CT16879)
Period 1	Day 1 and Day 2	
Period 2	Day 6 and Day 12 (30 min after Atomoxetine)	for 12 days

The following blood samples were taken with respect to the midazolam dose on Study Days 1 and 2 of Period 1 and on Study Days 6 and 12 of Period 2: prior to dosing, and 0.25, 0.5, 1, 1.5, 2.5, 3.5, 5.5, 7.5, 9.5, 11.5, 15, and 23.5 hours postdose. Blood samples for the measurement of atomoxetine and its metabolites were collected with respect to the morning atomoxetine dose on Days 6 and 12 of Period 2: prior to dosing, and 0.1, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdose.

Vital signs were recorded every 15 minutes starting approximately 0.5 hour prior to midazolam dosing, and continuing for 1 hour post dosing. Afterward, vital signs measurements were recorded every 30 minutes for up to 3 hours post dosing.

Table 1. Values of Midazolam Pharmacokinetic Parameters (Arithmetic Mean with %CV)

	C_{max} (ng /ml)	$AUC_{0-\infty}$ (ng.hr/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
Midazolam alone (n=8) Day 1	14.9 (40)	33.3 (47)	0.5 (0.3-1.0)	2.3 (0.9-5.2)
Midazolam alone (n=8) Day 2	16.5 (55)	41.1 (45)	0.8 (0.3-1.0)	2.6 (1.3-3.9)
M +A Day 6 (n=6)	16.5 (33)	40.7 (23)	1.0 (1.0-1.6)	2.8 (1.6-5.6)
M +A Day 12 (n=5)	22.9 (51)	49.3 (43)	1.0 (0.5-1.5)	2.8 (1.2-7.3)
Ratio of LS Mean (90% CI)	**1.16 (0.92, 1.46)**	**1.15 (0.90, 1.47)**		
	CL/F (L/hr/kg)	V_z/F (L/kg)		
Midazolam alone (n=8) Day 1	2.695 (44)	7.23 (38)		
Midazolam alone (n=8) Day 2	2.187 (43)	7.53 (38)		
M +A Day 6 (n=6)	2.006 (37)	7.53 (46)		
M +A Day 12 (n=5)	1.688 (53)	5.36 (66)		

Median with range for T_{max} and Mean with range for $t_{1/2}$.

Midazolam PK parameters (C_{max} and AUC) were numerically higher when midazolam and atomoxetine were coadministered (Days 6 and 12) than when midazolam was given alone. However, there is not a statistically significant difference between midazolam AUC and C_{max} geometric means in the presence or absence of atomoxetine. The changes noted did not necessarily increase with time. The largest changes were seen between Days 1 and 12; while Days 2 and 6 were almost identical. The intra-subject variability for C_{max}, $AUC_{0\text{-}inf}$ was 23%, and 19%, respectively.

Table 2. Values of Atomoxetine Pharmacokinetic Parameters (Arithmetic Mean with CV%)

N=21	C^{ss}_{max} (ng /ml)	C^{ss}_{min} (ng /ml)	C^{ss}_{avg} (ng/ml)	$AUC_{0\text{-}\tau}$ (µg.hr/ml)	CL^{ss}/F (L/hr/kg)
A+M Day 6 (n=6)	2610 (18)	1353 (26)	1946 (19)	23.4 (19)	0.042 (44)
A+M Day 12 (n=5)	2694 (27)	1490 (33)	2022 (27)	24.3 (27)	0.039 (51)
T_{max} 4.0 (1.5-6.0) for both Days (Median with range)					

Atomoxetine PK parameters essentially remained unchanged from Day 6 to Day 12 of Period 2.

The data comparison of hemodynamic measures obtained at similar times on control and dose days indicate that atomoxetine administration consistently increases supine pulse rate as well as systolic and diastolic blood pressure. When comparing hemodynamic measures of atomoxetine alone with combination treatment, there is a statistically significant increase after the combination treatment of midazolam and atomoxetine for each measures (p=0.005, 0.004 and 0.006 for supine pulse rate, systolic, and diastolic blood pressure, respectively).

The data comparison of ECG measures obtained at similar times on control day and dose days indicate that the least squares means for QT and QRS intervals are relatively similar when comparing ECG measures obtained at baseline and on Day 1 and 7 of Period 2. The decrease in the RR interval from baseline mean (no treatment) to Day 1 of Period 2 was statistically significant (p=0.0027), and is consistent with atomoxetine treatment. Subjects with increases in QT_c intervals of >30 msec from Baseline (Day-1) include Subjects 2002, 2005 and 2007. No subjects had QT_c intervals that exceeded the gender-based limits of normal (>450 msec for men and >470 msec for women).

Summary

- Due to subject variability higher than expected and small sample size, the ability of atomoxetine to act as an inhibitor of the CYP3A isozyme using midazolam as the probe drug could not be determined.
- The modest changes (approximately 16%) in midazolam pharmacokinetics in the most likely candidates to show an interaction (PM subjects) imply that atomoxetine is not likely an inhibitor of CYP3A metabolism.
- Coadministration of midazolam and atomoxetine was not well tolerated in all 8 enrolled subjects. Two subjects withdrew voluntarily from the study and one was discontinued by the investigator due to adverse events.

- The profile of adverse events occurring after atomoxetine administration was similar to those reported in other studies and corresponds to the expected pharmacology of atomoxetine.
- The QT_c intervals of ECG tracings conducted before and after atomoxetine treatment were not significantly different from baseline.

B4Z-LC-HFBL (Vol. 75-76): ***Evaluation of Atomoxetine-Paroxetine HCL Safety and Pharmacokinetic Interaction in Healthy Subjects***

The objectives of this study were to evaluate
(1) the effect of paroxetine HCl on the steady-state pharmacokinetics of atomoxetine,
(2) the safety and tolerance of coadministration of multiple doses of atomoxetine and paroxetine HCl, and
(3) the effect of atomoxetine HCl on the steady-state PK of paroxetine HCl.

A total of 22 healthy men (17) and women (5) of CYP2D6 EM genotype participated in this study (14 Caucasians, 6 Blacks, 2 Asians).

	Atomoxetine 20 mg q12h (20-mg Capsule Lot CT12232)	Paroxetine 20 mg QD (20-mg tablet, Lot 341/2-9B11)	Placebo (Lot CT12234)
Period 1	Days 1-5 for 9 doses		
Period 2	Days 12-16	Days 1-17	Days 1-11, 17

Table 1. Values of Pharmacokinetic Parameters for Atomoxetine (Mean with %CV)

	C_{max} (ng /ml)	$AUC_{0\text{-}12}$ (μg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)
A-SS with no Parox (P-1 n=21)	184 (36)	0.85 (45)	70.5 (45)	1.0 (0.5-2.0)
Single dose with Parox (P-2, n=15)	302 (33)	2.48 (35)	--	2.0 (1.0-4.0)
A-SS with Parox (P-2, n=14)	690 (37)	5.97 (42)	498 (42)	1.5 (0.5-4.0)
Ratio of LS Mean (90% CI)				
A-SD+P/A-SS	**1.61** (1.45, 1.80)	**2.91** (2.51, 3.39)		
A-SS+P/A-SS	**3.52** (3.15, 3.93)	**6.50** (5.57, 7.58)		
	$t_{1/2}$ (hr)	CL^{ss}/F (L/hr/kg)	V_z/F (L/kg)	
SS with no Paroxetine (P-1 n=21)	4.0 (2.9-7.2)	0.395 (55)	2.20 (50)	
Single dose with Parox (P-2, n=15)	Terminal phase could not be determined.			
SS with Parox (P-2, n=14)	11.0 (4.9-19.6)	0.060 (81)	0.80 (44)	

SS=steady state, A-SD=atomoxetine single dose, A-SS=atomoxetine steady state, P-1, -2=paroxetine at Period 1 or 2.

Table 2. Values of Pharmacokinetic Parameters for *N*-Desmethylatomoxetine

	C_{max} (ng /ml)	$AUC_{0\text{-}12}$ (μg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)
SS with no Parox (P-1 n=21)	6.7 (56)	0.052 (68)	4.2 (69)	1.5 (1.0-4.0)
A-SD with Parox (P-2, n=15)	19.3 (75)	0.164 (71)	--	12.0 (4.0-12.0)
SS with Parox (P-2, n=14)	125.5 (74)	1.32 (73)	109.8 (73)	4.0 (1.0-6.0)
Ratio of LS Mean (90% CI)				
A-SD+P/A-SS	**2.60** (2.04, 3.31)	**2.82** (2.06, 3.85)		
A-SS+P/A-SS	**15.4** 12.0, 19.8)	**21.0** (15.3, 28.7)		

	N-Desmethylatomoxetine		4-Hydroxyatomoxetine	
	$t_{1/2}$ (hr)		T_{max}(hr)	C_{max}(ng/ml)
A-SS with no Paroxetine (P-1 n=19)		6.4 (3.0-16.0)	1.5 (1.0-2.0)	2.1 (37)
A-SD with Parox (P-2, n=15)	–		–	–
A-SS with Parox (P-2, n=14)		19.1 (6.9-34.9)	–	–

SS=steady state, A-SD=atomoxetine single dose, A-SS=atomoxetine steady state, P-1, -2=paroxetine at Period 1 or 2.

Pharmacokinetic Comparison with B4Z-LC-LYAE Study

In order to evaluate the magnitude of the paroxetine inhibition on atomoxetine PK, a comparison with Study LYAE was performed. Study LYAE was a multiple-dose study with doses ranging from 30 to 75 mg twice daily conducted in both EM (n=10) and PM (n=6) subjects. Although the statistical analysis showed differences between the chemically induced PM and genotypic PM subjects, these data suggest the chemically induced PM subjects are fairly similar to genotypic PM subjects.

Table 3. Statistical Comparison of PK Parameters of Atomoxetine between in the Presence of Paroxetine (Study HFBL) and in Poor Metabolizers (Study LYAE)

	Treatment	Geometric Mean	Ratio of GM (90% CI)	p-Value
C^{ss}_{max} (ng/ml)/(mg/kg)	HFBL- A+P	2328	0.72 (0.59, 0.88)	0.014
	LYAE-PM	3240		
CL^{ss}/F (L/hr/kg)	HFBL- A+P	0.0511	1.56 (1.18, 2.06)	0.018
	LYAE-PM	0.0327		

Table 4. Values of Pharmacokinetic Parameters for Paroxetine

	C^{ss}_{max} (ng /ml)	$AUC_{0\text{-}24}$ (µg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)
P^{SS} with Placebo (P-2 n=15)	39.6 (57)	0.698 (65)	29.1 (55)	4.0 (2.0-12.0)
P^{SS} with Atomoxetine (P-2, n=14)	39.5 (63)	0.719 (58)	30.0 (58)	5.0 (4.0-18.0.)
Ratio of LS Mean (90% CI)				
P^{SS} / P^{SS} with Atomoxetine	**0.94** (0.86, 1.03)	**1.002** (0.93, 1.08)		
	$t_{1/2}$ (hr)	CL^{ss}/F (L/hr/kg)	Vz/F (L/kg)	
P^{SS} with Placebo (P-2 n=15)	–	0.689 (104)	–	
P^{SS} with Atomoxetine (P-2, n=14)	23.0 (11.5-54.4)	0.612 (113)	15.4 (66)	

Table 5. Least-Squares Mean Vital Signs (Average over first 5 days of exposure to treatment)

Variable	Atomoxetine	Paroxetine	Combination	A-P	C-P	C-A
Standing HR	87.4	80.2	101.6	0.0001	0.0001	0.0001
Orthostatic HR	19.3	15.1	32.3	0.0001	0.0001	0.0001
Orthostatic SBP	-10.2	-6.9	-16.6	0.0019	0.0001	0.0001
Orthostatic DBP	-1.76	-1.39	-6.24	0.61	0.0001	0.0001

Paroxetine is not known to exhibit cardiovascular effects at the dose given. The pharmacokinetics of paroxetine were unchanged by the presence of atomoxetine in the combination arm. The PD pattern suggests that most of the cardiovascular changes were due to increases in concentrations of atomoxetine and *N*-desmethylatomoxetine. In the previous and ongoing studies, atomoxetine was associated with postural hypotension and HR compensatory increases following single doses greater than 30 mg and in some

subjects, following multiple doses. The magnitude of the changes in this study was larger than would be predicted by atomoxetine concentrations alone. Therefore, a pharmacodynamic interaction involving paroxetine cannot be ruled out as a cause for these larger cardiovascular changes.

Table 6. Comparison of Cardiovascular Variable Least-Squares Means Averaged over Days 4 and 5 between PM Subjects (Study LYAE) and EM Subjects on Paroxetine (Study HFBL)

Variable	Paroxetine	Placebo	p-Value	P+A	A	p-Value
				(20mg BID)	(30 mg BID)	
	HFBL-EM	LYAE-PM	(Baseline)	HFBL-EM	LYAE-PM	(A)
Standing HR	79.5	71.5	0.072	105.6	83.6	0.0001
Orthostatic HR	15.5	8.3	0.089	33.9	18.6	0.0006
Orthostatic SBP	-8.5	-1.0	0.068	-16.4	-15.5	0.82

Summary

- Atomoxetine C_{max}, AUC, and half-life increased approximately 3.5-, 6.5-, and 2.5-fold, respectively, in the presence of paroxetine.
- Pharmacokinetic parameters of paroxetine were not altered when coadministered with atomoxetine.
- Plasma concentrations of atomoxetine after coadministration with paroxetine approached values similar to those expected in CYP2D6 poor metabolizers.
- Combination therapy with paroxetine may result in greater orthostatic tachycardia compared to atomoxetine therapy alone.
- There were no significant increases in the mean Fridericia QT_c intervals associated with atomoxetine or the combination treatment with paroxetine compared to predose mean intervals. There were no individual changes in QT_c interval >30 msec.

B4Z-LC-LYAY (Vol. 76-77): ***Evaluation of Atomoxetine-Fluoxetine Safety and Pharmacokinetic Interaction in Adult Subjects***

The objectives of this study were to evaluate (1) the safety and tolerance of the coadministration of multiple doses of atomoxetine and fluoxetine in healthy adults, and (2) the steady-state pharmacokinetics of atomoxetine in the presence of fluoxetine.

A total of 20 healthy subjects (15 males, 5 females, 17 Caucasians, 1 Black, 1 Hispanic and 1 Native American) participated in this single-blind, 4-period, sequential study of atomoxetine and fluoxetine at steady-state concentrations. Atomoxetine 20 to 150 mg/day were given every 12 hours as 10 mg (Lot CT16165), 25 mg (Lot CT17942)

Table 1. Study Drug Administration

Study Day (AM/PM)	Study Drug	Fluoxetine 20-mg Capsule (Lot 4AC80A)	Atomoxetine Placebo Capsule (Lot CT16162)	Atomoxetine 10 mg Capsule (Lot CT16165)	Atomoxetine 25-mg Capsule (Lot CT17942)
1-7 (AM)	F 60mg+P	3	3		
(PM)	P		3		
8-21 (AM)	F 20mg+P	1	3		
(PM)			3		
22-26 (AM)	F 20mg+A 10mg	1	2	1	
(PM)	A 10mg		2	1	

Study Day (AM/PM)	Study Drug	Fluoxetine 20-mg Capsule (Lot 4AC80A)	Atomoxetine Placebo Capsule (Lot CT16162)	Atomoxetine 10 mg Capsule (Lot CT16165)	Atomoxetine 25-mg Capsule (Lot CT17942)
27-31 (AM)	F 20mg+A 45mg	1		2	1
(PM)	A 45 mg			2	1
32-35 (AM)	F 20mg+A 75mg	1			3
(PM)	A 75mg				3
36 (AM)	F 20mg+A 75mg	1			3
(PM)	P		3		

CYP2D6 phenotype was determined for each subject prestudy and after treatment with fluoxetine to compare the ratio of dextromethorphan and the dextrorphan metabolite as a measure of the conversion of EM to PM status by fluoxetine administration.

Table 2. Pharmacokinetic Parameters for Atomoxetine when Given in Combination with Fluoxetine

	C_{max} (ng /ml)	AUC_{0-12} (μg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)	CL^{ss}/F (L/hr/kg)
Fluoxetine +Atomoxetine 10 mg q12h					
Day 25	328 (38)	2.82 (43)	235 (43)	2.0 (1.0-4.0)	0.0556 (28)
C/(mg/kg)	2291 (28)		1635 (32)		
Day 26	339 (41)	3.03 (45)	253 (45)	2.0 (1.0-12.0)	0.0522 (30)
C/(mg/kg)	2368 (29)		1756 (34)		
Fluoxetine + Atomoxetine 45 mg q12h					
Day 30	1712 (39)	15.1 (45)	1259 (45)	2.0 (1.0-4.00	0.0474 (29)
C/(mg/kg)	2626 (26)		1922 (32)		
Day 31	1686 (35)	14.4 (42)	1201 (42)	2.0 (1.0-8.0)	0.0489 (28)
C/(mg/kg)	2604 (21)		1843 (30)		
Fluoxetine + Atomoxetine 75 mg q12h					
Day 35	2635 (35)	22.7 (42)	1895 (42)	1.0 (1.0-4.0)	0.0513 (26)
C/(mg/kg)	2440 (22)		1739 (28)		
Day 36	2784 (40)	23.2 (43)	1936 (43)	2.0 (1.0-4.0)	0.0506 (28)
C/(mg/kg)	2549 (24)		1774 (29)		

C=concentration, Data resented as mean with CV%, median with range for T_{max}.

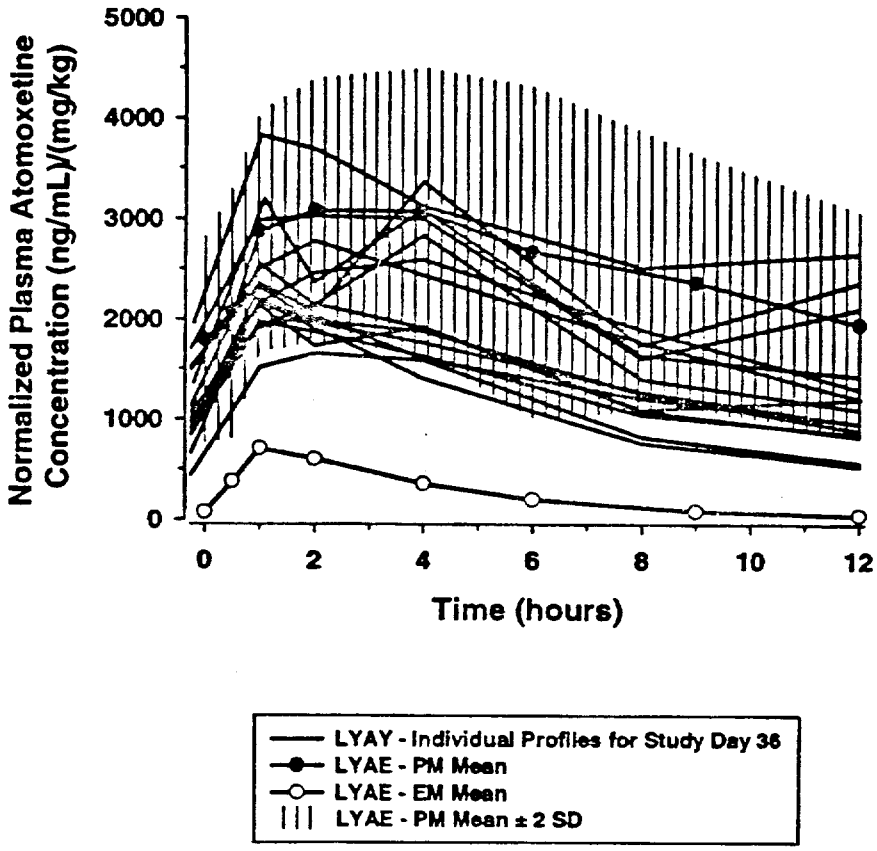
The mean C^{ss}_{max} of atomoxetine was reasonably similar for each of the 2 days sampled at each dose and when normalized for dose and body weight was similar across all doses. Mean AUC and normalized C^{ss}_{avg} were also very consistent over the 2 days studied at each dose. C_{max}, C_{1h} and AUC all increased proportionally with increasing dose. Mean CL^{ss}/F was very similar at all doses with an overall mean of approximately 0.05 L/hr/kg.

Table 3. Dose Proportionality Assessment from Power Model for Atomoxetine PK Coadministered with Fluoxetine

Variable	Power Model Equation	Atomoxetine Dose (mg/kg)	Predicted GM Concentration	Ratio of GM (90% CI)	Conclusion (10-75mg)
C_{1h} (ng/ml)	$2295*D^{1.065}$	0.1361	274	1.14 (1.07, 1.22)	Dose
		1.0207	2346		Proportional
C^{ss}_{max} (ng/ml)	$2558*D^{1.062}$	0.1361	308	1.13 (1.09, 1.18)	Dose
		1.0207	2614		Proportional
AUC_{0-t}(μg.hr/ml)	$21.3*D^{1.046}$	0.1361	2.64	1.10 (1.06, 1.130	Dose
		1.0207	21.77		Proportional

As shown in Figure 1, the individual subject dose and body weight normalized plasma concentrations obtained on Study Day 36 are similar to the mean normalized plasma concentration obtained for previously studied PM subjects (Study B4Z-LC-LYAE). Profiles for approximately 13 of 15 subjects are contained within 2 standard deviations of this mean with most being below the mean. This is in contrast to the data obtained from the EM subjects in the same study (LYAE). Thus EM subjects, pretreated with fluoxetine to approximate steady-state levels of fluoxetine, had atomoxetine plasma concentrations that approximated PM subject concentrations.

Figure 1. Mean Dose-Weight Normalized Plasma Atomoxetine Concentration-Time Profiles for CYP2D6 EM and PM Subjects (LYAE) and Individual Profiles for Subjects Receiving Fluoxetine-Atomoxetine Combination (LYAY)



The subjects in the current study were also administered dextromethorphan after pretreatment with fluoxetine. A comparison of baseline and post-fluoxetine dextromethorphan/dextrophan ratio shows a substantial increase in most subjects (Figure 2), demonstrating the inhibition of CYP2D6 activity by fluoxetine. As shown in Figure 2, dextromethorphan/dextrophan ratio was greater than 0.3 for only 3 subjects, thus dextromethorphan, generally considered a probe drug for CYP2D6 PM status, was a poor predictor of the ability to achieve high atomoxetine plasma concentrations through

fluoxetine CYP2D6 inhibition. There is little correlation between C_{1h} and the dextromethorphan/dextrophan ratio.

Figure 2. Comparison of Baseline (Day 1) and Post-Fluoxetine (Day 37) Dextromethorphan/Dextrorphan Ratio

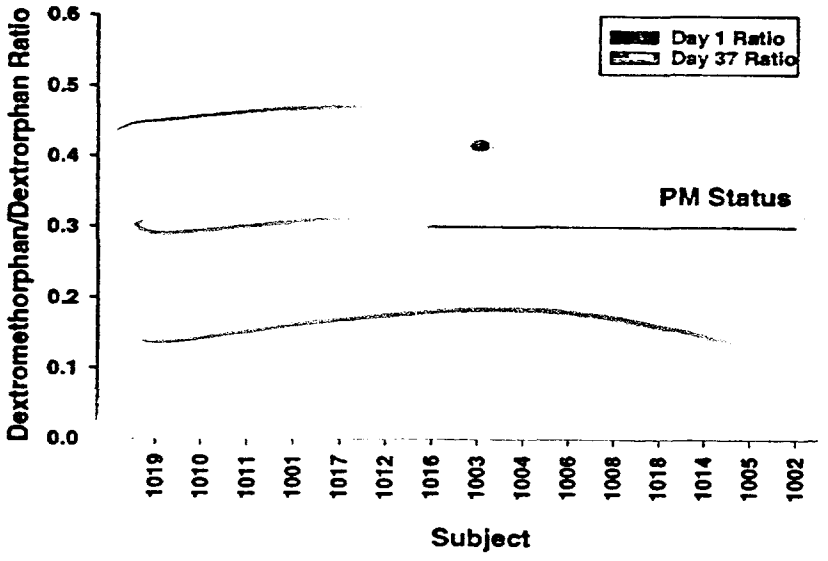


Table 4. Vital Signs in EM Subjects Coadministered Atomoxetine-Fluoxetine Compared to Placebo-Fluoxetine over Time on the Last 2 Days of 3 Atomoxetine Dose Regimens

Atomoxetine Dose (mg)	Least-Squares Mean, Difference from placebo (95% CI of Difference) 0 hr	1 hr	4 hrs
	Standing Heart Rate (BPM)		
Placebo	73.7	73.1	84.5
10	84.8, 11.1 (6.0, 16.2)	80.8, 7.8 (2.7, 12.9)	97.1, 12.7 (7.5, 17.8)
45	73.9, 0.1 (-5.1, 5.3)	78.0, 4.9 (-0.3, 10.1)	78.2, -6.3 (-11.5, -1.1)
75	78.9, 5.2 (-0.1, 10.5)	80.3, 7.2 (1.9, 12.5)	89.9, 5.4 (0.1, 10.7)
	Orthostatic Heart rate (BPM)		
Placebo	11.19.01	5.3	17.3
10	14.6, 3.5 (-2.0, 9.0)	12.0, 6.7 (1.2, 12.2)	21.7, 4.3 (-1.2, 9.8)
45	1.8, -9.2 (-14.8, -3.6)	5.5, 0.1 (-5.5, 5.7)	-0.3, -17.6 (-23.3, -12.0)
75	2.4, -8.7 (-14.4, -3.0)	6.1, 0.8 (-4.9, 6.5)	7.4, -10.0 (-15.7, -4.3)
	Orthostatic Systolic Blood pressure (mm Hg)		
Placebo	-0.2	-0.4	-1.4
10	-5.2, -5.0 (-10.3, 0.3)	-6.4, -6.0 (-11.3, -0.7)	-6.8, -5.4 (-10.7, -0.1)
45	-17.8, -17.6 (-23.0, -12.1)	0.8, 1.2 (-4.3, 6.6)	-3.4, -2.0 (-7.5, 3.4)
75	-4.9, -4.7 (-10.2, 0.9)	-9.9, -9.5 (-15.1, -4.0)	-8.1, -6.7 (-12.1, -1.2)

The largest mean changes in standing heart rate occurred just before (0 hour) and at 1 and 4 hours after administration of the 10-mg atomoxetine dose with changes of 11.1, 7.8, and 12.7 bpm, respectively. Dose escalation of atomoxetine resulted in no further increase in standing heart rates in these same individuals. All mean changes in heart rate were well below clinically relevant tachycardia (100 bpm).

Another prominent pharmacodynamic effect of atomoxetine is the apparent increase in orthostatic heart rate. The data in the table indicate a modest increase in orthostatic heart rate at 1 and 4 hours after the 10-mg twice-daily regimen. Increasing the atomoxetine dose in the study results in only smaller or negative orthostatic heart rate changes, none of which were clinically relevant.

A reduction in orthostatic systolic blood pressure is another prominent pharmacodynamic effect of atomoxetine treatment in PM subjects (LYAE). The data in the table show the modest drop in orthostatic SBP.

The magnitude of the pharmacodynamic changes of these fluoxetine-treated EM subjects are more similar to the pharmacodynamics of EM subjects than PM subjects in study LYAE. Pretreatment with fluoxetine may attenuate the reduction in orthostatic systolic blood pressure ordinarily seen in PM subjects at these doses of atomoxetine. In contrast, paroxetine, which also converted EM subjects to PM-like subjects, had stimulatory effects on the cardiovascular system (study B4Z-LC-HFBL).

Summary

- Steady-state plasma concentrations of atomoxetine after coadministration with fluoxetine in CYP2D6 EM subjects approximated values seen for atomoxetine in CYP2D6 poor metabolizers.
- Fluoxetine-treated EM subjects safely tolerated doses of 10-, 45- and 75-mg atomoxetine taken every 12 hours for up to 5 days. Two subjects discontinued due to syncope, which was the result of factors other than or in addition to atomoxetine pharmacology.
- The frequency of adverse events associated with atomoxetine pharmacology appears to diminish with time in spite of atomoxetine dose escalation in fluoxetine-treated EM subjects.
- There is no relationship between the Fridericia corrected QT interval length and atomoxetine concentration in the dose range 10 to 75 mg twice a day for 5 days in fluoxetine-treated EM subjects. The risk is no different than that of fluoxetine treatment of EM subjects alone.

B4Z-FW-HFBO (Vol. 77-78): ***Evaluation of the Effect of Oral Chronic Atomoxetine Dosing on Hemodynamic Parameters after a Single Intravenous Dose of Salbutamol***

Atomoxetine is a selective noradrenaline enhancer with little or no affinity for other neuronal transporters or neurotransmitter receptor sites. Salbutamol is a β_2-selective adrenoceptor agonist. Because both drugs are associated with hemodynamic effects, this study was designed to investigate possible hemodynamic drug-drug interactions between atomoxetine and salbutamol.

The objectives of this study were to evaluate

(1) the effect of chronic atomoxetine dosing on heart rate changes after a single IV dose of salbutamol, and

(2) the effect of chronic atomoxetine dosing and a single IV dose of salbutamol on systemic vascular resistance and diastolic/systolic blood pressure changes.

This was a double-blind, double-dummy, randomized, 2-period, Latin-square cross-over design study with restricted sequences. Twelve healthy male subjects (11 Chinese and 2 Indian, all EM metabolizers) received for 5 days either atomoxetine 120 mg/day (20-mg capsule, Lot CT16058, given 3 capsules twice daily) or placebo (Lot CT16062). In each of the 5-day periods, the subjects received an IV infusion of salbutamol (5 ug/min over 2 hours) or placebo (Dextrose 5% Lot B0599CE) on the 1st, 3rd and 5th day. Two 5-day periods of either atomoxetine or placebo was separated by a minimum of 14 days between study periods.

After administration of atomoxetine/placebo on the 3rd and 5th day of each study period, blood samples were collected for plasma concentration measurement at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, and 12 hours postdose.

Table 1. Values of Pharmacokinetic Parameters for Atomoxetine

	C^{ss}_{max} (ng /ml)	$AUC_{0\text{-}12}$ (μg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)	$t_{1/2}$ (hr)
Atom alone (n=12)	479 (30)	2.13 (36)	177 (36)	1.0 (0.5-4.0)	2.3 (1.8-2.9)
Atom+Sal (n=13)	412 (34)	2.08 (36)	174 (36)	1.0 (0.5-4.0)	2.3 (1.9-3.2)
Ratio of LS Mean (90% CI)					
Atom+Sal /Atom alone	**0.86** (0.72, 1.02)	**0.98** (0.91, 1.05)	**0.98** (0.91, 1.05)		
		CL^{ss}/F (L/hr/kg)	Vz/F (L/kg)		
Atomoxetine alone (n=12)		0.461 (24)	1.53 (21)		
Atomoxetine+Sal (n=13)		0.480 (30)	1.54 (27)		

Table 2. Values of Pharmacokinetic Parameters for *N*-Desmethylatomoxetine

	C^{ss}_{max} (ng /ml)	$AUC_{0\text{-}12}$ (μg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)	$t_{1/2}$ (hr)
Atom alone (n=12)	11.2 (39)	0.072 (50)	6.0 (50)	2.0 (1.0-6.0)	3.4 (2.4-4.5)
Atom+Sal (n=13)	8.7 (51)	0.059 (61)	5.1 (57)	4.0 (1.0-4.0)	3.8 (2.8-5.3)
Ratio of LS Mean (90% CI)					
Atom+Sal /Atom alone	**0.81** (0.71, 0.92)	**0.86** (0.78, 0.95)	**0.90** (0.831, 0.97)		

Table 3. Values of Pharmacokinetic Parameters for 4-Hydroxyatomoxetine

	C^{ss}_{max} (ng /ml)	$AUC_{0\text{-}12}$ (μg.hr/ml)	C^{ss}_{avg} (ng /ml)	T_{max} (hr)	$t_{1/2}$ (hr)
Atom alone (n=12)	9.3 (46)	0.057 (27)	4.7 (27)	1.0 (1.0-6.0)	4.8 (3.7-6.5)
Atom+Sal (n=13)	7.2 (18)	0.052 (22)	4.4 (190	2.0 (1.0-4.0)	5.5 (3.7-10.2)
Ratio of LS Mean (90% CI)					
Atom+Sal /Atom alone	**0.83** (0.69, 1.00)	**0.92** (0.85, 0.98)	**0.94** (0.88, 1.00)		

A synergistic effect of salbutamol and atomoxetine was observed at 45 min and 2 hr time point with a 12 and 10 bpm increase, respectively. Chronic atomoxetine dosing had a significant effect on increasing the HR effect of an IV infusion of salbutamol. The increase in heart rate observed with either IV infusion of salbutamol or chronic atomoxetine dosing are consistent with previous reported results. Comparing single and

chronic doses of atomoxetine with IV salbutamol, acute dosing resulted in a greater increase in heart rate. This suggests that there may be adaptation to the heart rate response with prolonged atomoxetine dosing.

Atomoxetine alone increased SBP from 1 hr to 2 hr 30 min after dosing, and salbutamol alone increased SBP up to four hours after the end of infusion. The effect of the combination of drugs was additive. Chronic atomoxetine alone increased DBP from 1 hr to 3 hr 30 min after dosing, whereas salbutamol alone had no effect. The effect of the combination of drugs on DBP was similar to that of atomoxetine alone. Salbutamol alone showed a small but statistically significant increase of 12 msec in $QT_{C(F)}$ interval 1.5 hours after dosing. Salbutamol has been shown in some previous studies to cause QT_c prolongation. Atomoxetine alone also showed a small (7 msec) increase in QT_c interval at 1.5 hours after dosing but only on chronic treatment.

Summary

- At 60-mg twice daily doses, atomoxetine had limited additional effects on the cardiovascular changes attributable to salbutamol infusion, the most prominent of which was elevation of heart rate. The incremental clinical impact of these changes was small compared to the effect of IV salbutamol. With inhaled β-2 agonists, one may expect these effects to be even less.
- Administration of the usual therapeutic dose of salbutamol intravenously with oral atomoxetine had no effect on the steady-state pharmacokinetics of atomoxetine, or its metabolites, 4-hydroxyatomoxetine and N-desmethylatomoxetine.
- Chronic dosing of atomoxetine with single doses of IV salbutamol was not associated with $QT_{c(F)}$ interval prolongation or other clinically important ECG changes.
- Chronic dosing of atomoxetine was generally well tolerated in the Asian population studied.

B4Z-LC-LYAP (Vol. 78): ***Evaluation of the Effect of Oral Chronic Atomoxetine Dosing on Hemodynamic Parameters in the Presence of Oral Methylphenidate***

Methylphenidate (MP) is an amphetamine-like psychostimulant that releases dopamine from reserpine-sensitive storage pools in the CNS presynaptic neuron, which blocks dopamine reuptake, and which has been shown to increase plasma adrenaline levels (but not noradrenaline levels), with hemodynamic changes occurring in parallel to the plasma catecholamine level. It is currently the drug of choice in the treatment of ADHD. As expected for a sympathomimetic drug, undesirable cardiovascular effects of MP include tachycardia. Several studies, in patients with ADHD as well as in healthy subjects, have shown significant increase in heart rate after administration of MP in both pediatric/adolescent and adult populations.
Atomoxetine is associated with hemodynamic effects. According to the sponsor, statistically, but not clinically significant increases in mean standing diastolic blood pressure and mean heart rate were found in many but not all of the placebo-controlled studies of atomoxetine in adults with depression. Atomoxetine has been shown to enhance the pressor response to exogenous intravenous noradrenaline. The effects of atomoxetine on endogenous plasma catecholamine levels have not been assessed.

The objective of this study were

(1) to evaluate the effects on heart rate of acute and steady-state dosing of atomoxetine and methylphenidate (MP) alone and in combination in healthy subjects,

(2) to compare the effects of acute and steady-state dosing with atomoxetine in the presence of steady-state MP and of acute and steady-state dosing with MP in the presence of steady-state atomoxetine, and

(3) to evaluate the effect of chronic atomoxetine dosing in the presence and absence of MP on supine and standing diastolic and systolic blood pressure changes, on systemic vascular resistance and on plasma catecholamine levels.

This study was a randomized, double-blind, placebo-controlled, three-period design in 12 healthy young male Asian subjects. All subjects were identified as being extensive metabolizers (EM) of CYP2D6 substrates by genotyping with a valid assay. The subjects each received 5 days of MP 60 mg (as 10 mg capsules, Lot CT17384) QD orally at 8 am in one period, 5 days of placebo administration in a second period, and 5 days of atomoxetine 60 mg (as 20 mg capsules, Lot CT17380) BID orally at 8 am and 8 pm in the third period. The order of these periods was randomized. On study Day 3, 4 and 5 of each period, the subjects were administered other study drugs as shown in the following table:

Table 1. Dosing Schedule

Period	Day 1	Day 2	Day 3	Day 4	Day5
1 (Methylphen.)	M	M	M	M	M
	P	P	P/A	P/A	P/A
2 (Placebo)	P	P	P	P	P
	P	P	P/M/A	P/M/A	P/M/A
3 (Atomox.)	A	A	A	A	A
	P	P	P/M	P/M	P/M

M=methylphenidate, A=atomoxetine, P=placebo

After administration of the morning dose of methylphenidate, placebo or atomoxetine on Study Day 1, 3, and 5 of each study period, supine heart rate, blood pressure and systemic vascular resistance (SVR) measurements were obtained over 8 hours. There was a minimum of 7 and a maximum of 17 days between each study period.

Table 2. Heart Rate Effects

Time (h) 0	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0
Comparison of Mean Heart Rate at Chronic Dosing of Atomoxetine and Methylphenidate										
M vs. P		**	**	**	**	**	**	**	*	
A vs. P				*						
AM vs. P		**	*	**	**	**	**	**	**	
AM vs. M										
Comparison of Mean Heart Rate at Acute Dosing of Atomoxetine and Methylphenidate										
M vs. P	**	**	*	**	**	**	**	**	**	**
A vs. P	**	**		**	**	**	*	*		
A vs. M					**		**	**	**	**
Comparison of Mean Heart Rate at Chronic Dosing of Methylphenidate										
AM vs. P	**	**	*	*	**	**	**	**		*
AM vs. A			*		*	**	**	*		
AM vs. A							*			

*p<0.05, **p<0.01, M=methylphenidate, A=atomoxetine, P=placebo, AM=atomoxetine + methylphenidate

Table 3. Blood Pressure Effect

Time (h) 0	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0
Comparison of Mean Systolic Blood Pressure at Chronic Dosing of Atomoxetine and Methylphenidate										
M vs. P *	*		*	**	**	**	**			
A vs. P *										
AM vs.P*	*	*	**	**	**	**	**	*		
AM vs. M										
Comparison of Mean Diastolic Blood Pressure at Chronic Dosing of Atomoxetine and Methylphenidate										
M vs. P				*	*	**				
A vs. P **										
AM vs.P*	*	**		*	**	**		**		
AM vs. M								*		

*p<0.05, **p<0.01, M=methylphenidate, A=atomoxetine, P=placebo, AM=atomoxetine + methylphenidate

Plasma Catecholamines: Chronic dosing of atomoxetine had no effect on plasma adrenaline. Methylphenidate alone increased adrenaline levels from 2 hr to 8 hr, whilst MP plus atomoxetine increased plasma adrenaline levels from 3 hr to 4 hr. There was no apparent incremental effect of atomoxetine on MP's effect on adrenaline levels. For plasma noradrenaline levels, the effects of MP alone, atomoxetine alone and the combination were not significant when compared to placebo.

Summary

- Acute and chronic atomoxetine 60 mg twice daily resulted in a transient increase in the heart rate. Acute atomoxetine also caused a transient increase in the systolic and diastolic blood pressure whereas chronic atomoxetine had no effect on blood pressure.
- Acute and chronic MP 60-mg once daily resulted in a transient increase in the heart rate, systolic and diastolic blood pressure.
- Acute and chronic atomoxetine 60 mg twice daily dosing had markedly less cardiovascular effects than acute and chronic MP given 60 mg a day.
- In combination, there was no incremental effect of atomoxetine on the cardiovascular changes attributed to MP in healthy CYP2D6 EM Asian subjects.

- MP's cardiovascular effects may be due to the observed increase in plasma adrenaline concentrations, which was not seen following atomoxetine dosing.
- Atomoxetine alone or in combination with acute or chronic dosing of MP was safe and well tolerated in the healthy CYP2D6 EM Asian population studied.

B4Z-EW-E002 (Vol. 79): ***A Study to Determine the Psychomotor Effect of Ethanol in Combination with Atomoxetine in Subjects Classified as "Extensive" or "Poor" Metabolizers of Atomoxetine***

Atomoxetine has been shown to have clinically effective antidepressant activity in man. In vitro studies in rat brain synaptosomes show it to inhibit norepinephrine uptake. It appears to have no anticholinergic activity common to the tricyclic antidepressants. The response to ethanol given concomitantly with a centrally active drug, such as atomoxetine, needs to be evaluated with the possible differential effects in 'poor' and 'extensive' metabolizers (PM and EM) taken into account.
The objectives of this study were to evaluate the effects of ethanol when given to healthy subjects and to compare those effects after pretreatment with atomoxetine or placebo, in EM and PM subjects. This was a randomized, double-blind, crossover study in 12 healthy Caucasian subjects (6 males and 6 females) with known CYP2D6 phenotype based on debrisoquine metabolic ratio. Dosing schedule is shown below:

Table 1. Dosing Schedule

Treatment	Multiple Dose (Days 1-5) At 16:00, within 5 minutes with the last dose of atomoxetine or placebo	Single Dose (Day 5)
1	Atomoxetine 40 mg BID (capsules, Lot CT9343-8A)	Alcohol 0.6 mg/kg (2 ml/kg)
2	Match Placebo (Lot CT9344-8A)	Alcohol 0.6 mg/kg (2 ml/kg)

Blood samples were collected prior to ethanol dosing and at 0.75, 1, 1.5, 2, 2.5, 3, 4, and 14 hours after ethanol dosing for determination of atomoxetine and *N*-desmethylatomoxetine plasma concentrations by —— assay over the concentration range of 5 to 700 ng/ml, and for plasma ethanol concentrations by —— assay over the concentration range of 10 to 300 mg/dL. Blood samples were also taken on Study Days 3, 8, 11 and 16 for estimation of atomoxetine and N-desmethylatomoxetine concentrations. Pharmacodynamic measurements included Mood Rate Scale, Continuous Attention, Salford Tracking Test, Choice Reaction Time, Critical Flicker Fusion Frequency, and Word List Recall. Safety monitoring included adverse events, clinical biochemistry and hematology.

Table 2. Atomoxetine Plasma Concentrations after Administration of Ethanol

Time after Ethanol Dose	0 h	1 h	2 h	4 h	14 h
C (ng/ml) EM, N=6	39.6	242.1	279.4	268.1	22.4
C (ng/ml) PM, N=6	1402.1	1435.0	1817.5	2050.8	1287.3

Summary

- Based on the psychomotor and cognitive tests used in this study, there is no evidence that PM subjects are likely to have a greater pharmacodynamic interaction with

ethanol than EM subjects. Atomoxetine did not differentiate from placebo in the absence of ethanol.

- Pretreatment with 40 mg atomoxetine BID for 5 days in EM and PM subjects when combined with ethanol does not increase or reduce the intoxicating effects of ethanol.
- Atomoxetine was well tolerated in both EM and PM subjects, although a greater incidence of adverse events was reported in PM subjects. No difference in tolerability was seen in combination with ethanol.

Population PK Study Reports (Vol. 79-80)

Population Pharmacokinetic Analysis of Atomoxetine in Pediatric Patients

The objective of this study was to characterize atomoxetine pharmacokinetics, its variability, and the potential influence of patient factors such as age, weight, gender, and cytochrome P450 2D6 (CYP2D6) genotype on atomoxetine pharmacokinetics in the target population, pediatric patients diagnosed with ADHD.

Studies involved - B4Z-MC-HFBC, -HFBD, -HFBE, -HFBF, and –HFBK
Number of Patients - Male 349, female 71, total 420 healthy pediatric patients who met diagnostic criteria for DSM-IV ADHD
Duration of Treatment - For the patients who contributed plasma-concentration data to the analysis, the mean duration of treatment was 131 days with a range of 9 to 616 days.
Criteria for Evaluation - Sparse and serial blood samples were obtained following atomoxetine treatment for population pharmacokinetic analysis. A total of 2354 samples were used in the analysis.

Pharmacokinetic Methods

A population pharmacokinetic model was developed using the combined data from 5 pediatric studies. A one-compartment model with first-order absorption and elimination was selected as the base structural model. Patient factors with clinical and demographic significance were identified *a priori* and evaluated on parameters of the pharmacokinetic model. Patient factors were tested individually using a base model that incorporated poor metabolizer (PM) status and body weight. After a full model was developed which included all potentially significant patient factors, backward selection criteria was used to develop the final model. The final pharmacokinetic model was validated using parameter sensitivity, leverage analysis, and external validation.

Genotyping

NDA from whole blood samples were isolated and purified and analyzed for CYP2D6 genotype using a validated PCR (polynucleotide chain reaction) method. CYP2D6 genotype was evaluated by testing the *3, *4, *5, *6, *7, and *8 alleles. If patients were homozygous for any combination of these alleles, a PM genotype was assigned;

otherwise, an EM genotype was assigned. Gene duplication was also evaluated and used to designate the ultra-rapid metabolizer (UM) genotype.

Dose and Formulation

The same 5-, 10- and 20-mg capsules were used across all studies. Patients were instructed to take atomoxetine twice daily without regard to meals. Patients with PM genotype in Study HFBE and Study HFBF, were allowed once daily dosing regimen.

PK Blood Samples and Analytes

Study	Sampling Time or Day
HFBC	at 1, 2, 4, 8, 12 and 24 hours post a single dose (10 mg) and multiple dose (20-45 mg BID)
	A single PK sample was collected for the following studies:
HFBD	at Visits 5, 8, 10, 12
HFBE	at Visits 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28
HFBF	at Visits 5, 10, 11, 12, 14, 15, 16, 18, 20, 22, 24, 25
HFBK	at Visits 5, 8, 10, 12 and early study discontinuation.

The population pharmacokinetic analysis was limited to the parent compound, atomoxetine. The two primary circulating metabolites, N-desmethylatomoxetine and 4-hydroxyatomoxetine, were analyzed graphically. The metabolites were not incorporated into the model since they circulate in plasma at relatively low levels compared to atomoxetine and because 26% of the active metabolite 4-hydroxyatomoxetine concentrations measured were below the limit of quantitation.

Table 1. Date Available for Population Pharmacokinetic Analysis Studies

Study	HFBC	HFBD	HFBE	HFBF	HFBK	Total
Patients	25	60	163	60	112	420
Concentrations	220	185	813	209	927	2354

Table 2. Summary Statistics for Categorical Covariates

Demographic	Category (n with % of total)		
Genotype	EM n=384 (91.4%)	UM n=11 (2.6%)	PM n=25 (6.0%)
Gender	Male n=349 (83.1%)		Female n=71 (16.9%)
Age group	<12 yr n=351 (83.6%)		≥12 yr n=69 (16.4%)
Ethnic origin	Caucasian n=342 (81.4%)	African n=36 (8.6%)	East Asian n=2 (0.5%)
	West Asian n=3 (0.7%)	Hispanic n=23 (5.5%)	Other n=14 (3.3%)
Caffeine consumer	No n=117 (27.9%)	Yes n=155 (36.9%)	Unknown n=148 (35.2%)
Food within 1 hr of dose	No n=417 (17.7%)	Yes n=1892 (80.4%)	Unknown n=45 (1.9%)

Covariates Influence on PK Parameters

Effect of Potential Covariates

Genotype

Table 1. Predicted Steady-State Atomoxetine after a 1 mg/kg Twice-Daily Dosing Regimen

Genotype	C^{SS}_{max} (ng/ml)	$AUC_{0-\tau}$ (μg.hr/ml)
EM	325	2.07
UM	248	1.13
PM	1665	18.39

Body Weight

Table 2. Effect of Body Weight on Clearance and Volume of Distribution Estimates

Weight[a] (kg)	Population Estimate CL/F (L/hr)	Weight-normalized CL/F (L/hr/kg)	Population Estimate V/F (L)	Weight-normalized V/F (L/kg)
23	12.2	0.53	50.5	2.2
35.3	17.4	0.49	75.8	2.1
125	49.9	0.40	251.0	2.0

[a]Body weights are the minimum, median and maximum of the population in this analysis.

Food

The final model predicted a decrease in the rate of absorption when atomoxetine is administered with food, resulting in a 9% lower C_{max} value. This small change in C_{max} value is not considered to be clinically significant. This minimum change (9%) is lower than the C_{max} intrasubject variability of 22% observed in adult study (B4Z-LC-HFBJ: Single and Multiple Dose Studies in Adults of Known CYP2D6 Status).

Albumin

The final model predicted a decrease in atomoxetine CL/F with an increase in albumin concentration. While linear relationship was established, the range of albumin values in the patient population is very narrow resulting in very little difference in atomoxetine clearance values. This change is considered clinically insignificant.

Lack of Effect of Potential Covariates

Dose - Dose was evaluated as a potential covariate on CL/F, V/F and Ka and was not retained in the final model, which indicated that dose was not significant covariate. Therefore, atomoxetine pharmacokinetics in pediatric patients are linear across the dose range evaluated (5 to 45 mg administered twice daily).

Age and Gender – These two factors were evaluated separately and in combination. An interaction between these two factors was also evaluated and separate parameters for four subgroups were estimated: males <12 yr, males≥12 yr, females<12 yr, and females≥12 yr. The analyses revealed no influence on atomoxetine disposition by age or gender alone or in combination.

Ethnic Groups – Based on the ethnic groups represented in these studies, patients of Caucasian, Hispanic, and African descent had no statistically significant difference in atomoxetine pharmacokinetics.

Hepatic Function – Hepatic function as reflected by total bilirubin and ALT were not associated with changes in atomoxetine pharmacokinetics. The range of total bilirubin and ALT values observed in this analysis are representative of those for normal healthy children.

Caffeine – Caffeine consumption was not associated with changes in atomoxetine pharmacokinetics.

Summary

- Atomoxetine pharmacokinetics in pediatric patients are linear across the evaluated dose range of 5 to 45 mg administered twice daily.
- Pediatric poor metabolizer (PM) patients have a 9-fold lower mean clearance estimate compared to extensive metabolizer (EM) patients.
- Pediatric ultra-rapid (UM) patients have a 2-fold higher mean clearance estimate compared to EM patients. UM patients are not distinguishable from EMs based on the distribution of clearances in the 2 populations.
- Atomoxetine clearance and volume of distribution increased nearly proportionally to increased body weight (range 23 to 125 kg), indicating that dosing based on body weight is appropriate.
- Atomoxetine dosing based on body weight provides a more narrow and predictable range of exposures in the patient population.
- Age does not influence atomoxetine disposition (range 7 to 15 years).
- Based on the ethnic groups represented in these studies, patients of Caucasian, Hispanic, and African descent had no statistically significant difference in atomoxetine pharmacokinetics.
- The observed slight decrease in atomoxetine clearance with increasing albumin concentration is not clinically significant.
- Hepatic function as reflected by total bilirubin and ALT, within the ranges for normal healthy children, are not associated with changes in atomoxetine pharmacokinetics.
- Administration of atomoxetine within an hour after food (self-reported) had a decrease in the rate of absorption resulting in a 9% lower Cmax, which is considered clinically insignificant.
- Caffeine consumption was not associated with changes in atomoxetine pharmacokinetics.

Population PK/PD (Vol. 80-85)

B4Z-MC-LYAC: ***Population PK/PD Data in Clinical Study Report LYAC.***

This was a phase 3 randomized, double-blind, placebo-controlled efficacy and safety comparison of fixed-dose ranges (mg/kg/day) of atomoxetine with placebo in children and adolescent outpatients with ADHD, aged 8 to 18 years.

The primary objectives of this study was to test the hypothesis that acute treatment for approximately 8 weeks with atomoxetine, either 1.2 mg/kg/day or 1.8 mg/kg/day, would be statistically significantly more effective in reducing the severity of attention-deficit/hyperactivity disorder (ADHD) symptoms than placebo. A total of 213 patients (male 152, female 61) received atomoxetine treatment and 84 patients (male 60, female 24) received placebo treatment.

All patients provided blood samples for assessment of plasma concentrations and PK of atomoxetine and its metabolites. A population pharmacokinetic analysis using NONMEM was performed to analyze the atomoxetine concentration data and obtain an individual atomoxetine clearance estimate for each patient. The clearance estimates were then used to estimate $AUC_{0-\tau}$ for each patient. The relationship between $AUC_{0-\tau}$ and the primary efficacy measure was evaluated.

Study Period I: washout, screening, and assessment from Day 12 to Day 28, Visits 1-3,
Study Period II: Acute treatment, approximately 8-week, Visits 4-9
Study Period III: the nonresponder assessment period, Study Period IV: the long-term responder extension, and Study Period V: the discontinuation period are not discussed in this report.

At Visit 3, patients were randomized in a 2:1:2:2 ratio to placebo or atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day groups. During Study Period II, all patients were administered study drug BID, 1 dose before school and 1 dose after school. At all visits, each patient's use of concomitant medications and study drug compliance were reviewed, weight and vital signs were measured. Patients were assessed for response to treatment at Visit 9. Patients whose CGI-ADHD-S score was at most 2 were considered responders.

In a previous open-label study, B4Z-MC-HFBE, efficacy was not different between patients dosed at higher (up to 1.6 to 2.0 mg/kg/day) and moderate (approximately 1.0 to 1.2 mg/kg/day) dosages. Based on this information, 1.2 mg/kg/day and 1.8 mg/kg/day were selected for the intermediate and higher dose groups in this study. A lower-dose arm was also included (0.5 mg/kg/day) to determine the threshold for the lowest effective dose.

CYP2D6 Metabolic Status Information for Dosage Adjustments

Investigators were blinded to CYP2D6 metabolic status but were provided a sealed envelope containing this information for each patient. These envelopes were opened only in case of a medical emergency. Any opening of these envelopes during the course of the study was documented. The rationale for blinding was to ensure that assessments of efficacy and tolerability were unbiased by knowledge of metabolic status.

Patient Disposition by Visit-Study Period II Randomized Patients (B4Z-MC-LYAC)

Visit (Week)	Placebo (N)	Atomoxetine 0.5 mg/kg/day (N)	Atomoxetine 1.2 mg/kg/day (N)	Atomoxetine 1.8 mg/kg/day (N)
3 (0)	83	44	84	84
4 (1)	81	43	81	78
5 (2)	81	39	76	76
6 (3)	80	39	75	76
7 (4)	78	39	70	75
8 (6)	75	36	69	74
9 (8)	72	34	69	73
CYP2D6 PM	6	3	4	4

Primary Efficacy Analysis

Each of the 4 dosing groups showed an overall improvement (decrease) from baseline in mean ADHDRS-IV Parent:Inv total score. Observed mean reduction from baseline were –5.8, -9.9, -13.6, and –13.5 for placebo, atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day, respectively. These improvements were statistically significantly larger for the atomoxetine intermediate and high doses than for placebo (adjusted p-values <0.001). The mean improvements seen for the atomoxetine low dose group, while numerically better than those seen for the placebo group, were not statistically significant.

Table 1. ADHD Rating Scale IV-Parent Version: Investigator Score (ADHDRS-IV-Parent:Inv) Total Score Change from Baseline to Endpoint – Study Period II B4Z-MC-LYAC (8-17 yrs)

Treatment	n	Baseline	Endpoint	Change	p-Value vs. Placebo	
ADHDRS-IV-Parent:Inv Total Score (primary)					Adj.	(Unadj.)
Placebo	83 (6)*	38.3±8.9	32.5±13.8	**-5.8±10.9**		
0.5 mg/kg/day	43 (3)	40.2±9.6	30.3±15.2	**-9.9±14.6**	(0.155)	
1.2 mg/kg/day	84 (4)	39.2±9.2	25.5±13.8	**-13.6±14.0**	<0.001	(<0.001)
1.8 mg/kg/day	82 (4)	39.7±8.7	26.2±14.8	**-13.5±14.8**	<0.001	(<0.001)
Inattention Subscale (secondary)					Within	Vs. Placebo
Placebo	83	21.4±4.0	18.85±6.7	**-2.5±6.6**	0.002	
0.5 mg/kg/day	43	22.4±3.6	17.3±7.6	**-5.1±7.5**	<0.001	0.085
1.2 mg/kg/day	84	22.2±4.0	15.2±8.2	**-7.0±8.1**	<0.001	<0.001
1.8 mg/kg/day	82	22.1±4.2	15.3±8.4	**-6.8±7.9**	<0.001	<0.001
Hyperactivity/Impulsive Subscore (secondary)						
Placebo	83	16.9±6.6	13.7±8.4	**-3.2±5.6**	<0.001	
0.5 mg/kg/day	43	17.8±7.4	13.0±9.2	**-4.8±7.9**	<0.001	0.234
1.2 mg/kg/day	84	16.9±7.1	10.3±7.2	**-6.6±7.1**	<0.001	<0.001
1.8 mg/kg/day	82	17.6±6.2	10.9±7.7	**-6.7±7.5**	<0.001	<0.001

*Poor metabolizer

Assessment of Dose Response

A statistically significant linear component to dose response in ADHDRS-IV Parent:Inv total score was noted indicating some increase in efficacy with increasing dose. While no statistically significantly significant nonlinear components to dose response were seen, there is indication that the relationship between dose and efficacy is not purely linear. In fact, the numerical improvements seen for the atomoxetine 1.2 mg/kg/day group were slightly better than those seen for the 1.8 mg/kg/day group, suggesting a possible leveling off of efficacy beyond atomoxetine 1.2 mg/kg/day.

Population Analysis of Exposure-Response

The final data set used to conduct the population pharmacokinetic analysis contained 682 concentrations from 189 patients. All samples were collected at scheduled sampling Visits 6, 7, 8, or 9. The number of blood samples collected per patient ranged from 1 to 4. There were 7 patients with a single concentration. Seventy-five percent of the patients had blood samples collected at all 4 scheduled sampling visits. There were 171 EM, 8 UM, and 10 PM patients included in this analysis. The model used to analyze the data was developed in the combined analysis of studies HFBC/HFBD/HFBE/HFBF/HFBK.

Relationship between Drug Concentration and Response

Scatter plots of the change from baseline to endpoint in ADHDRS-IV Parent:Inv total score and atomoxetine AUC are provided. Only atomoxetine patients with at least 2 plasma level measurements are included. Pearson's correlation coefficients between response and AUC was –0.438 and –0.068 for PMs and EMs, respectively. These low correlation values coupled with the previously observed efficacy results by dosing group suggest that the relationship between AUC and efficacy, like the relationship between dosing group and efficacy, cannot be explained by a simple linear relationship.

A nonlinear model (inhibitory E_{max} model) was fit to the observed AUC and change from baseline ADHDRS-IV Parent:Inv total scores data to further explore the relationship between efficacy and AUC. Patients randomized to placebo were used in this analysis by assigning an AUC of zero. The modeling was limited to EM data since there was minimal amount of PM data.

The resulting fit of this model suggests that the expected maximal improvement from baseline would be –17.4 (compared to –6.2 for 8 weeks of placebo dosing). This suggests a net overall maximum benefit over placebo of –11.2. At the observed median AUCs for the atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day groups, 62%, 78% and 85% of the maximum improvement over baseline would be expected. Therefore, there appears to be a relationship between systemic exposure and efficacy that is similar to the relationship between dose and efficacy.

Summary

- Symptom reduction in both the 1.2 mg/kg/day and 1.8 mg/kg/day groups was superior to that observed in the placebo group on the primary outcome efficacy measure as well as secondary outcome measures.
- The 0.5 mg/kg/day group was not statistically significantly different from placebo as assessed by the ADHDRS-IV-Parent:Inv, but did show evidence of superiority to placebo on a number of secondary measures, including parent report (for example, Conners' Parent Rating Scale), even though fewer patients were randomized to 0.5 mg/kg/day (by design).
- The data strongly suggested a graded dose-response, with maximal symptom reduction at 1.2 mg/kg/day and no further benefit related to higher 1.8 mg/kg/day dose.
- Outcomes in adolescents were similar to those in children on the primary outcome measure.
- These data provide further support for the efficacy of atomoxetine for treating ADHD, information that will guide dosing, and evidence of a graded dose response related to atomoxetine treatment.
- No difference in the adverse event profile was detected when patients were categorized by gender, age, and cytochrome P450 2D6 (CYP2D6) genotype.
- Laboratory data did not reveal any pattern suggesting abnormalities associated with atomoxetine administration.
- Analysis of vital signs data showed a statistically significant dose-related increase in diastolic blood pressure.

- Mean height increases were less for all doses of atomoxetine than for placebo, but no statistical evidence of a dose relationship was seen.
- Weight changes were clearly dose-related for all doses versus placebo. At the 2 higher atomoxetine doses, a mean weight loss was observed that was significantly different from the weight gain observed on placebo.
- Data also showed a statistically significant dose-related mean heart rate increase that was confirmed by analysis of ECG data; however, no evidence of an effect on cardiac repolarization was seen, as measured by QT_c interval.

Assay Description and Validation Reports (Vol. 85-88)

The individual bioanalytical method used for the measurement of atomoxetine (LY404363), 4-hydroxyatomoxetine (LY424478) and *N*-desmethylyatomoxetine (LY137877) concentrations in clinical plasma and urine samples, and validation reports are provided. Proper quality samples were included in each run. Long term storage stability of atomoxetine, LY424478 and LY137877 in plasma and urine were tested and they were stable at - . The analytical methods have been validated for linearity, precision, accuracy, recovery, sensitivity and stability. They are acceptable.

Drug Formulation Development

Both capsule and tablet dosage forms were considered for atomoxetine hydrochloride; a hard gelatin capsule has been chosen to be marketed and provides a convenient and stable dosage form. Capsules of the same formulation as intended for marketing have been used in clinical trials. For blinded studies, different capsule shell colors were used than those intended for marketing. Additionally, 2.5 mg and 20 mg capsules using similar formulas have been used in clinical trials.

The formulations for the six capsule atomoxetine strengths are shown in Table 1. The 5, 10, 18, 25, and 40 mg capsules have the same target fill weight (230 mg), containing the same amount of dimethicone, and differ only in the amount of atomoxetine hydrochloride and pregelatinized starch in the formulation. The 60 mg strength has a higher target fill weight (310 mg). All strengths are differentiated by capsule shell color and identification imprint, and the 60 mg strength is also differentiated by a larger capsule size.

Table 1. Capsules Atomoxetine Formulations

Ingredient Strength	Atomoxetine Hydrochloride	Dimethicone NF	Pregelatinized Starch, NF *mg/cap (%)*	Target Fill Weight	Capsule Size
5 mg	5.71 (2.5%)	1.15 (0.5%)	223.14 (97.0%)	230 (100.0%)	3
10 mg	11.43 (5.0%)	1.15 (0.5%)	217.42 (94.5)	230 (100.0%)	3
18 mg	20.57 (8.9%)	1.15 (0.5%)	208.28 (90.6)	230 (100.0%)	3
25 mg	28.57 (12.4%)	1.15 (0.5%)	200.28 (87.1%)	230 (100.0%)	3
40 mg	45.71 9(19.9%)	1.15 (0.5%)	183.14 (79.6%)	230 (100.0%)	3
60 mg	68.56 (22.1%)	1.55 (0.5%)	239.89 (77.4%)	310 (100.0%)	2

Biowaiver Request

The bioequivalence of the 40-mg and 60-mg market-image formulations to clinical capsule formulations was established. The sponsor is requesting a waiver of *in vivo* bioequivalence studies for the lower strengths of atomoxetine capsules (5-, 10-, 18- and 25-mg) which are proportionally similar to the atomoxetine 40-mg capsule. To support the biowaiver request, the sponsor has submitted the following information:

- unit formulas for different capsule strengths
- results from pivotal bioequivalence study
- dissolution data for different capsule strengths
- pH solubility profile of atomoxetine hydrochloride

Atomoxetine Hydrochloride Solubility Profile

Table 1. Atomoxetine Hydrochloride Solubility in Organic Solvent

Methanol	Ethanol	Isopropanol	Acetone	Acetonitrile	Ethyl Acetate	Hexane	Diethyl Ether	Octanol
>100.0	>56.3	9.3	4.1	4.1	0.3	<0.1	<0.1	5.5

Table 2. Atomoxetine Hydrochloride pH Solubility Profile

pH (Phosphate Citrate Buffer)	2.2	3.0	4.0	6.0	7.0	Water
Solubility (mg/ml)	28.0	31.2	37.1	13.0	3.9	25.5

pH (Acetate Buffer)	3.6	4.0	5.0	0.1 N HCL
Solubility (mg/ml)	26.4	27.3	27.4	16.0
pH (Phosphate Buffer)	6.0	7.0	8.0	
Solubility (mg/ml)	27.2	31.3	12.7	
Solubility Cutoff 60 mg/250 ml=0.24 mg/ml				

Solubility data were determined at 25°C and represent equilibrium values.

Dissolution Test

Dissolution testing was performed in water, 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer. The proposed dissolution method is as follows:

Apparatus: USP apparatus II (paddle) at 50 rpm
Medium: 1000 ml of 0.1 N HCL
Specification: NLT — at 30 minutes.

Table 1. Dissolution Data in 0.1 N HCl (N=12)

Strength (Lot)	15 min	30 min	45 min	f_2
5 mg (CT22893)				
10 mg (CT22895)				
18 mg (DPD16681)				
25 mg (CT22896)				
40 mg (D40313)				
60 mg (CT17611)				

Table 2. Dissolution Data in pH 4.5 Buffer

Strength (Lot)	15 min	30 min	45 min	f_2
5 mg (CT22893)				
10 mg (CT22895)				
18 mg (DPD16681)				
25 mg (CT22896)				
40 mg (D40313)				
60 mg (CT17611)				

Table 3. Dissolution Data in pH 6.8 Buffer

Strength (Lot)	15 min	30 min	45 min	f_2
5 mg (CT22893)				
10 mg (CT22895)				
18 mg (DPD16681)				
25 mg (CT22896)				
40 mg (D40313)				
60 mg (CT17611)				

Table 4. Dissolution Data in Water

Strength (Lot)	15 min	30 min	45 min
5 mg (CT08753)			
10 mg (CT08754)			
20 mg (CT14366)			

Table 5. Dissolution Data for Biobatch in 0.1 N HCl (n=6)

Strength (Lot)	15 min	30 min	45 min	
20 mg				
40 mg				

Summary

- Data from the primary stability and BE batches indicated that 15 minutes may be required for equilibration and dissolution of atomoxetine into the medium. Much variability has been observed at the 15-minute timepoint. Therefore, 30 minutes has been selected as the most relevant time for the specification of dissolution for atomoxetine capsules.
- Atomoxetine capsules rapidly dissolved in 0.1 N HCl and pH 4.5 buffer media, but somewhat slower in pH 6.8 buffer for higher strengths (40- and 60-mg, — in 30 minutes).
- The sponsor calculated f_2 values for dissolution profiles of lower strengths comparing with the 40-mg strength. Since there were no more than 2 timepoints that dissolution below —% in any medium, f_2 calculation is not necessary.

Conclusions

- Biowaiver can be granted for lower strengths (5-, 10-, 18- and 25-mg) based on the bioequivalence between 40-mg to-be-marketed capsule and 2x20 mg clinical capsules, the proportionally similar formulations between these lower strengths and the 40-mg capsule, the linear pharmacokinetics of atomoxetine as well as the similar dissolution performance of these capsules in 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer. Although the lower strengths had faster release than the 40-mg capsule in pH 6.8 buffer, an average of — released from the 40-mg capsules in 30 minutes.
- Although atomoxetine hydrochloride drug substance is highly soluble and highly permeable, the slower release of the highest strength (60-mg) in pH 6.8 buffer (— in 30 minutes) disqualifies the atomoxetine drug product as BCS Class I drug product.
- The dissolution method and specification proposed by the sponsor for atomoxetine capsules are acceptable.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-411	Brand Name	[redacted]
OCPB Division (I, II, III)	DPE-I	Generic Name	Atomoxetine Hydrochloride
Medical Division	HFD-120 (Neuropharm)	Drug Class	Non-stimulant
OCPB Reviewer	Zhao, Hong	Indication(s)	ADHD
OCPB Team Leader	Baweja, Raman	Dosage Form	Capsule
		Dosing Regimen	
Date of Submission	10/11/01	Route of Administration	Oral
Estimated Due Date of OCPB Review	6/11/02	Sponsor	Lilly
PDUFA Due Date	8/11/02	Priority Classification	S
Division Due Date	6/1/02		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	X	2		
Isozyme characterization:	X	7		
Blood/plasma ratio:				
Plasma protein binding:	X	4		
Pharmacokinetics (e.g., Phase I) -	[redacted]			
Healthy Volunteers-				
single dose:	x	1		
multiple dose:	X	2		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	8		
In-vivo effects of primary drug:	x	7		
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1		
gender:	x	1		
pediatrics:	X	2		
geriatrics:				
renal impairment:	X	1		

hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:	X PK only	1		
Data sparse:	X PK/PD	1		
Ii. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	x	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS	x			
BCS class	I			
III. Other CPB Studies				
Genotype/phenotype studies:	X	4		
Chronopharmacokinetics	X	1		
Pediatric development plan				
Literature References				
Total Number of Studies		31		

Filability and QBR comments

	"X" if yes	Comments
Application fileable?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	See attached Review.	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Should dose regimens be based on age or body weight? Whether dosage adjustments are needed for special populations (CYP2D6 poor metabolizers, hepatic or renal impairment, coadministration of CYP3A4 or CYP2D6 substrates or inhibitors, etc.)?	
Other comments or information not included above	Request for Pharmacometrics consult: This NDA has one population pharmacokinetic analysis of Atomoxetine in pediatric patients (Vol. 79-80) and one population PK/PD data in clinical study report B4Z-MC-LYAC (Vol. 80-85). Pharmacometrics consult is requested.	
Primary reviewer Signature and Date	Hong Zhao, 12/4/01	
Secondary reviewer Signature and Date	Raman Baweja, 12/4/01	

Office of Clinical Pharmacology and Biopharmaceutics
Pharmacometrics Consult Request Form

NDA:	21-411	**Sponsor:**	Lilly
IND:			
Brand Name:	——	**Priority Classification:**	S
Generic Name:	Atomoxetine	**Indication(s):**	ADHD
Dosage Form:	Oral Capsules	**Date of Submission:**	10/11/01
Dosing Regimen:	0.5 mg/kg/day as starting dose, increase to 1.2 mg/kg/day after 3 to 7 days, given either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon /early evening. After 2 to 4 additional weeks, the total daily dose may be increased to a maximum of 1.8 mg/kg/day or 120 mg/day, whichever is less.	**Due Date of PM Review:**	4/30/02
Division:	DPE-1	**Medical Division:**	HFD-120, Neuropharm
Reviewer:	Hong Zhao	**Team Leader:**	Raman Baweja

Tabular Listing of All Human Studies That Contain PK/PD information (This can be requested at the pre-NDA stage as indicated on the PM roadmap)
(may attach tabular summary of all studies from NDA to this document)

See attached NDA filing.

List the following for this compound (if known. The list will be confirmed by PM Scientist during the review):

Clinical endpoint(s):	ADHDRS-IV Parent:Inv total score
Surrogate endpoint(s):	
Biomarker(s):	
Any reported optimal dose based on PK/PD ?:	Yes/No
Any reported dose/concentrations associated with efficacy/ toxicity ?:	Yes/No
Principal adverse event(s):	Aggregation (0.5%), irritability (0.5%), somnolence (0.5%) and vomiting (0.5%)

Pharmacometrics Request: (Jointly filled out with PM Scientist)
(Briefly state the objective(s) of the consult. The request should be as explicit as possible, and should state whether a review or additional analysis is needed. An assessment of the impact that the data will have on labeling should be included (Questions to be answered in QBR). The proposed labeling and the HPK Summary along with the relevant volumes should be available to the PM Scientist.)

This NDA has one population PK analysis of atomoxetine in pediatric patients (Vol. 79-80). The objective of this analysis was to characterize atomoxetine pharmacokinetics, its variability, and

the potential influence of patient factors such as age, weight, gender, and CYP2D6 genotype on atomoxetine pharmacokinetics in the target population, pediatric patients diagnosed with ADHD.

A population pharmacokinetic model was developed using the combined data from 5 pediatric studies. A one-compartment model with first-order absorption and elimination was selected as the base structural model. Patient factors with clinical and demographic significance were identified *a priori* and evaluated on parameters of the pharmacokinetic model. Patient factors were tested individually using a base model that incorporated poor metabolizer (PM) status and body weight. After a full model was developed which included all potentially significant patient factors, backward selection criteria was used to develop the final model. The final pharmacokinetic model was validated using parameter sensitivity, leverage analysis, and external validation.

This NDA also includes one population PK/PD data analysis in Clinical Study Report LYAC (Vol.80-85). This was a phase 3 randomized, double-blind, placebo-controlled efficacy and safety comparison of fixed-dose ranges (mg/kg/day) of atomoxetine with placebo in child and adolescent outpatients with ADHD, aged 8 to 18 years.

The primary objectives of this study was to test the hypothesis that acute treatment for approximately 8 weeks with atomoxetine, either 1.2 mg/kg/day or 1.8 mg/kg/day, would be statistically significantly more effective in reducing the severity of attention-deficit/hyperactivity disorder (ADHD) symptoms than placebo. A total of 213 patients (male 152, female 61) received atomoxetine treatment and 84 patients (male 60, female 24) received placebo treatment.

All patients provided blood samples for assessment of plasma concentrations and PK of atomoxetine and its metabolites. A population pharmacokinetic analysis using NONMEM was performed to analyze the atomoxetine concentration data and obtained an individual atomoxetine clearance estimate for each patient. The clearance estimates were then used to estimate $AUC_{0-\tau}$ for each patient. The relationship between $AUC_{0-\tau}$ and the primary efficacy measure was evaluated.

The following information generated from these population analyses has impacts on the labeling:
(1) Pediatric poor metabolizer (PM) patients have a 9-fold lower mean clearance estimate compared to extensive metabolizer (EM) patients.
(2) Atomoxetine clearance and volume of distribution increased nearly proportional to increased body weight, indicating that dosing based on body weight is appropriate.
(3) Administration of atomoxetine within an hour after food (self-reported) had a decrease in the rate of absorption resulting in a 9% lower Cmax.
(4) Age does not influence atomoxetine disposition (range 7 to 15 years).
(5) Ethnic origin did not influence atomoxetine disposition.
(6) Gender did not influence atomoxetine disposition.

Pharmacometrics consult is requested to verify the information generated from these population PK or PK/PD analyses that has impacts on labeling.

Due Date to the Reviewer 4/30/02

Primary Reviewer Hong Zhao **Signature** Date **12/4/01**

Team Leader Raman Baweja **Signature**_____ Date 12/4/01

PM Scientist Jogarao Gobburu **Signature**_____ **Date** _____

CC: HFD-860 (Mehta, Baweja, Zhao, Gobburu) HFD-850 (Lee)

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/s/

Hong Zhao
6/18/02 03:53:07 PM
BIOPHARMACEUTICS

Raman Baweja
6/18/02 05:03:22 PM
BIOPHARMACEUTICS

Pharmacometrics Review

NDA:	21-411
Drug name:	——— (atomoxetine HCl)
Dosage strength:	5, 10, 18, 25, 40 and 60 mg capsules
Submission date:	9/26/02
Applicant:	Eli Lilly and Company, Indianapolis, IN
Reviewer:	John Duan, Ph.D.
Team Leader:	Joga Gobburu, Ph.D.

Background:

——— (atomoxetine HCl) is a non-stimulant treatment for Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD was formerly known as Attention Deficit Disorder (ADD) with or without hyperactivity. Atomoxetine is a potent inhibitor of the pre-synaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Atomoxetine HCl is the R(-) isomer as determined by x-ray diffraction. The chemical designation is benzenepropanamine, N-methyl-gamma (2-methylphenoxy) hydrochloride(-).

In the original NDA submission, a study showed that CYP2D6 poor metabolizer subjects exposed to the highest atomoxetine doses and with the highest plasma levels had QTc prolongation compared to baseline. Since there was no evidence of increased efficacy at these highest doses, the Agency requested that the maximum recommended atomoxetine dose be decreased. In the approvable letter, the applicant was requested to estimate the proportion of patients expected to achieve plasma levels >2,000ng/mL, given the new recommended highest dose.

In the response, the applicant estimated that 3/100,000 exposed poor metabolizer patients would achieve plasma levels >2,000ng/mL. This estimate was derived from a simulation using a model developed previously in the original NDA submission. They also plotted the available data which demonstrated that 1/65 subjects exposed reached a plasma level>2,000ng/mL.

This review will comment on the simulation and the estimate of the proportion expected to achieve a plasma level >2,000ng/mL and related issues.

Objectives:

1. To examine the validity of the PK simulation.
2. To extend the simulations to include effects on QTc.

Design

The applicant's analysis

Population pharmacokinetic simulation:

Simulations were performed to estimate the proportion of PM patients who might be expected to achieve plasma concentrations higher than 2000 ng/mL at various doses, with a focus on the recommended target

dose of 1.2 mg/kg/day. The population pharmacokinetic model (base model) was used for the simulations. Details of the model are provided in the review of the original NDA submission. Briefly, the model included separate CL/F estimates for CYP2D6 poor metabolizers and CYP2D6 extensive/ultra-rapid metabolizers. Clearance was approximately 9-fold lower in PMs than the remaining patients. The model also included the effect of weight on both CL/F and V/F using a power model. Both CL/F and V/F increased with increasing weight.

The reviewer's analysis:

QTc Prolongation:

Study LYAE was used for modeling the relationship between concentrations and QTc prolongation. It was a single-blinded, placebo-controlled, multiple-dose escalation study. Placebo or atomoxetine 60 to 150 mg/day was given as a twice daily doses of 30 mg, 45 mg, 60 mg, and 75 mg for 5 days in 6 periods as shown below.

Period 1: Placebo BID for 5 days
Period 2: Tomoxetine at 30 mg BID for 5 days (0.70-1.12 mg/kg/day)
Period 3: Tomoxetine at 45 mg BID for 5 days (1.05-1.68 mg/kg/day)
Period 4: Tomoxetine at 60 mg BID for 5 days (1.40-2.24 mg/kg/day)
Period 5: Tomoxetine at 75 mg BID for 5 days (1.75-2.80 mg/kg/day)
Period 6: Washout/Observation for 5 days

The subjects are 16 healthy volunteers including 11 males and 5 females, among them there were 6 Poor Metabolizers and 10 Extensive Metabolizers.

Pharmacokinetics

Subjects were administered the atomoxetine or placebo dose every 12 hours for a total of 10 doses at each dose level. A trough sample was taken immediately prior to the morning and evening doses of atomoxetine on Study Day 4 of Study Periods 1 through 5. The following blood samples were taken with respect to the morning dose of atomoxetine on Study Day 5 of Study Periods 1 through 5: 0, 0.5, 1, 2, 4, 6, 9, and 12 hours postdose. The 12-hour samples should have been taken just prior to the evening dose of atomoxetine; however, some samples were taken immediately after the evening dose.

Pharmacodynamics

Electrocardiogram tracings were obtained at screening on Study Day 5 of Study Periods 1 through 5 at approximately 0, 1, 2, 4, and 12 hours after the morning dosing of placebo or atomoxetine, and at the time of the final assessment. ECGs consisted of a 12-lead tracing taken at 25 mm/minute paper speed. The ECG tracings were analyzed for change in the PR, QT, RR, and QRS intervals. The correction of the QT interval (QTc(F)) used the Fridericia method. Bazett corrected QTc intervals were also read at the time ECG tracings were made due to the program on the ——— ECG recording machines. Changes in QTc intervals were derived from hand-measured QT intervals from the original tracings from at least 2 leads and 5 complexes per lead by cardiologists at the same site..

Models

The applicant's analysis

Simulation Model

The simulation used the basic population pharmacokinetic model developed during the combined analysis of atomoxetine studies HFBC/HFBD/HFBE/HFBF/HFBK. This was a 1-compartment model, parameterized in terms of absorption rate constant (Ka), apparent clearance (CL/F), and apparent volume of distribution (V/F), with first order absorption and elimination. The model incorporated the effects of genotype, body weight on atomoxetine CL/F, and the effect of body weight on V/F.

The reviewer's analysis

PK/PD study LYAE

Pharmacokinetics model

Data from this study were analyzed using the final population pharmacokinetic model developed during the combined analysis of atomoxetine studies HFBC/HFBD/HFBE/HFBF/HFBK. This was a 1-compartment model, parameterized in terms of absorption rate constant (Ka), apparent clearance (CL/F), and apparent volume of distribution (V/F), with first order absorption and elimination. The model incorporated the effect of food intake on Ka, the effects of genotype, body weight, and plasma albumin concentrations on atomoxetine CL/F, and the effect of body weight on V/F.

Pharmacodynamic model

To investigate if there is a relationship between concentration and QTc prolongation, the following two models were tested.

$$QT = \alpha \times RR^{\beta} + CP \times SLOPE1 \qquad \text{and}$$

$$QT = \alpha \times RR^{\beta} + CE \times SLOPE2$$

Where QT is the QT interval, RR is 60/(heart rate), CP is the plasma concentration of atomoxetine, CE is the concentration of hypothetical effect compartment, α and β are the coefficients, SLOPE1 and SLOPE2 show the relationship between QT interval and concentrations.

For the link model, the central compartment transfers the drug to hypothetical effect compartment with very small constant K1e (i.e., negligible amount is transferred). The elimination constant of the drug in effect compartment is Keo.

Results and Discussion

Simulation Results by the applicant

Based on the simulations of 1000 PM patients, summary statistics of Css,max are shown in the Table 1 and Figure 1. These simulations show that only a very small proportion of PM pediatric patients might be expected to achieve peak plasma concentrations higher than 2000 ng/mL at doses of 1.6 mg/kg/day and 1.8 mg/kg/day. At the recommended dose of up to 1.4 mg/kg/day, no concentrations exceeded 2000 ng/mL, and therefore the simulation predicts that in clinical settings exposures to plasma concentrations greater than 2000 ng/mL would occur only rarely. Using the mean peak concentration of 1164 ng/mL and the standard deviation of 171 ng/mL, a plasma atomoxetine concentration of 2000 ng/mL represents a value more than 4 standard deviations above the mean. Thus based on the simulation, the likelihood of a patient taking 1.4 mg/kg/day and exceeding a plasma concentration of 2000 ng/mL is approximately 3/100,000. These simulations were based on the variability of the PM patients previously evaluated in the population pharmacokinetic analysis, and interpatient variability in clinical settings may be higher, resulting in a higher proportion of patients exceeding 2000 ng/mL.

Table 1. Simulated Css, max for PM pediatric patients after a BID dosing (uncorrected).

Dose (mg/kg/day)	Mean	Median	SD	5th Percentile	95th Percentile	% Values >2000 ng/mL
1.0	827	819	125	640	1037	0.0
1.2	986	975	145	766	1237	0.0
1.4	1164	1152	171	891	1456	0.0
1.6	1316	1296	190	1036	1641	0.2
1.8	1482	1467	221	1151	1854	1.8

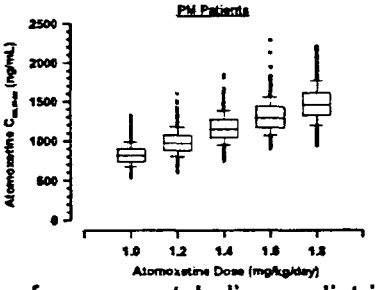

Figure 1. Simulated Css, max for poor metabolizer pediatric patients after a BID dosing regimen.

Figure 2 shows the actual plasma concentrations measured in patients in the Phase 3 studies.

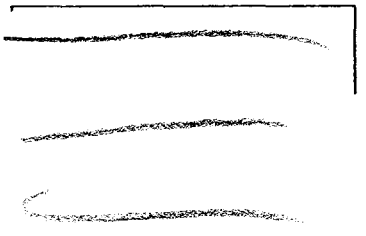

Figure 2. Atomoxetine exposures observed in patients treated with doses <1.4 mg/kg/day.

Pharmacodynamic Model by the reviewer

The QT model without covirate, the direct effect model (using plasma concentrations as coviarate) and the link model (using concentration in effect compartment as covirate) were attempted by using first order conditional estimation (FOCE) method. The objective functions and the parameter estimations are summarized in the following table.

Table 2. The QTc-Concentration model parameters.

Model	Obj. function	Alpha	Beta	Keo (h^{-1})	Slope (msec/μg/mL)
Without coviate	2625.60	386	0.313	-	-
Direct model	2614.27	385	0.327	-	0.0027
Link model	2612.15	385	0.329	0.068	0.361

When incorporating plasma concentration (Cp) or the concentration of effect compartment (Ce) as covariates, the objective function value dropped 11.3 (significant over the model without Cp effect) and 2.3 (not significant over the model with Cp effect). The direct effect model showed a very low slope (0.0027) between the plasma concentrations and QTc as shown in the following figure (a simulated relationship between QTc and plasma concentration based on results from the direct effect model).

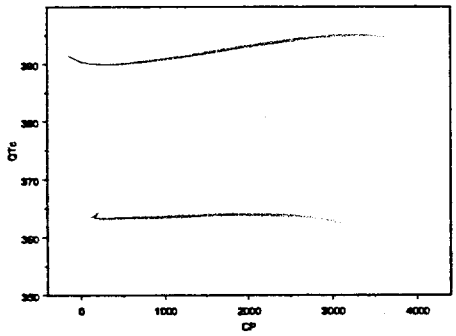

Figure 3. The model predicted relationship between QTc and plasma concentrations.

The population model predicted steady state atomoxetine C_{max} and AUC for EM, UM and PM patients are shown in the following table. The two extreme situations can be compared. For the UM patients with Css,max of 247.5 ng/mL will have a QTc of 375 msec based on the direct effect model, whereas the PM patients with Css,max of 1664.7 ng/mL will have a QTc of 379 msec. The 4 msec difference in QTc resulted from 8-fold concentration difference.

Table 3. The model predicted steady state maximum plasma concentrations (uncorrected).

Genotype	Css, max (ng/mL)	$AUC_{0-\tau}$ (μg•hr/mL)
EM		
UM		
PM		

Discussion (analysis by the reviewer)

The validity of the results

1. The simulation used the basic pharmacokinetic model instead of the final model because the base model has already incorporate the effects of genotype, which is relevant to the simulation. Another reason is that comparing to the base model, the final model retained 3 additional covariates, they explained a minimal amount of inter-patient variability. The addition of these 3 covariates had essentially no effect on the residual error and resulted in no apparent improvement in the goodness of fit plots as shown in the following figure. The left four panels show the goodness-of-fit for the base model. The right four panels for the final model.

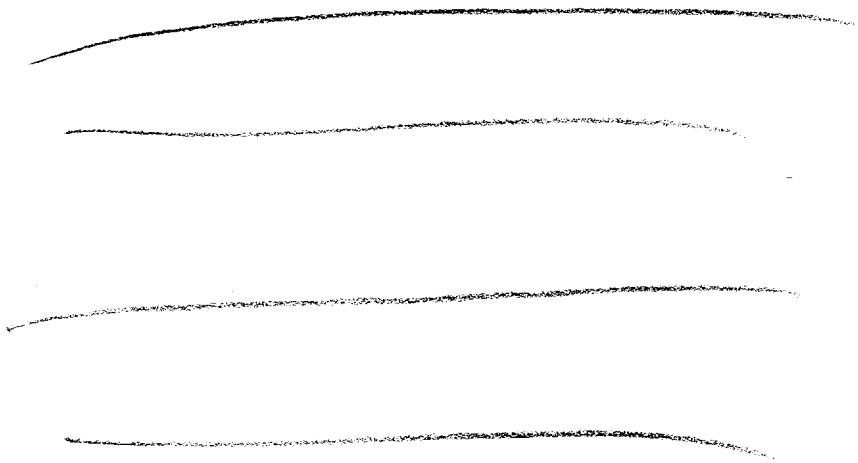

Fig 4. Comparison of goodness-of-fit between the base model and final model.

2. As shown in Figure 4, the model appeared to underpredict the observed values at higher plasma concentrations. The serial sampling data (samples at 0, 1, 2, 4, 8, 12, and 24 hours after dosing) from Study HFBC were used to evaluate the model fit of the overall plasma concentration-time profile within an individual patient.

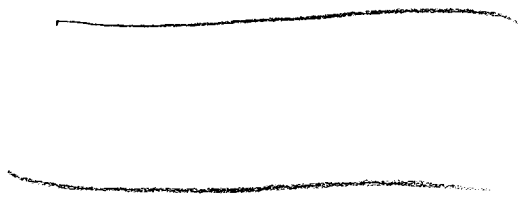

Fig 5. The goodness-of-fit for a representative patient.

Figure 5 shows a representative individual patient plots from Study HFBC. This evaluation suggested there was a bias in the model fit around the Cmax value and the Cmax was generally underpredicted (note the logarithemic scale of y-axis).

The observed Cmax is underpredicted by about 40% on average. Therefore, if this model is used to simulate Cmax at a given dose, the simulated Cmax should be corrected for this bias. The following table (Table 4) shows the corrected predictions.

Table 4. Corrected predicted $C_{ss,max}$ for poor metabolizer pediatric patients after a BID dosing.

Dose (mg/kg/day)	Mean (ng/mL)	Median	SD	5th Percentile	95th Percentile	% Values >2000 ng/mL
1.0	1378.3	1365	208.3	1066.667	1728.333	0.0
1.2	1643.3	1625	241.7	1276.667	2061.667	7
1.4	1940	1920	285	1485	2426.667	42
1.6	2193.3	2160	316.7	1726.667	2735	72
1.8	2470	2445	368.3	1918.333	3090	90

The significance of the results

The corrected simulation results show that the $C_{ss,max}$ at dose up to 1.2 mg/kg/day would have approximately 7% probability to exceed the 2000 ng/mL.

On the other hand, the direct effect model showed a very low slope (0.0027) between the plasma concentrations and QTc. Based on the model, Css,max increases from 247.5 ng/mL to 1664.7 ng/mL will have a QTc change of 4 msec from 375 msec to 379 msec. The 4 msec difference in QTc resulted from 8-fold concentration difference. However, due to the variability, the real QTc prolongation in clinical setting may be much higher than this average prediction as shown in the following figure.

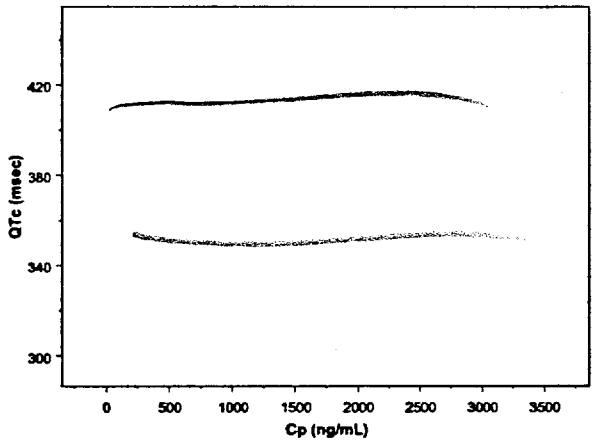

Fig 6. The predicted and observed relationship between QTc and plasma concentrations.

Conclusions and Recommendations

Conclusions

1. Due to the fact that the model underpredicted the Cmax about 40%, the simulation results needs to be corrected for this bias. After the adjustment, the recommeded doses would produce the following predicted concentration profiles.

Dose (mg/kg/day)	Mean (ng/mL)	Median	SD	5th Percentile	95th Percentile	% Values >2000 ng/mL	% Values >2500 ng/mL
1.2	1643.3	1625	241.7	1276.667	2061.667	7	0.0
1.4	1940	1920	285	1485	2426.667	42	2.5

2. The model predicted QTc change under the situation where the concentrations exceed 2000 ng/mL may not cause significant QTc prolongation. However, because of the variability, the possibility of clinical significant QTc prolongation caused by concentration exceeding 2000 ng/mL can not be excluded.

Recommendations

1. The model used in the submission is not adquate to make predication for Cmax, because the model underpredicted the observation, especially for the higher concentrations (about 40%). Assuming the underprediction is 40%, and the mean, median, SD and 5th and 95th percentiles have the same percentage change, the estimated percentages of concentration more than 2000 and 2500 ng/mL for the recommended doses are as follows.

Dose (mg/kg/day)	% Values >2000 ng/mL	% Values >2500 ng/mL
1.2	7	0.0
1.4	42	2.5

There is a good chance for the C_{max} to be more than 2000 ng/mL although this is a conservative prediction. Therefore, the prediction made by the applicant is not adequate.

2. The QTc-concentration model built from study LYAE data is a linear model. The slope is very shallow, indicating that the increases of concentrations may not cause significant increases of QTc. However, the database is relatively small for the model building (only from one study LYAE) and the data has relatively large variabilities (both for the drug concentrations and QTs).

Therefore, the clinical significance of the concentration increases (especially above 2000 ng/mL) is subject to medical judgement.

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/s/

John Duan
11/7/02 03:15:38 PM
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Jogarao Gobburu
11/7/02 04:06:56 PM
BIOPHARMACEUTICS