CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-411

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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Brand Name	STRATTERA, ———
Generic Name	Atomoxetine Hydrochloride
Reviewer	Hong Zhao
Pharmacometrics Reviewer	John Duan
Team Leader	Raman Baweja
Pharmacometrics Team Leader	Jogarao Gobburu
OCPB Division	DPE 1 (HFD-860)
ORM Division	DNDP (HFD-120)
Sponsor	Eli Lilly and Company
Relevant IND(s)	IND ——
Submission Type; Code	NME, 1 S
Formulation; Strength(s)	Capsule in 5, 10, 18, 25, 40 and 60-mg
Indication	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children, Adolescents and Adults

1 Executive Summary

1.1 Recommendation

This submission (NDA21-411) for Atomoxetine Hydrochloride Capsules has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements. The sponsor is requested to adopt the OCPB labeling as provided in this review. Also, the sponsor is requested to adopt the dissolution methodology and specification for all six strengths of atomoxetine capsules, as outlined in the Comments to the Sponsor.

Comments to Clinical Division

Dosage Adjustment

In the proposed labeling for atomoxetine, the sponsor states that "Adjustment of dosing regimens based on metabolism through the CYP2D6 pathway is not necessary" although there are 10-fold differences in atomoxetine exposure between the poor metabolizers (PMs) and the extensive metabolizers (EMs).

Potent CYP2D6 inhibitors such as paroxetine and fluoxetine converted EMs to PMs (6.5 fold increase in atomoxetine exposure). The sponsor proposed to make dosage adjustment for paroxetine but not for fluoxetine.

Atomoxetine apparent clearance reduced to one quarter of the normal value in severe hepatically impaired (HI) patients, and one half of the normal value in moderate HI patients. For ADHD patients with HI, the sponsor proposed cautious titration of atomoxetine to the desired clinical response.

Based on the impact of body weight (BW) on atomoxetine clearance (13.2 L/hr for 25 kg BW and 23 L/hr for 50 kg BW), the sponsor proposed a weight-based dosing regimen (mg/kg) for atomoxetine in pediatric patients.

The sponsor's recommendation for dosage adjustment is not consistent since maximum difference in atomoxetine clearance due to body weight is no more than 2-fold yet they recommend a weight-based dosing regimen, but for patients with PM genotype whose atomoxetine clearance is 10-fold slower than the EMs, they claim "adjustment of dosing regimens based on metabolism through the CYP2D6 pathway is not necessary". Sponsor's justifications for not recommending dosage adjustment based on genotype and other conditions are (1) therapeutic doses were tolerated by the PM subjects; (2) genotyping is not clinically practical at present time and phenotyping with a probe drug (dextromethorphan) has poor prediction of atomoxetine pharmacokinetics; (3) the increase in drug exposure with CYP2D6 selective inhibitors is less or similar to the exposure of PM subjects.

OCPB recommends dosage adjustment for all conditions that will result in a significant increase in drug exposure based on the following reasons: (1) dose-related mean heart rate increase and orthostatic systolic blood pressure reduction were confirmed by analysis of ECG data, and 40-mg dose of atomoxetine BID for 7 days resulted in standing heart rate increases in both EM and PM subjects with PM subjects reaching maximum heart rates about 10 bpm higher than EM subjects; (2) although there was no clear and direct relationship between atomoxetine exposure and QT_c changes, QT_c prolongation was seen more frequently in PM subjects whose atomoxetine exposure was much higher than that in EM subjects; (3) it is unnecessary to expose patients to drug concentrations more than the treatment needed especially for this drug that may have abuse potential. For all these reasons, dosage adjustment is recommended for the following conditions:

- Genotype: The ten-fold difference in atomoxetine clearance warrants dosage adjustment in PM patients. Laboratory tests are available to identify CYP2D6 PMs. Although there does not appear to be an increased risk of adverse events associated with atomoxetine in PMs, patients who are refractory to treatment or who exhibit toxicities associated with atomoxetine should be considered for testing of CYP2D6 genotype.

- Hepatic Impairment (HI): In the EM patients with HI, their mean exposure to active moieties are much higher (2-fold increase for atomoxetine and 7-fold increase for 4-

hydroxyatomoxetine) compared to healthy subjects. It is predicted that PM patients with HI will have even higher atomoxetine exposure compared with PM patients without HI whose steady state concentration of atomoxetine is already 10-fold of that of EM subjects. Based on the differences in atomoxetine apparent clearance (half of the normal value in patients with moderate HI, and one quarter of the normal value in patients with severe HI), dosage adjustment should be made accordingly, i.e., for patients with moderate HI, half of the normal starting dose (20 mg/day for adults, and 0.25 mg/kg/day for children) and for patients with severe HI, one quarter of the normal starting dose (10 mg/day for adults and 0.125 mg/kg/day for children) are recommended. The target dose for HI patients should also be reduced from normal (80 mg/day or 1.2 mg/kg/day for children) to 40 mg/day (0.6 mg/kg/day for children) for moderate HI and 20 mg/day (0.3 mg/kg/day for children) for severe HI patients after 1 to 2 weeks.

- Selective Inhibitors of CYP2D6: Co-administration of atomoxetine with CYP2D6 inhibitors (paroxetine or fluoxetine) increased atomoxetine steady-state plasma concentrations in EM subjects to exposures similar to those observed in PM subjects. In addition, paroxetine has similar cardiovascular effects as atomoxetine and combination with paroxetine resulted in greater orthostatic tachycardia compared to atomoxetine alone. In the drug interaction study with fluoxetine, the worst-case scenario that fluoxetine is added to atomoxetine at steady state has not been tested. Dosage adjustment is recommended for the following scenarios:

  (a) When a selective CYP2D6 inhibitor (paroxetine or fluoxetine) is added to atomoxetine therapy, atomoxetine dose should be reduced to one fifth of its normal dose.
  (b) When atomoxetine is added to the fluoxetine or paroxetine therapy, one fifth of the starting dose should be used initially and the target dose should also be reduced to one fifth of the normal dose after 1 to 2 weeks.

Comments to the Sponsor

Dissolution Method and Specification
The sponsor is requested to adopt the following dissolution method and specification for all strengths of STRATTERA Capsules (5, 10, 18, 25, 40 and 60-mg):

Apparatus: USP apparatus II (paddle) at 50 rpm
Medium: 1000 ml of 0.1 N HCL at 37°C
Specification: NLT [illegible] at 30 minutes.

BCS Classification
Although atomoxetine hydrochloride is highly soluble and highly permeable, the slower release of the highest strength (60-mg) capsule in pH 6.8 buffer ([illegible]% in 30 minutes) does not meet the criteria for being classified as a BCS Class 1 drug product.

The sponsor is encouraged to test whether atomoxetine is a substrate of the PGP transporter or an inhibitor of the PGP transporter.

1.2 Phase IV Commitments

None

Hong Zhao, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

OCPB Briefing on June 12, 2002,

Attendees: Lawrence Lesko, Malcolm Rowland, Peter Lee, Mehul Mehta, Hank Malinowski, Arzu Selen, Patrick Marroum, Ray Baweja, Jogarao Gobburu, Veneeta Tandon

cc: NDA21-411 (Atomoxetine Hydrochloride Capsules), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (Biopharm-CDR)

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Bioavailability Study Reports

B4Z-LC-LYAM: Atomoxetine Hydrochloride: Absolute Bioavailability and the Effect of Maalox and Omeprazole Treatments Relative Bioavailability.

B4Z-LC-LYAK: Atomoxetine Hydrochloride: Pilot Bioavailability Study in Poor Metabolizer Subjects.

B4Z-LC-HFBG: Atomoxetine Hydrochloride Relative Bioavailability Study.

Bioequivalence Study Reports

B4Z-LC-LYAL: Atomoxetine Hydrochloride: Pivotal Bioequivalence and Food Effects Study.

B4Z-LC-LYAZ: Atomoxetine Hydrochloride: 60-mg Bioequivalence and Food Effects Study.

Human Pharmacology Studies

Plasma Protein Binding Study Reports

ADME Report 05: *In Vitro* Plasma Protein Binding of Atomoxetine in the Mouse, Rat, Rabbit, Dog, and Human.

ADME Report 48: *In Vitro* Plasma Protein Binding of Atomoxetine, *N*-Desmethylatomoxetine in Mouse, Rat, Dog, and Human.

ADME Report 50: *In Vitro* Protein Binding of ^{14}C-Tomoxetine to Purified Human Plasma proteins and Interaction Studies with ^{14}C-Warfarin, ^{14}C-Acetylsalicylic Acid, ^{14}C-Phenytoin, ^{3}H-Desipramine, ^{14}C-Diazepam, ^{3}H-Paroxetine, and Midazolam in Human Plasma.

Metabolism Studies Using Hepatocytes, Microsomes, etc. Reports

ADME Report 08: In Vitro Metabolism of Atomoxetine by Rat, Mouse, Dog, Monkey and Human Liver Microsomes.

ADME Report 22: In Vitro Metabolism of Atomoxetine by Cultured Human Precision-Cut Liver Slices.
ADME Report 01: In Vitro Interaction of Atomoxetine (LY139603) with Human Cytochrome P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2.

ADME Report 36: In Vitro Interaction of *N*-Desmethylatomoxetine (137877) and 4-Hydroxytomoxetine (424478) with Human Cytochrome P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2.

ADME Report 34: Identification of the Human Cytochrome P450 Responsible for the Formation of 424478, the 4-Hydroxy Metabolite of LY139603 (Atomoxetine HCl).

ADME Report 42: Identification of the Human Enzyme(s) Responsible for the Formation of 137877, the *N*-Desmethyl metabolite of Atomoxetine Hydrochloride (LY139603).

ADME Report 52: Examination of CYP1A2 and CYP3A Induction by LY139603 in Primary Cultures of Human Hepatocytes.

Human Pharmacokinetics (PK) Study Reports

In Vivo Human Metabolism

B4Z-LC-HFBH: Metabolism and Disposition of ^{14}C-LY139603 in Healthy CYP2D6 EM and PM Men and Women.

In Healthy Volunteers

B4L-LC-HFBJ: Single and Multiple Dose Studies in Adults of Known CYP2D6 Status.

B4Z-LC-LYAE: Tolerance and Safety of Multiple Dose Regimens of Atomoxetine Hydrochloride in Healthy Adults.

In Patients

B4Z-MC-HFBC: Safety and Pharmacokinetic study of Atomoxetine Hydrochloride in Pediatric Patients with ADHD.

Evaluation of Effects of Intrinsic Factors

B4Z-LC-HFBM: Single Dose Pharmacokinetics of Atomoxetine Hydrochloride in Subjects with End Stage Renal Disease.

B4Z-LC-HFBN: Single Dose Pharmacokinetics of Atomoxetine Hydrochloride in Patients with Liver Disease.

B4Z-LE-LYAN: Phase I Study of LY139603 in Healthy Adult Male Subjects – Single Dose Oral Administration Study (Dose Escalation), Multiple Oral Administration.

Evaluation of Effects of Extrinsic Factors (DDI, Food)

B4Z-LC-HFBP: Safety and Pharmacokinetic Interaction of Coadministered Atomoxetine and Desipramine in Healthy Subjects.

B4Z-LC-LYAJ: Safety and Pharmacokinetic Interaction of Atomoxetine and Midazolam in CYP2D6 PM Healthy Adults.

B4Z-LC-HFBL: Evaluation of Atomoxetine-Paroxetine HCl Safety and Pharmacokinetic Interaction in Healthy Subjects.

B4Z-LC-LYAY: Evaluation of Atomoxetine-Fluoxetine Safety and Pharmacokinetic Interaction in Adult Subjects.

B4Z-LC-LYAL: Atomoxetine Hydrochloride Pivotal Bioequivalence and Food Effects Study.
B4Z-LC-LYAZ: Atomoxetine Hydrochloride 60-mg Bioequivalence and Food Effects Study.

B4Z-LC-LYAM: Atomoxetine Hydrochloride Absolute Bioavailability and the Effect of Maalox and Omeprazole Treatments on Relative Bioavailability.

B4Z-FW-HFBO: Evaluation of the Effect of Oral Chronic Atomoxetine Dosing on Hemodynamic Parameters after a Single Intravenous Dose of Salbutamol.

B4Z-LC-LYAP: Evaluation of the Effect of Oral Chronic Atomoxetine Dosing on Hemodynamic Parameters in the Presence of Oral methylphenidate.

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

Population PK Study Reports

Population Pharmacokinetic Analysis of Atomoxetine in Pediatric Patients

Population PK/PD

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

3 Summary of CPB Findings

Metabolism and Genotype

Atomoxetine is primarily biotransformed by CYP2D6 resulting in the formation of the active metabolite, 4-hydroxyatomoxetine, which is rapidly *O*-glucuronidated and excreted in the urine (30-85%). The metabolism and pharmacokinetics of atomoxetine are highly influenced by the genetic polymorphism associated with CYP2D6 activity. The polymorphic expression of CYP2D6 results in a bimodal distribution (poor metabolizer-PM and extensive metabolizer-EM) in the rate at which atomoxetine is metabolically eliminated among individuals.

- *EM Genotype*: The majority of people are designated EM of CYP2D6 substrates and possess a range of activities considered to be normal CYP2D6 activity. Atomoxetine, *N*-desmethylatomoxetine (20-fold less potent), and 4-hydroxyatomoxetine-*O*-glucuronide (inactive) were the measurable circulating species in the plasma of EM subjects after 20-mg ^{14}C-atomoxetine administration and the relative percentage of these three moieties were 27.8%, 1.6% and 70.6%, respectively with limited exposure to the equally active metabolite, 4-hydroxyatomoxetine (<1%). The EM population can be subdivided into three groups based on the number of available wild type alleles. The subgroups are ultra-rapid metabolizers (UM, multiple wild type alleles), homozygous (two wild type alleles) and heterozygous (one wild type allele). The UM genotype accounts for 3% to 7% of the EM population and had 2-fold higher mean atomoxetine clearance estimate compared to other EM subjects. However, the pharmacokinetic differences among these EM subgroups are minor when compared to the differences between EM and PM individuals overall.

- *PM Genotype*: Mutations or deletion of the CYP2D6 gene results in a minority of people (5 to 10% of Caucasians) who are known as PM of CYP2D6 substrates. Atomoxetine, *N*-desmethylatomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide were also the measurable circulating species in the plasma of PM subjects after 20-mg ^{14}C-atomoxetine administration and the relative percentage of these three moieties were 69.2%, 23.1% and 7.7%, respectively with the concentration of the active metabolite, 4-hydroxyatomoxetine below the limit of quantitation —— The rate at which atomoxetine is cleared from the body is 10-fold slower in PM subjects compared to EM subjects although both groups produced the same metabolites. Compared to EM subjects, the slower elimination of atomoxetine in PM subjects resulted in the accumulation and higher plasma exposures to atomoxetine (C^{ss}_{avg} 1554 vs 216 ng/ml, $AUC_{0-\tau}$, 18.6 vs 2.6 µg.hr/ml) and *N*-desmethylatomoxetine (C^{ss}_{avg} 811 vs 17 ng/ml, $AUC_{0-\tau}$, 9.7 vs 0.2 µg.hr/ml) after the same 40-mg dose of atomoxetine BID for 7 days. Exposure to the active metabolite 4-hydroxyatomoxetine was lower in PM subjects compared to that in EM subjects (C^{ss}_{avg} 1.6 vs 2.8 ng/ml, AUC 0.019 vs 0.033 µg.hr/ml).

Basic Pharmacokinetic Information

Atomoxetine pharmacokinetics in adult subjects are linear over the therapeutic dosing range (10-120 mg) with proportional increases in both C_{max} and AUC with increasing

dose. It was rapidly absorbed with a median T_{max} of 1 hour in EM subjects and 2.5 hours in PM subjects. Atomoxetine absolute bioavailability was 94% in PM subjects and 63% in EM subjects; urine recovery of atomoxetine and its metabolites was 89% in both EM and PM subjects. The relative bioavailability of atomoxetine capsule to solution is 100%. After single oral doses, mean C_{max} is 2-fold higher and mean half-life is 4-fold longer (21.6 hours vs 5.2 hours) in PM subjects compared to EM subjects. At steady state, mean C^{ss}_{max} is 5-fold higher, mean C^{ss}_{avg} is 10-fold higher, and mean CL/F is 10-fold slower in PM subjects compared to EM subjects. Although only minimal accumulation of atomoxetine was observed in EM subjects (1.1) after multiple dosing, its accumulation is evident in PM subjects (3.3). The elimination half-life of 4-hydroxyatomoxetine was similar to that of *N*-desmethylatomoxetine (6-8 hrs) in EM subjects, whereas it was much longer in PM subjects (40 hrs for *N*-desmethylatomoxetine, unable to determine for 4-hydroxyatomoxetine).

Population PK Analysis

Conventional and population pharmacokinetic analyses in the pediatric patient population parallel the pharmacokinetics observed in adult population. Smoking, body weight, gender, CYP2D6 genotype, ethnic origin, age, alcohol use, single dose/steady state, albumin concentration and atomoxetine dose were all covariates examined in the analyses. In both populations evaluated, body weight and CYP2D6 status were the primary covariates determined to affect atomoxetine pharmacokinetics:

- *CYP Genotype*: CYP2D6 genotype had a significant effect on atomoxetine clearance. The distribution of the log-transformed individual empirical Bayesian estimates of apparent clearance (CL/F) for the 3 genotypes shows that the PM and EM genotypes can be described by a bimodal distribution with no overlap of clearance values in the 2 groups. The UM population appears to be comparable to the upper end of the EM range, with a great deal of overlap of CL/F values between UM and the rest of EM patients. The 10-fold difference in atomoxetine clearance between EMs and PMs warrants dosage adjustment in PM patients.

- *Body Weight*: Body weight had significant effect on atomoxetine pharmacokinetics. As body weight increased, both clearance and volume of distribution increased in an essentially proportional manner (e.g., CL for 25 kg BW was 13.2 L/hr, and for 50 kg BW was 23 L/hr). The predicted effect of body weight on atomoxetine plasma concentrations were notably different between patients of different body weights when the fixed dosing regimen was used, and this effect was minimized after a 1 mg/kg dosing was used. Based on this relationship a weight-based dosing regimen (mg/kg) for atomoxetine is recommended in pediatric patients.

PK/PD Analysis

- *Efficacy*: At the doses of 0.5, 1.2, 1.8 mg/kg/day, the observed responses (change in ADHDRS from baseline) were –9.9, -13.6 and –13.5, respectively in one clinical study in pediatric patients. Cumulative plot (by week) shows that the 1.2 mg/kg/day dose had better efficacy than the 1.8 mg/kg/day dose after 5 weeks of atomoxetine treatment. Scatter plots of the change from baseline to endpoint in ADHDRS-IV

Parent:Inv total score and atomoxetine AUC were provided and Pearson's correlation coefficient between response and AUC was –0.438 for PMs and –0.068 for EMs. Pharmacokinetic/pharmacodynamic modeling indicates a relationship between systemic exposure or dose and efficacy: population PK model predicts that at doses of 0.5, 1.2 and 1.8 mg/kg/day, the AUC are 0.47, 1.39 and 2.46 μg.hr/ml, respectively; the E_{max} model predicts that these exposures will produce the following corresponding response rates (maximum improvement over baseline): 62%, 78% and 85%. Examination of population subsets (race, gender, age, or prior stimulant treatment) did not reveal any differential responsiveness on the basis of these-groupings.

- *Safety*: Increase in standing heart rate (HR) and orthostatic HR, and reduction in orthostatic systolic and diastolic blood pressure (BP), especially in PM subjects, are predominant pharmacodynamic effects of atomoxetine. Dose-related mean standing HR increase and orthostatic systolic BP reduction after single doses were confirmed by analysis of ECG data. After 40 mg BID doses for 7 days in one study, the mean standing HR was 101 bpm in EM subjects and 116 bpm in PM subjects. In another multiple dose study, exposure to atomoxetine resulted in considerable orthostatic BP drop (-6 mm Hg for EM subjects and –18 mm Hg for PM subjects). The direct effect model analysis showed a negligible slope (0.0027) between plasma concentration and QT prolongation. It predicts that more than 6-fold difference in C_{max} between UM and PM groups will have 4 msec difference in QT_c (375 vs 379 msec). This change is not considered clinically important.

Food Effect and Stomach pH Effect

In adult subjects, the effect of a standard high-fat meal decreased atomoxetine C_{max} by 38% and delayed T_{max} by 3 hours. However, in a population analysis of pediatric patients, food had a lesser effect with a 9% decrease in C_{max} was observed (not formal study, self-reported). The effect of food on atomoxetine pharmacokinetics is considered not to be clinically important given the small decrease in C_{max} observed in clinical practice in the pediatric population analysis. Therefore, it is recommended that atomoxetine may be taken with or without food. Alterations in gastric pH through administration of omeprazole or Maalox did not affect the bioavailability of atomoxetine.

Special Populations

- *Hepatic Impairment*: Ten subjects with hepatic insufficiency due to compensated liver cirrhosis classified as moderate (Child-Pugh B, n=6) or severe (Child-Pugh C, n=4), and 10 healthy subjects completed the study. After single 20-mg dose of atomoxetine, the clearance for the parent drug is half of the normal value in moderate HI subjects and one quarter of the normal value in severe HI subjects (41.5 L/hr, 20.0 L/hr and 10.8 L/hr, respectively). Atomoxetine mean C_{max} was 22% lower, its mean AUC was 2-fold higher, and its mean $t_{1/2}$ was 3-fold longer in EM subjects with HI compared to the EM healthy subjects. There were 73% increases in 4-hydroxyatomoxetine C_{max} and approximately 7-fold increase in its AUC. Proper dosage adjustment should be made in this patient population.

- *ESRD*: In six ESRD (end stage renal deficiency) EM subjects, exposure of all measurable species in plasma after single 20-mg dose of atomoxetine were considerably higher than that in healthy subjects: 164% for atomoxetine, 2-fold for 4-hydroxyatomoxetine, 15-fold for *N*-desmethylatomoxetine and 8-fold for 4-hydroxyatomoxetine-*O*-glucuronide. However, body weight normalized atomoxetine clearance is not much different between ESRD subjects and healthy subjects (0.422 L/hr/kg vs. 0.470 L/hr/kg). Therefore, atomoxetine can be administered to ADHD patients with ESRD or lesser degrees of renal insufficiency without changing the normal dose-escalation sequence.

Drug-Drug Interaction

- *Pharmacokinetic Interaction*: *In vivo* and *in vitro* studies have confirmed that atomoxetine does not inhibit or induce cytochrome P450 enzymes, including CYP3A4, CYP1A2, CYP2D6, and CYP2C9. *In vitro* studies indicate that co-administration of CYP2D6 inhibitors to individuals lacking CYP2D6 activity is not expected to increase the plasma concentrations of atomoxetine. In extensive metabolizers, selective inhibitors of CYP2D6 (paroxetine or fluoxetine) increased atomoxetine steady-state plasma concentrations to exposures similar to those observed in PM subjects, which was 10-fold of that seen in EM subjects. Proper dosage adjustment should be made for patients taking atomoxetine in combination with selective CYP2D6 inhibitors (paroxetine or fluoxetine).

- *Pharmacodynamic Interaction*: Salbutamol (Albuterol) and methylphenidate increased the rise in heart rate associated with atomoxetine. No pharmacological interactions were observed when atomoxetine was administered with alcohol. Co-administration of atomoxetine and paroxetine in EM subjects resulted in an exacerbation of the hemodynamic effects of both drugs, probably due to their similar cardiovascular effects. Dosage adjustment is recommended for co-administration of atomoxetine and paroxetine.

Bioequivalence and Biowaiver

Although atomoxetine hydrochloride is highly soluble and highly permeable, the slower release of the highest strength (60-mg) capsule in pH 6.8 buffer (— % in 30 minutes) does not meet the criteria for being classified as a BCS Class 1 drug product.

The bioequivalence of the 40-mg and 60-mg market-image formulations to clinical capsule formulations was established. A biowaiver is requested for strengths lower than 40 mg (5, 10, 18, and 25 mg) based on following facts: (1) the bioequivalence between 40-mg to-be-marketed capsule and 2x20-mg clinical capsules; (2) the proportionally similar formulations between these lower strengths and the 40-mg capsule; (3) the linear pharmacokinetics of atomoxetine; and (4) 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 —% atomoxetine was released from the 40-mg capsule in 30 minutes and the higher release rate of the lower strengths is not considered to be clinically important. Therefore, the biowaiver for 5-, 10-, 18- and 25-mg strengths of atomoxetine capsules can be granted.

4 QBR

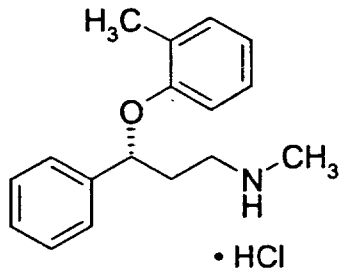
4.1 General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?

- Atomoxetine hydrochloride is indicated for the non-stimulant treatment of Attention Deficit Hyperactivity Disorder (ADHD) as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association 1994) in children, adolescents, and adults.

- Atomoxetine enhances norepinephrine function through a highly selective blockade (a potent inhibitor) of the presynaptic norepinephrine transporter and has low affinities for other neuronal transporters or neurotransmitter receptor sites (dopaminergic, muscarinic-cholinergic, histaminic, serotonergic, α_1 or α_2 adrenergic).

- Atomoxetine hydrochloride (LY139603; LY404363 hydrochloride formerly tomoxetine hydrochloride) is known chemically as benzenepropanamine, *N*-methyl-γ-(2-methylphenoxy), hydrochloride, (-). Atomoxetine HCl is the R(-) isomer as determined by x-ray diffraction. The molecular formula is $C_{17}H_{21}NO.HCl$, which corresponds to a molecular weight of 291.82.



Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.

- Atomoxetine capsules are intended for oral administration only. Each capsule contains atomoxetine HCl equivalent to 5 mg, 10 mg, 18 mg, 25 mg, 40 mg, or 60 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients.

- Dosage and Administration (as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening).

	Initial
Children and adolescents up to 70 kg body weight	0.5 mg/kg/day to a target1.2 mg/kg/day (after 3 to 7 days) to a maximum 1.8 mg/kg/day (after 2 to 4 weeks) or 120 mg/day
Children and adolescents over 70 kg body weight and adults	40 mg/day to a target 80 mg/day (after 3 to 7 days) to a maximum 120 mg/day (after 2 to 4 weeks)
	Maintenance/Extended Treatment
There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with atomoxetine. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use atomoxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.	

Atomoxetine may be taken with or without food. The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated. For those ADHD patients who have hepatic insufficiency or end stage renal disease, cautious titration of atomoxetine to the desired clinical response is recommended by the sponsor. Atomoxetine may be discontinued without tapering the dose.

4.2 General Clinical Pharmacology

1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Primary Clinical Endpoint - Patients who met DSM-IV (*Diagnostic and Statistical Manual 4th edition*) criteria were diagnosed as having ADHD. In both adult and pediatric populations, the primary efficacy variable was the ADHD Rating Scale (ADHDRS)-IV-Parent:Inv total score including hyperactive/impulsive and inattentive sub-scales. The total score is the sum of the scores for each of the 18 items, with higher scores indicating greater severity of ADHD symptoms. Each item is scored on a 0 to 3 scale (total score ranges from 0 to 54) and each item corresponds to one of the 18 DSM-IV symptoms of ADHD. The primary efficacy analysis is based on baseline, last-observation-carried-forward (LOCF) endpoint, and change from baseline to endpoint in ADHDRS-IV-Parent:Inv total score. In adults, signs and symptoms of ADHD were evaluated using the investigator administered CAARS (*Conners Adult ADHD Rating Scale Screening Version*), a 30-item scale.

Safety Measures - Vital signs and blood pressure were monitored in clinical pharmacology and clinical studies. ECG tracings were also obtained at screening at 0, 1, 2, 4, and 12 hours after the morning dosing of placebo or atomoxetine, and at the time of the final assessment. The correction of the QT interval (QT_c) used the Fridericia method.

2. ***Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?***

The primary metabolites of atomoxetine, 4-hydroxyatomoxetine and *N*-desmethylatomoxetine, are also pharmacologically active as norepinephrine reuptake inhibitors. While 4-hydroxyatomoxetine (K_i=3.0 nM) possesses similar inhibitory activity at the norepinephrine transporter as atomoxetine, *N*-desmethylatomoxetine (K_i=92 nM) is approximately 20-fold less active than atomoxetine. 4-hydroxyatomoxetine also has potent pharmacological activity as a serotonin reuptake inhibitor (K_i=43 nM); however, both *N*-desmethylatomoxetine and 4-hydroxyatomoxetine, like atomoxetine, show very little relative affinity for other receptor systems.

Both 4-hydroxyatomoxetine and *N*-desmethylatomoxetine in the plasma were measured along with the parent drug to assess pharmacokinetic parameters. Exposure-response relationships were not explored for these two species due to their relatively smaller exposure compared to the parent drug. In pediatric EM population, parent to metabolite exposure ratio is 23 for *N*-desmethylatomoxetine and 37 for 4-hydroxyatomoxetine at steady state after 20-45 mg BID. In adults with CYP2D6 PM metabolic status, after 75 mg BID for 5 days, exposure to *N*-desmethylatomoxetine is 85-fold of the EMs (45% of the parent), but exposure to 4-hydroxyatomoxetine is only 1/5 of the EMs (0.1% of parent).

Atomoxetine and *N*-desmethylatomoxetine are highly bound to human plasma proteins (98% and 99%, respectively) while protein binding for 4-hydroxyatomoxetine is much less (67%). Assuming that only unbound free drug is available for pharmacological effect (as norepinephrine reuptake inhibition), only 2% of atomoxetine but 33% of 4-hydroxyatomoxetine are pharmacologically active. This assumption markedly reduces the differences between EM and PM subjects in systemic exposure to active moieties. However, there is no evidence to support this assumption unless experimental data show that doses based on resulting comparable free concentration for atomoxetine and 4-hydroxyatomoxetine (dose ratio, 16:1) will produce the same clinical efficacy.

3. ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?***

Atomoxetine pharmacokinetics is linear in EM and PM subjects with proportional increases in C_{max} and AUC with increasing dose. Accumulation is minimal (1.1) in EM subjects and steady state pharmacokinetics of atomoxetine can be predicted from single doses.

Efficacy - The efficacy of atomoxetine in the treatment of ADHD was established in a total of six randomized, double-blind, placebo-controlled studies in children, adolescents, and adults who met DSM-IV (*Diagnostic and Statistical Manual 4th edition*) criteria for

ADHD. The highest dose used was 1.8 mg/kg/day in pediatric clinical trials and 120 mg/day in adult trials.

Clinical trial 1 in pediatric population (8-17 years, N=297, Study LYAC) showed that after 8-week BID treatment at the two higher doses of 1.2 and 1.8 mg/kg/day, improvements in ADHD symptoms were superior in atomoxetine-treated patients compared with placebo-treated patients as measured on the ADHDRS and CGI-S scales (the Clinical Global Impression Severity) and atomoxetine was effective in reducing both inattentive and hyperactive/impulsive symptoms (Figures 1 and 2).

Assessment of Dose-Response

Figure 1. Atomoxetine response by dose (Study Period II)

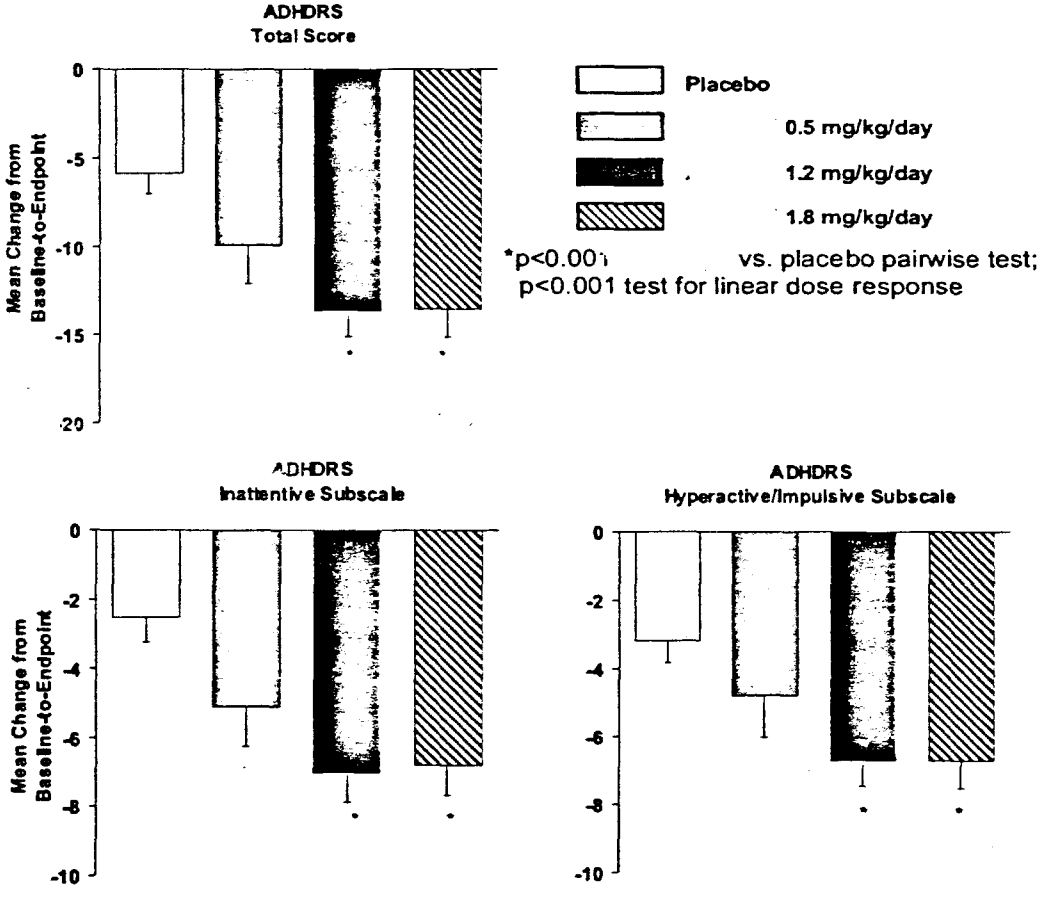
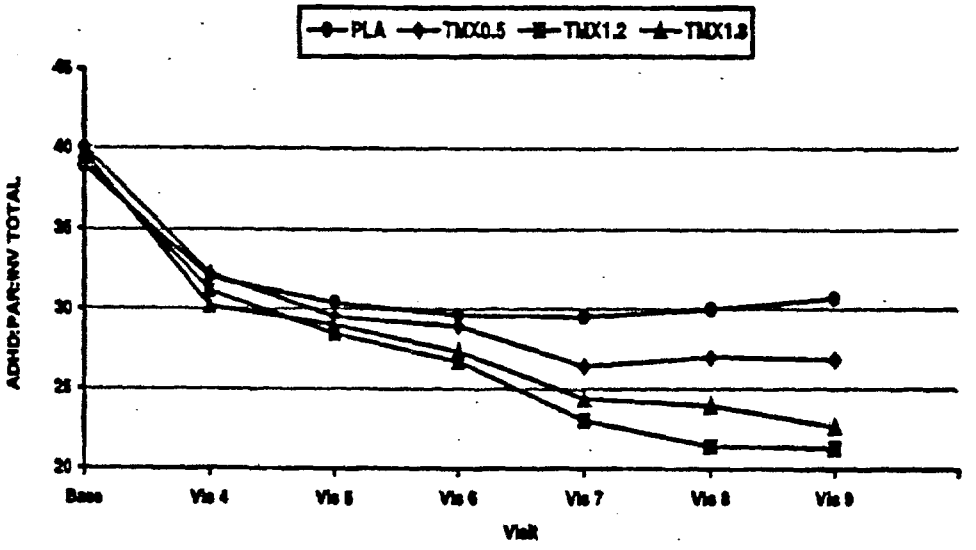


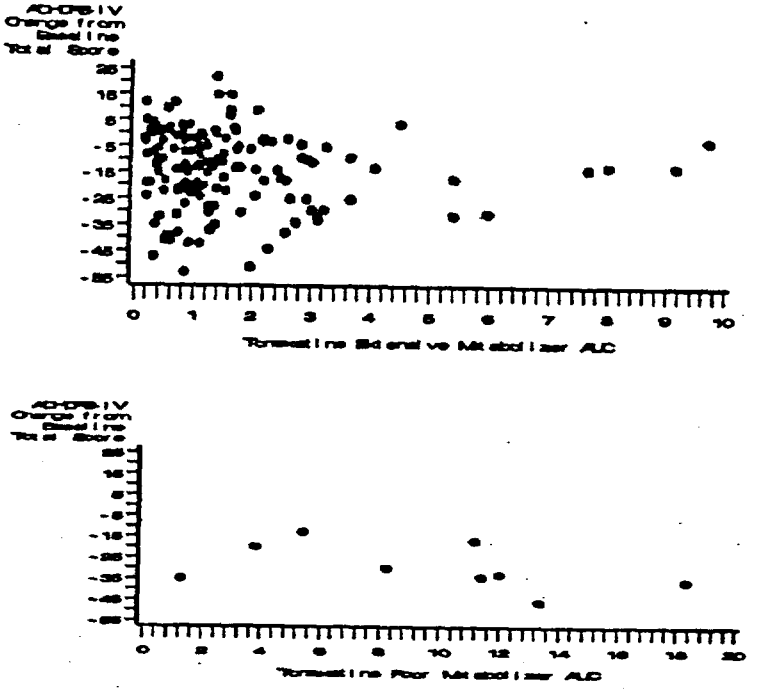
Figure 2. ADHDRS-IV-Parent:Inv total score repeated measures least square means



Relationship of Drug Concentration-Response

Scatter plots of the change from baseline to endpoint in ADHDRS-IV Parent:Inv total score and atomoxetine AUC are provided below (Figure 3). Pearson's correlation coefficient between response and AUC was –0.438 for PM patients and –0.068 for EM patients.

Figure 3. Scatter plots of the change from baseline to endpoint in ADHDRS-IV Parent:Inv total score and atomoxetine AUC for EM patients and PM patients



Population Analysis of Exposure-Response

Population PK model and exposure-response model (E_{max}) predict that doses of 0.5, 1.2 and 1.8 mg/kg/day (AUC 0.47, 1.39 and 2.46 µg.hr/ml), will produce corresponding response rates (maximum improvement over baseline) of 62%, 78% and 85%. 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.

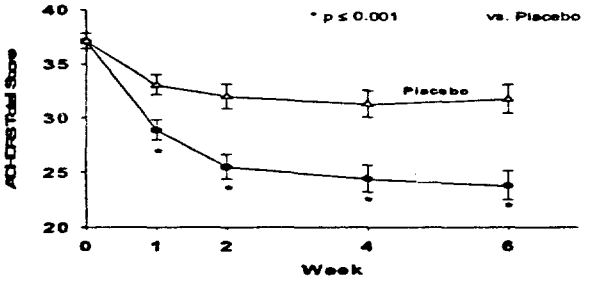
Table 1. Dose-Response and Exposure Response

Dose (mg/kg/day)	Response (observed) Change in ADHDRS	$AUC_{0-\tau}$ (PK model) (µg.hr/ml)	Response (E_{max} Model) Maximum improvement over baseline
0.5	-9.9	0.47	62%
1.2	-13.6	1.39	78%
1.8	-13.5	2.46	85%

Assessment of Once-Daily Dosing

Clinical trial 2 in pediatric population (6-16 yrs, N=171) showed that improvements in ADHD symptoms were superior in atomoxetine-treated patients (once daily for 6 weeks at mean dose of 1.3 mg/kg/day) compared with placebo-treated patients as measured on the ADHDRS and CGI-S scales (Figure 4). This study demonstrates that atomoxetine is effective when administered once daily in the morning.

Figure 4. Once-daily administration of atomoxetine



Examination of population subsets (race, gender, age, or prior stimulant treatment) did not reveal any differential responsiveness on the basis of these sub-groupings.

The efficacy of atomoxetine beyond 9 weeks and safety of atomoxetine beyond 1 year of treatment have not been systematically evaluated. The safety and efficacy of atomoxetine in pediatric patients less than 6 years of age and in geriatric patients have not been established.

Safety - In the pharmacological studies, atomoxetine was associated with postural hypotension and heart rate compensatory increases following single dose greater than 30 mg and in some subjects, following multiple doses. Increases in standing heart rate, (clinically relevant tachycardia-100 bpm), increases in orthostatic heart rate, and

reduction in orthostatic systolic and diastolic blood pressure, especially in PM subjects, are prominent pharmacodynamic effects of atomoxetine.

Dose-related mean heart rate increase and mean orthostatic systolic blood pressure reduction were confirmed by analysis of ECG data (Tables 2 and 3), and 40-mg dose of atomoxetine BID for 7 days resulted in standing heart rate increases in both EM and PM subjects with PM subjects reaching maximum heart rates about 10 bpm higher than EM subjects (Table 4). In another study, exposure to atomoxetine resulted in larger orthostatic systolic blood pressure drop in PMs (-18 mm Hg) than in EMs (-6 mm Hg) (Table 5).

Table 2. Standing Heart Rate (bpm) after Single Doses of Atomoxetine

Dose (mg)	10	30	60	90	120
EM (N=15)	87.8	91.4	94.4	100.3	101.7
PM (N=11)	87.6	90.7	99.2	100.0	104.7

Study HFBJ in adults

Table 3. Changes in Vital Signs after Single Doses of Atomoxetine

Dose (mg)	10	40	90	120
Orthostatic Systolic BP Δ (mmHg)	-3.7	-6.7	-11.9	-13.3

Study LYAN in Japanese adults (EMs). N=23 males

Table 4. Standing Heart Rate (bpm) after 40 mg BID (at Day 7 morning)

Time (hr)	-0.5	0	0.5	1	1.5	2	2.5	3
Placebo	79.0	79.0	73.7	71.7	84.8	85.3	88.8	90.2
EM (N=8)	94.9	92.2	90.0	95.6	97.4	109.2	115.5	115.7
PM (N=6)	113.6	114.9	109.0	110.8	112.7	124.5	122.3	123.6

Study HFBJ in adults. Mean=101.3 (EMs) and Mean=116.4 (PMs)

Table 5. Effect of Multiple-Dose on Vital Signs

	Reference*	Naïve to Drug	Exposure to Drug
Standing HR (bpm)			
EMs (N=10)	92.5	76.5	93.3
PMs (N=6)		71.7	86.9
Orthostatic HR Change (bpm)			
EMs	12.3	12.1	26.1
PMs		10.2	20.9
Orthostatic Systolic BP Change (mmHg)			
EMs	-6.5	-1.5	-6.0
PMs		-0.8	-18.0

Study LYAE in adults. * Reference population as noted in Streeten, 1987.

QT_c - The direct effect model analysis resulted in a negligible slope (0.0027) between plasma concentration and QT prolongation. It predicts that more than 6-fold difference in C_{max} between UM and PM groups will have 4 msec difference in QT_c (375 vs 379 msec). This change is not considered clinical important. Although there was no clear and direct relationship between atomoxetine exposure and QT_c changes, QT_c prolongation was seen

more frequently in PM subjects whose atomoxetine exposure was much higher than that of EM subjects (Tables 6 and 7).

Table 6. Effect of Single Doses of Atomoxetine on QT_c Intervals

Dose (mg)	0	10	30	60	90	120
2-hr Postdose		Least Square Mean (msec)				
EM (16)	**376.6**	375.4	382.4	377.8	380.0	378.2
Δ from Placebo		-1.2	5.8	1.2	3.4	1.5
PM (11)	**382.8**	383.3	389.4	387.8	390.7	388.8
Δ from Placebo		0.5	6.5	5.0	7.9	6.0
24-hr Postdose						
EM (16)	**378.0**	372.9	373.7	373.8	374.2	374.1
Δ from Placebo		-5.2	-4.3	-4.3	-3.9	-4.0
PM (11)	**383.9**	382.2	385.6	390.9	390.7	384.9
Δ from Placebo		-1.8	1.6	7.0	6.8	1.0

Study HFBJ in adults.

Table 7. Effect of Multiple-Dose of Atomoxetine on QT_c Intervals

	Placebo (Day 1-7)	EM (N=8)	PM (N=6)
Least Square Mean (msec)	369.0	374.5	376.9
Δ from Placebo		5.5	7.9

Study HFBJ in adults

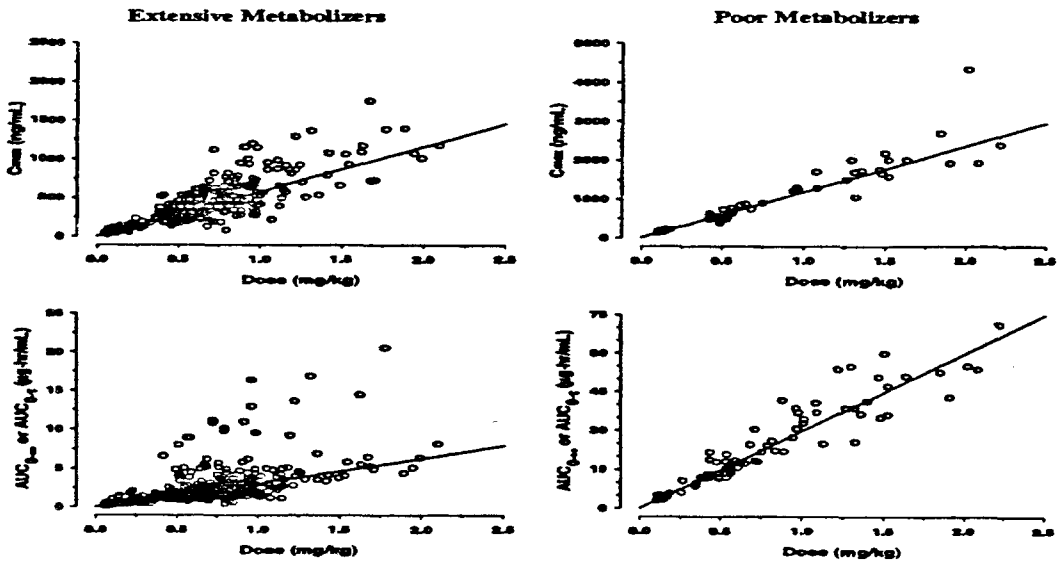
In Study HFBJ, individual changes in QT_c interval >30 msec were equally represented in the EM and PM subjects and were nearly equally represented by placebo and drug administration. In Study LYAE, QT_c interval changes were time dependent in PM subjects. The largest QT_c interval change (30 msec after 75 mg BID) were at the highest predose (trough) concentrations in PM subjects. No statistically significant changes in QT_c interval were noted 1 hour postdose.

4. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

There is no evidence to show that the pharmacokinetics of atomoxetine and its active metabolites are different between healthy volunteers and patients or between adults and children.

Basic PK - Atomoxetine pharmacokinetics in adult subjects are linear over the therapeutic dosing range with proportional increases in both C_{max} and AUC with increasing dose (see Figure 5).

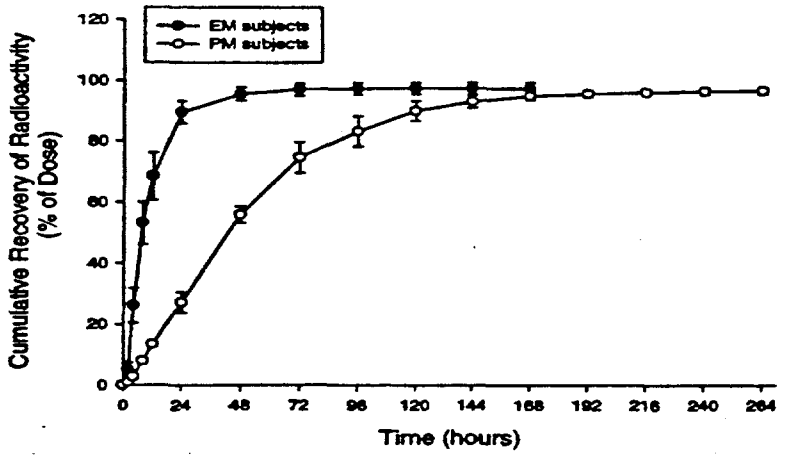
Figure 5. Dose proportionality assessment for atomoxetine Cmax and AUC for combined adult clinical pharmacology studies



Lines represent the power model fit of the data.

Atomoxetine was rapidly absorbed with a median T_{max} of 1 hour in EM and 2.5 hours in PM subjects. Its absolute bioavailability was 94% in PM and 63% in EM subjects. Urinary recovery of atomoxetine and its metabolites was approximately 90% in both EM subjects (in 168 hrs) and PM subjects (up to 312 hrs) indicating nearly complete absorption in all subjects and modest first pass metabolism in EM subjects (Figure 6).

Figure 6. Cumulative elimination (mean±SEM) of total radioactivity after a single oral 20-mg dose of ^{14}C-atomoxetine to healthy EM and PM male subjects

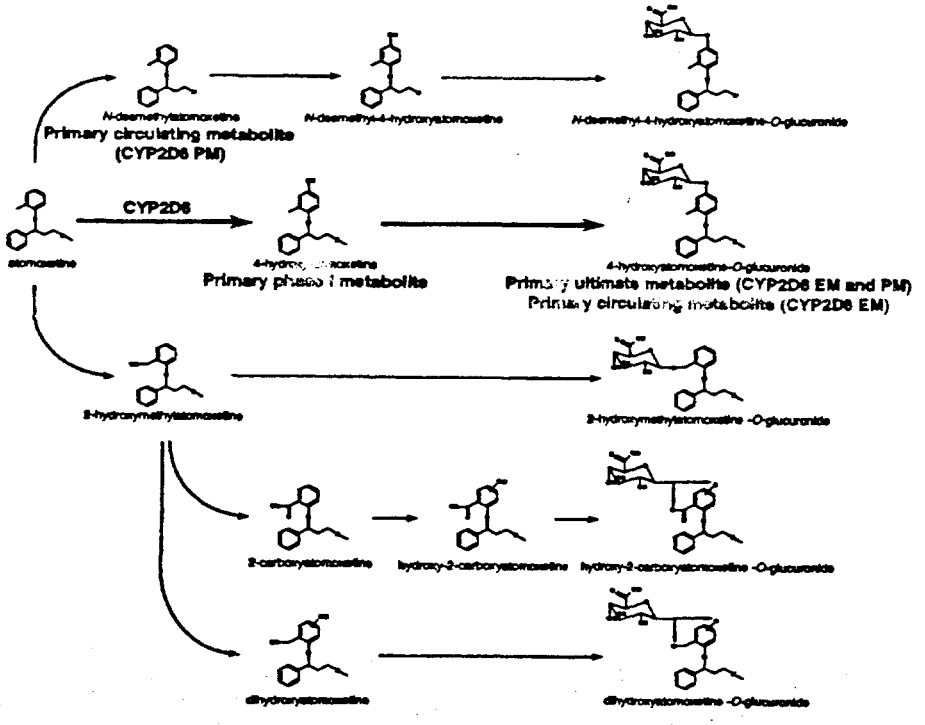


In adults, the effect of a standard high-fat meal decreased C_{max} by 37% and delayed T_{max} by 3 hours. Alterations in gastric pH through administration of omeprazole and Maalox did not affect the bioavailability of atomoxetine.

After single oral doses, mean C_{max} is 2-fold higher and mean half-life is 4-fold longer (21.6 hours vs 5.2 hours) in PM subjects compared to EM subjects. At steady state, mean C^{ss}_{max} is 5-fold higher, mean C^{ss}_{avg} is 10-fold higher, and mean CL/F is 10-fold slower in PM subjects compared to EM subjects. Although only minimal accumulation of atomoxetine was observed in EM subjects (1.1) after multiple dosing, its accumulation is evident in PM subjects (3.3).

Hepatic Metabolism and Renal Excretion – In both EM and PM subjects, atomoxetine was well absorbed from the gastrointestinal tract and primarily cleared from the body by oxidative metabolism with nearly all its metabolites being eliminated by excretion into the urine. There are three oxidative (phase 1) metabolic pathways identified for the transformation of atomoxetine: aromatic ring-hydroxylation, benzylic/aliphatic oxidation, and *N*-demethylation. Atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide are the principal circulating species in the plasma of EM subjects, while atomoxetine and *N*-desmethylatomoxetine are the principle circulating species in PM subjects. Figure 7 shows the proposed scheme for the metabolism of atomoxetine in humans:

Figure 7. Proposed scheme for the metabolism of atomoxetine in humans



The primary phase I metabolite of atomoxetine produced by both EM and PM subjects is 4-hydroxyatomoxetine, which is subsequently conjugated forming the primary ultimate metabolite of atomoxetine, 4-hydroxyatomoxetine-*O*-glucuronide. However, the amount of the dose excreted as 4-hydroxyatomoxetine-derived metabolites was greater in the EM subjects (85%) compared to PM subjects (45%). Although the same major metabolites of atomoxetine are produced regardless of CYP2D6 metabolic status, the rate of metabolic elimination for atomoxetine is substantially slower in PM subjects (10-fold difference).

The relative amount of metabolites derived from secondary routes of biotransformation, such as *N*-desmethylatomoxetine- and 2-hydroxymethylatomoxetine-derived metabolites, was greater in PM subjects (55%) as compared to EM subjects (15%).

Differences in atomoxetine concentrations between EM and PM subjects are due to a decrease in the rate of formation of 4-hydroxyatomoxetine (and subsequently 4-hydroxyatomoxetine-*O*-glucuronide), which results in a reduction in the rate of elimination of atomoxetine in PM subjects. Regardless of CYP2D6 metabolic status, very little atomoxetine was excreted into the urine unchanged (<3%), indicating a relatively minor role for renal clearance.

Metabolic Pathways - The primary phase I metabolites of atomoxetine are 4-hydroxyatomoxetine and *N*-desmethylatomoxetine.

CYP2D6 is the enzyme primarily responsible for the formation of 4-hydroxyatomoxetine (aromatic hydroxylation). *In vitro* human liver microsomes study showed that detectable levels of 4-hydroxyatomoxetine were found by CYP1A2, -2A6, -2B6, -2C9, -2C19, -2D6, -2E1 and –3A4 when very high concentration of atomoxetine was used (100 μM). However, the formation rate by CYP2D6 was >400-fold greater than the rate observed for the other enzymes at low atomoxetine concentration (1 μM). The formation of 4-hydroxyatomoxetine was substantially reduced in microsomes with low levels of CYP2D6 and completely absent in microsomes deficient of CYP2D6. Thus, CYP2D6 plays a central role in aromatic hydroxylation of atomoxetine.

CYP2C19 is the primary enzyme responsible for *N*-desmethylatomoxetine formation. At a higher substrate concentration (75 μM), multiple enzymes appear to be capable of metabolizing atomoxetine to *N*-desmethylatomoxetine.

Six atomoxetine-related metabolites were identified in the human liver slice preparations. The predominant metabolite produced by human liver slices, as well as slices from each of the other species evaluated, was identified as 4-hydroxyatomoxetine-*O*-glucuronide. Minor metabolites included 4-hydroxyatomoxetine, 2-hydroxymethylatomoxetine, *N*-desmethylatomoxetine, 4-hydroxy-*N*-desmethylatomoxetine, and 4-hydroxy-*N*-desmethylatomoxetine-*O*-glucuronide. Based on the structures of the identified metabolites, three oxidative (phase I) metabolic pathways are proposed for the biotransformation of atomoxetine in human liver slices: aromatic ring-hydroxylation, benzylic/aliphatic oxidation, and *N*-demethylation. Subsequent *O*-glucuronidation of the hydroxylated metabolites was the only conjugation (phase II) pathway to participate in the formation of atomoxetine-related metabolites in human liver slices.

Protein Binding - Atomoxetine is highly bound to human plasma proteins (98%). No difference in the binding of atomoxetine was observed between plasma from adult and pediatric subjects. Its plasma protein binding was independent of concentration up to and including the highest concentration tested (3,000 ng/ml). Plasma protein binding was 99% for *N*-desmethylatomoxetine and 67% for 4-hydroxyatomoxetine.

5. *What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?*

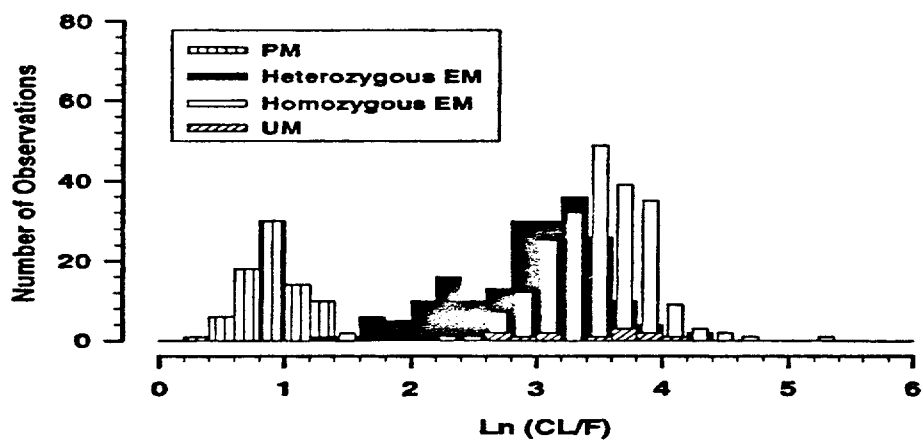
Table 8. Geometric Means and Variance Components of Pharmacokinetic Parameters for Combined Adult Clinical Pharmacology Studies

Variable	Geo Mean (N/n)	Intra-CV%	Inter-CV%	Geo Mean (N/n)	Intra-CV%	Inter-CV%
	EM Subjects			PM Subjects		
C^{ss}_{avg} (ng/ml)/(mg/kg)	249 (76/106)	58.5	11.5	2537 (15/32)	13.9	14.0
C_{max} (ng/ml)/(mg/kg)	568 (155/333)	27.4	25.3	1165 (19/54)	10.8	14.8
C^{ss}_{max} (ng/ml)/(mg/kg)	667 (76/106)	15.5	41.3	3223 (15/33)	15.1	11.3
$T_{1/2}$ (hr)	3.6 (223/431)	18.0	27.5	20.6 (22/56)	10.9	17.3
Percent Fluctuation (%)	245 (76/106)	17.3	27.3	58 (15/32)	27.0	12.3
Accumulation	1.13 (76/106)	1.6	8.7	3.25 (9/9)	16.0	2.6
CL/F (L/hr/kg)	0.352 (223/431)	18.8	55.7	0.034 (28/79)	10.4	18.8
V_z/F (L/kg)	1.82 (223/431)	25.6	32.8	1.01 (22/56)	10.5	19.5
V^{SS}/F (L/kg)	1.88 (155/325)	24.3	29.4	0.92 (19/47)	7.7	16.5
T_{max} (hr) (Median)	1.0			2.5		

Geo Mean (N/n)= Geometric mean (number of subjects/number of observations)

In adult healthy volunteers with EM status, moderate intersubject variability and low intrasubject variability were observed for pharmacokinetic parameters. Intersubject variability in PM subjects is smaller. Similar variabilities were observed in pediatric population: inter-patient variability in pediatric EM population is 44.5% for CL/F and 32.6% for V/F. The reason for larger variability in EM subjects than that in PM subjects is mainly due to metabolic differences in EM subpopulations based on the number of available wild type alleles: ultra-rapid metabolizers who have multiple wild type alleles, homozygous who have two wild type alleles, and heterozygous who have one wild type allele (Figure 8).

Figure 8. Frequency distribution of all atomoxetine log-transformed CL/F (L/hr) values based on CYP2D6 genotype for the combined adult clinical pharmacology studies



4.3 Intrinsic Factors

1. *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or*

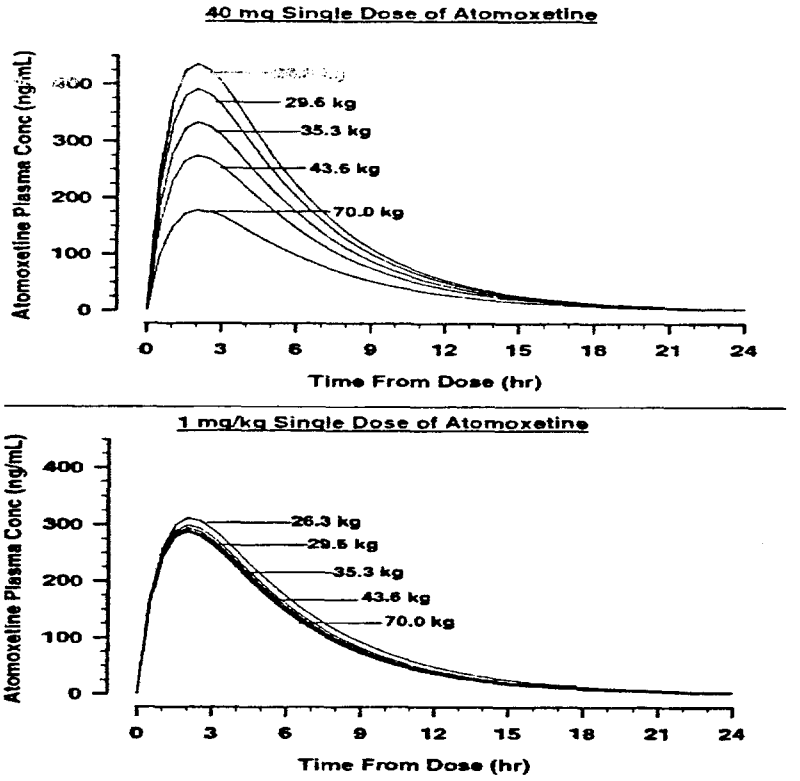
response and what is the impact of any differences in exposure on the pharmacodynamics?

Conventional and population pharmacokinetic analyses in the pediatric patient population parallel the pharmacokinetics observed in adult subjects. Smoking, body weight, gender, CYP2D6 genotype, ethnic origin, age, alcohol use, caffeine consumption, single dose/steady state, albumin concentration and atomoxetine dose were all covariates examined in the analyses. In both populations evaluated, dose, body weight and CYP2D6 status were the primary covariates determined to affect atomoxetine pharmacokinetics:

Dose: In the PM subjects, CL/F decreased with increasing dose (28.2 L/hr for 10 mg and 23.7 L/hr for 120-mg), however, this decrease does not represent a meaningful departure from dose proportionality over a 12-fold range of dose (90% CI: 1.10, 1.24).

Body Weight: Body weight had significant effect on atomoxetine pharmacokinetics. As body weight increased, both clearance and volume of distribution increased in an essentially proportional manner (e.g., CL for 25 kg, 13.2 L/hr, for 50 kg, 23 L/hr). The predicted effect of body weight on atomoxetine plasma concentrations were notably different between patients of different body weights when the fixed dosing regimen was used, and this effect is minimized after a 1 mg/kg dosing is used (Figure 9). A weight-based dosing regimen (mg/kg) for atomoxetine is recommended in pediatric patients based on this relationship.

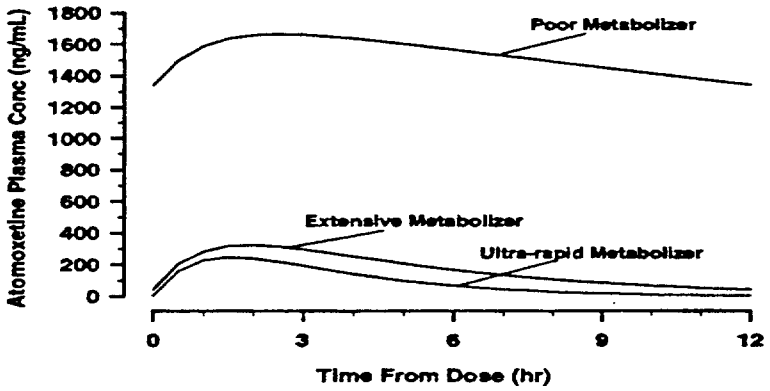
Figure 9. Predicted effect of body weight on atomoxetine plasma concentration for a 40-mg dose and a 1 mg/kg dose



These weights represent the 5th, 25th, median, 75th, and 95th percentile of body weight from this patient population.

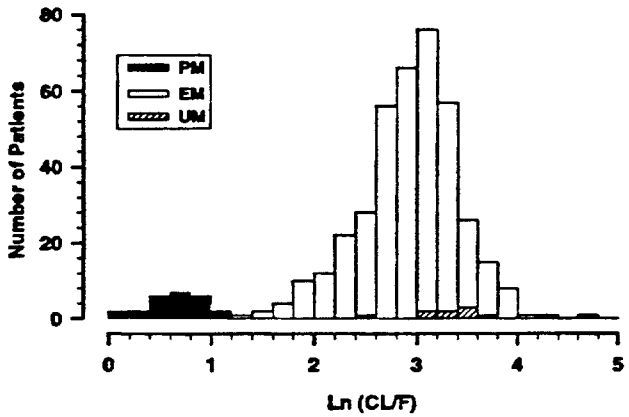
CYP Genotype: CYP2D6 genotype had a significant effect on atomoxetine clearance (Figure 10). The distribution of the log-transformed individual empirical Bayesian estimates of apparent clearance (CL/F) for the 3 genotypes shows that the PM and EM genotypes can be described by a bimodal distribution with no overlap of clearance values in the 2 groups (Figure 11). The UM (ultra-rapid metabolizer) population appears to be comparable to the upper end of the EM range, with a great deal of overlap of CL/F values between UM and the rest of EM patients. The 10-fold difference in atomoxetine clearance between EMs and PMs warrants dosage adjustment in PM patients.

Figure 10. Predicted steady-state atomoxetine plasma concentrations over a 12-hour dosing interval in EM, PM and UM after a 1 mg/kg twice daily dosing regimen.



An EM, UM, or PM patient weighing 40 kg receiving 40 mg doses of atomoxetine every 12 hours.

Figure 11. Frequency distribution of individual post-hoc estimates from the final population model based on CYP2D6 genotype.



2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Elderly - Pharmacokinetics of atomoxetine have not been evaluated in the geriatric population. The number of ADHD patients in geriatric population is expected to be very limited. The safety and efficacy of atomoxetine in geriatric patients have not been established.

Pediatric Patients - Body weight had significant effect on atomoxetine pharmacokinetics. As body weight increased, both clearance and volume of distribution increased in an essentially proportional manner. A weight-based dosing regimen (mg/kg) for atomoxetine is recommended in pediatric patients based on this relationship.

Gender - Gender did not influence atomoxetine disposition in both adult and pediatric populations.

Age - Age did not affect atomoxetine pharmacokinetics when dose was based on body weight in pediatric population.

Race - Based on the ethnic groups represented in clinical pharmacology studies, patients of Caucasian, Hispanic, and African descent as well as Japanese had no statistically significant differences in atomoxetine pharmacokinetics.

Renal Impairment – Pharmacokinetics of atomoxetine was studied in six EM subjects with end stage renal disease (ESRD). Exposure of all measurable species in plasma after a single dose of 20 mg atomoxetine were considerably higher in these subjects than that in healthy subjects: atomoxetine (64% increase), 4-hydroxyatomoxetine (2-fold), *N*-desmethylatomoxetine (15-fold) and 4-hydroxyatomoxetine-*O*-glucuronide (8-fold). However, body weight normalized atomoxetine clearance is not much different between ESRD subjects and healthy subjects (0.422 L/hr/kg vs. 0.470 L/hr/kg). Therefore, atomoxetine can be administered to ADHD patients with ESRD or lesser degrees of renal insufficiency without changing the normal dose-escalation sequence.

Hepatic Impairment – Ten EM subjects with hepatic insufficiency due to compensated liver cirrhosis classified as moderate (Child-Pugh B, n=6) or severe (Child-Pugh C, n=4), and 10 healthy subjects completed the pharmacokinetic study. After 20 mg single dose of atomoxetine, mean atomoxetine C_{max} was 22% lower, mean AUC was 2-fold higher, and mean $t_{1/2}$ was 3-fold longer in EM patients with HI compared to the EM healthy subjects. For 4-hydroxyatomoxetine, there was a 73% increase in C_{max} and approximately 7-fold increase in AUC. It is predicted that PM patients with HI will have even higher exposure compared to PM patients without HI whose steady state average concentration of atomoxetine are already 10-fold of that of EM subjects. Based on that atomoxetine apparent clearance in patients with moderate hepatic impairment is one half of the normal

value, and in patients with severe hepatic impairment is one quarter of the normal value, dosage adjustments should be made accordingly.

Pregnancy and Lactation – No adequate and well-controlled studies have been conducted in pregnant women. Atomoxetine should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Atomoxetine and its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Caution should be exercised if atomoxetine is administered to nursing women.

4.4 Extrinsic Factors

1. ***What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?***

The results of the population pharmacokinetic analyses indicated that smoking, caffeine consumption and alcohol use did not affect atomoxetine pharmacokinetics.

2. Drug-Drug Interactions

Pharmacokinetic Interactions

Although numerous CYP enzymes including CYP1A2, -2A6, -2B6, -2C9, -2C19, -2D6, -2E1 and –3A4 are capable of metabolizing atomoxetine resulting in 4-hydroxyatomoxetine and *N*-desmethylatomoxetine, CYP2D6 is primarily responsible for the 4-hydroxylation and CYP2C19 is primarily responsible for the *N*-demethylation of atomoxetine at clinically relevant atomoxetine concentrations.

In Vitro Studies

Enzyme Inhibition - *In vitro* studies were conducted to evaluate the possibility that atomoxetine as well as its phase I metabolites are enzyme inhibitors. Inhibition of CYP2D6 mediated metabolism by *N*-desmethylatomoxetine and 4-hydroxyatomoxetine and atomoxetine (total predicted inhibition of 65%) suggested there may be an effect of these compounds on the metabolic clearance of co-administered agents metabolized by CYP2D6 in the EM population. Little effect of atomoxetine administration is predicted on CYP3A metabolism in the EM population (15%). In the PM population in which atomoxetine and *N*-desmethylatomoxetine accumulate to levels that are higher than EM population, CYP3A mediated metabolism was predicted to be inhibited by a total of 73%. Due to lack of CYP2D6 in a PM population, inhibition of CYP2D6 mediated metabolism could not occur in this population. Little inhibition of CYP1A2 and CYP2C9 mediated metabolism was predicted in either the PM or EM populations based on the studies reported.

The antibody to the CYP2C subfamily of enzymes was the only antibody able to the formation of *N*-desmethylatomoxetine (≥34% inhibition). At an atomoxetine

concentration of 10 μM, the only inhibitor able to decrease *N*-desmethylatomoxetine formation were the inhibitors of CYP2C19 (omeprazole and S-mephenytoin) and CYP1A2 (furafylline). A number of the inhibitors exhibited the ability to inhibit the formation of *N*-desmethylatomoxetine at atomoxetine concentrations of 75 μM.

A prediction concerning the amount of inhibition expected *in vivo* from *in vitro* results cannot be definitely modeled without information as to the concentrations of atomoxetine, *N*-desmethylatomoxetine and 4-hydroxyatomoxetine at the active site of the enzymes.

Enzyme Induction - The known inducers 3-methylcholanthrene and rifampicin, which served as positive controls for CYP1A and CYP3A induction, respectively, produced significant induction (>2-fold, CYP1A2 mediated 7-ethoxyresorufin O-deethylase, EROD, and CYP3A4 mediated midazolam 1'-hydroxylase, MZD-1OH). Atomoxetine in turn was not an inducer of CYP1A2 or CYP3A in the three human hepatocyte preparations examined.

In Vivo Drug-Drug Interactions

Desipramine: Coadministration of atomoxetine and desipramine, a selective CYP2D6 probe drug, was used to assess atomoxetine's ability to inhibit metabolism of CYP2D6 substrates in 22 EM (11 males and 11 females) healthy subjects. Atomoxetine at steady state condition (60 mg twice daily for 13 days) did not alter CYP2D6-mediated metabolism of desipramine (single 50 mg dose). Similarly, atomoxetine steady state pharmacokinetics was not influenced by a single dose of desipramine.

Adding desipramine to atomoxetine seems to have little change on orthostatic systolic blood pressure (SBP). However, standing and orthostatic heart rates (HR) at 24 hours were affected by the combination treatment than atomoxetine alone (p=0.0015 and 0.072, respective) although the changes may not be clinically important. The potential safety and tolerance of multiple desipramine dosing with chronic atomoxetine dosing cannot be determined from this study. Because desipramine has noradrenergic effects, it should not be used with atomoxetine in combination.

Midazolam: The ability of atomoxetine to act as an inhibitor of the CYP3A metabolic pathway was evaluated using midazolam as a probe drug in healthy PM subjects. A total of 8 healthy subjects (4 M, 4 F) participated and 5 subjects (4 M and 1 F, all Caucasians) competed the study. Atomoxetine was administered 60 mg twice daily for 12 days and on Days 6 and 12, a single 5 mg dose of midazolam oral syrup was given 30 minutes after atomoxetine dosing. Atomoxetine PK parameters essentially remained unchanged from Day 6 to Day 12. Midazolam systemic exposure was 16% higher (90% CI: 0.90, 1.47) compared to that when midazolam was given alone. Due to subject variability higher than expected and the small sample size, conclusion could not be made firmly. Nevertheless, the modest changes 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 with two voluntarily withdrawing and one discontinuing due to adverse events. There is a statistically significant increase after the combination treatment in supine pulse rate (p=0.005), systolic and diastolic blood pressure (p=0.004 and 0.006, respectively). No subjects had QT_c intervals that exceeded the gender-based limits of normal (450 msec for men and 470 msec for women).

Paroxetine: Coadministration of paroxetine (20 mg QD), a known inhibitor of CYP2D6, with atomoxetine (at 20 mg BID) in 14 healthy male and female EM subjects resulted in large increase in steady state plasma exposure (AUC) for atomoxetine (6.5-fold) and *N*-desmethylatomoxetine (20-fold), and elimination half-life of atomoxetine was 3 times longer (11 hrs) compared to that at steady state without paroxetine coadministration (4 hrs). Plasma concentrations of atomoxetine after coadministration with paroxetine approached values similar to those expected in CYP2D6 PM subjects.

Pharmacokinetic parameters of paroxetine were not altered when coadministered with atomoxetine.

Combination therapy with paroxetine resulted in greater orthostatic tachycardia (standing HR and orthostatic HR were 101.6 and 32.3 beats/min) compared to atomoxetine therapy alone (87.4 and 19.3 beats/min). Orthostatic systolic blood pressure and diastolic blood pressure were –16.6 and –6.2 mm Hg after the combination compared to –10.2 and –1.8 mm Hg after atomoxetine therapy alone. Paroxetine has similar cardiovascular effects as atomoxetine. The PD pattern suggests that most of the cardiovascular changes were due to increases in concentrations of atomoxetine and *N*-desmethylatomoxetine. 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. Dose adjustment is recommended when these two drugs are used in combination.

Fluoxetine: Coadministration of fluoxetine (20 mg QD for 36 days), a known inhibitor of CYP2D6, with atomoxetine (at sequential dosing of 10, 45 and 75 mg BID for up to 5 days of each dose) in 20 healthy male and female EM subjects resulted in plasma concentrations of atomoxetine that approximated values seen in CYP2D6 PM subjects. Two subjects discontinued due to syncope, and the sponsor claimed that this was the result of factors other than or in addition to atomoxetine pharmacology.

The subjects in the 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, demonstrating the inhibition of CYP2D6 activity by fluoxetine. However, this 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 concentration through fluoxetine CYP2D6 inhibition.

According to the sponsor, the frequency of AEs 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 of 10 to 75 mg twice daily for 5 days in fluoxetine-treated EM subjects.

In the current study atomoxetine was added to the steady state fluoxetine in a titrated manner. The worst-case scenario that fluoxetine is added to atomoxetine at steady state condition has not been tested. Dose adjustment should be made when these two drugs are used in combination.

Pharmacodynamic Interactions

Salbutamol: Atomoxetine is a selective noradrenaline enhancer, salbutamol is a β-2 selective adrenoceptor agonist and both drugs are associated with hemodynamic effects. At 60 mg twice daily doses for 5 days in 11 Chinese and 2 Indian EM healthy male subjects, atomoxetine had limited additional effects on the cardiovascular changes attributable to salbutamol single dose infusion (5 μg/min over 2 hours), 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. Chronic dosing of atomoxetine with single doses of IV salbutamol was not associated with QT_c interval prolongation or other clinical important ECG changes. The steady state pharmacokinetics of atomoxetine and its *N*-desmethyl and 4-hydroxy metabolites were not altered by administration of the usual therapeutic dose of salbutamol intravenously.

Methylphenidate: In 12 Asian male EM subjects, acute atomoxetine (60 mg BID) resulted in transient increase in the heart rate, and systolic and diastolic blood pressure, while chronic atomoxetine (60 mg BID for 5 days) only had effect on heart rate. Acute and chronic methylphenidate (60 mg once daily) caused a transient increase in the heart rate, and systolic and diastolic pressure. In combination, there was no incremental effect of atomoxetine on the cardiovascular changes attributed to MP in healthy CYP2D6 EM Asian subjects. MP's marked cardiovascular effects may be due to the observed increase in plasma adrenaline concentrations, which was not seen following atomoxetine dosing.

Alcohol: Pretreatment with 40 mg atomoxetine BID for 5 days in 6 EM and 6 PM subjects (6 M; 6 F) did not increase or reduce the intoxicating effects of ethanol (0.6 mg/kg). There is no evidence that PM subjects are likely to have a greater PD interaction with ethanol than EM subjects however, a greater incidence of AEs was reported in PM subjects.

Summary

Pharmacokinetic Interaction: *In vivo* and *in vitro* studies have confirmed that atomoxetine does not inhibit or induce cytochrome P450 enzymes, including CYP3A4, CYP1A2, CYP2D6, and CYP2C9. *In vitro* studies indicate that co-administration of CYP2D6 inhibitors to individuals lacking CYP2D6 activity is not expected to increase the plasma concentrations of atomoxetine. In extensive metabolizers, selective inhibitors

of CYP2D6 (paroxetine and fluoxetine) increased atomoxetine steady-state plasma concentrations to exposures less than or similar to those observed in PM subjects, which was 10-fold higher than that seen in EM subjects. Proper dose adjustment should be made for patients with combination drug therapy.

Pharmacodynamic Interaction: Salbutamol and methylphenidate increased the rise in heart rate associated with atomoxetine. Co-administration of atomoxetine and paroxetine resulted in an exacerbation of the hemodynamic effects of both drugs, probably due to their similar cardiovascular effects. No pharmacological interactions were observed when atomoxetine was administered with alcohol.

Protein Binding Interaction: Atomoxetine was most highly bound to albumin (97.5%) and, to a lesser extent, bound to α_1--acid glycoprotein (76.7%) and IgG (14.5%). At therapeutic concentrations, acetylsalicylic acid, desipramine, diazepam, midazolam, paroxetine, phenytoin, and warfarin have no effect on the plasma protein binding of atomoxetine. Atomoxetine, at therapeutic concentrations, does not affect the plasma protein binding of acetylsalicylic acid, desipramine, diazepam, paroxetine, phenytoin, and warfarin. Acetylsalicylic acid at toxic concentrations (>300 μg/ml) can reduce the plasma protein binding of atomoxetine resulting in an approximately 3-fold increase in the fraction of unbound atomoxetine.

4.5 General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Atomoxetine hydrochloride is highly soluble and highly permeable and can be classified as a BCS Class 1 drug substance.

Solubility

Table 9. 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 Cut-off 60 mg/250 ml=0.24 mg/ml						

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

Table 10. 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

Permeability

Atomoxetine absolute bioavailability was 94% in PM subjects and 63% in EM subjects, and urine recovery of atomoxetine and its metabolites was 89±3.5% in both EM and PM

subjects, which indicate nearly complete absorption in all subjects and modest first pass metabolism in EM subjects.

Dissolution

The capsule formulation was rapidly dissolved in water, 0.1 N HCl, pH 4.5 buffer (— % in 30 minutes), but somewhat slower in pH 6.8 buffer for higher strengths (40- and 60-mg, —% in 30 minutes).

Table 11. Dissolution Performance in pH 6.8 Buffer

Strength	5-mg	10-mg	18-mg	25-mg	40-mg	60-mg
15 min	85 (76-96)	87 (73-99)	84 (68-98)	72 (59-94)	64 (52-83)	36 (26-46)
30 min	95 (88-99)	96 (86-101)	97 (89-102)	90 (81-99)	81 (67-97)	53 (43-69)

Conclusion: Although atomoxetine hydrochloride drug substance is highly soluble and highly permeable, the slower release of the highest strength (60-mg) of the capsule dosage form in pH 6.8 buffer (— % in 30 minutes) disqualifies atomoxetine drug product to be BCS Class I drug product.

2. ***What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure? Is there a biowaiver request?***

Bioequivalence of the 40-mg and 60-mg market-image formulations to clinical capsule formulations was established. A biowaiver is requested for the proportionally similar capsule strengths lower than 40 mg (5, 10, 18, and 25 mg).

Formulation: The formulation for all six strengths of atomoxetine capsules contains pregelatinized starch as a diluent and dimethicone as a lubricant. The 5, 10, 18, 25, and 40 mg capsules have the same target fill weight (230 mg), containing the same amount of dimethicone, and differing 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 12. 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

Dissolution Profile Comparison: Dissolution profiles in three pH media (0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer) were compared between each of the lower strengths and the 40-mg strength. Since there were no more than 2 timepoints that releases were below

85% in any medium, f_2 calculation is not necessary. Although the lower strengths had faster release than the 40-mg capsule in pH 6.8 buffer, an average of 80% released from the 40-mg capsules in 30 minutes; this difference is not judged to have considerable impact on drug absorption.

Table 13. Dissolution Profiles

Strength	15 min	30 min	15 min	30 min	15 min	30 min
	0.1 N HCl		pH 4.5 Buffer		pH 6.8 Buffer	
5-mg	98 (90-105)	100 (98-104)	97 (90-100)	99 (96-101)	85 (76-96)	95 (88-99)
10-mg	97 (89-101)	100 (93-103)	97 (84-100)	99 (96-102)	87 (73-99)	96 (86-101)
18-mg	97 (83-103)	100 (93-103)	101 (95-104)	103 (100-104)	84 (68-98)	97 (89-102)
25-mg	96 (80-103)	100 (89-104)	99 (91-103)	101 (98-103)	72 (59-94)	90 (81-99)
40-mg	93 (85-100)	99 (94-101)	101 (91-106)	101 (99-102)	64 (52-83)	81 (67-97)

Conclusion: Biowaiver can be granted for lower strengths of atomoxetine capsules (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; and the similar dissolution performance of these capsules in 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer.

3. ***What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?***

Food effect study was conducted on the highest strength of the atomoxetine capsules, 60 mg. In adult subjects, the effect of a standard high-fat meal decreased C_{max} 38% and delayed T_{max} about 3 hours. The frequency of adverse events was reduced during the administration of atomoxetine 60 mg with food. However, in a population analysis of pediatric patients, food had a lesser effect than in adults and a 9% decrease in C_{max} was observed (not formal study, self-reported). The effect of food on atomoxetine pharmacokinetics is considered not to be clinically important given the small decrease in C_{max} observed in clinical practice in the pediatric population analysis. Therefore, it is recommended that atomoxetine may be taken with or without food. Alterations in gastric pH through administration of omeprazole and Maalox did not affect the bioavailability of atomoxetine.

4. ***What are the proposed dissolution method and dissolution specifications?***

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.

14 page(s) of revised draft labeling has been redacted from this portion of the review.

Pharmacometrics Review

NDA:	21-411
Drug name:	—— (atomoxetine HCl)
Dosage strength:	5, 10, 18, 25, 40 and 60 mg capsules
Submission date:	10/11/01
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(-).

Objectives:

To establish exposure - response (desired / undesired) relationship and answer the following questions.

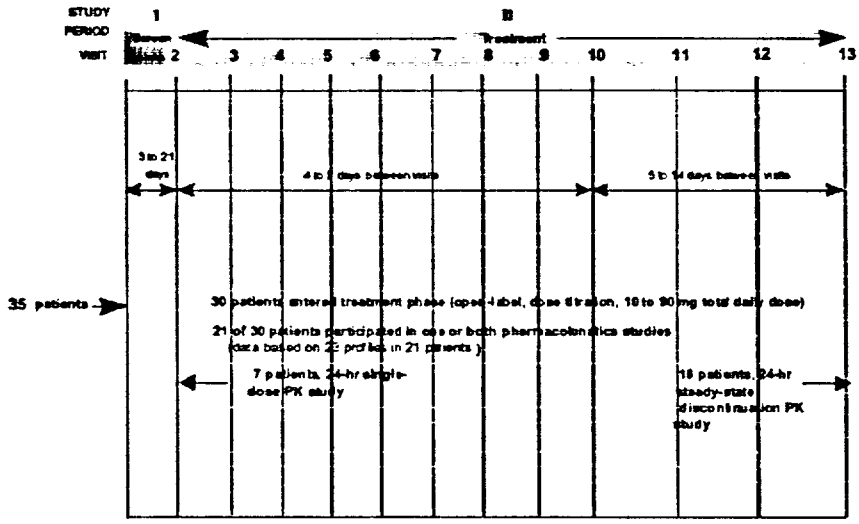
Is there an exposure (or concentration)-efficacy relationship?
Is there an exposure (or concentration)-adverse events relationship?
Is it necessary to adjust dose?

Design

Study HFBC

This was a Phase 1b, single-site, open-label, dose-titration study of atomoxetine. The pediatric patients are of ages 7 through 13, who meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for Attention-Deficit/Hyperactivity Disorder (ADHD).

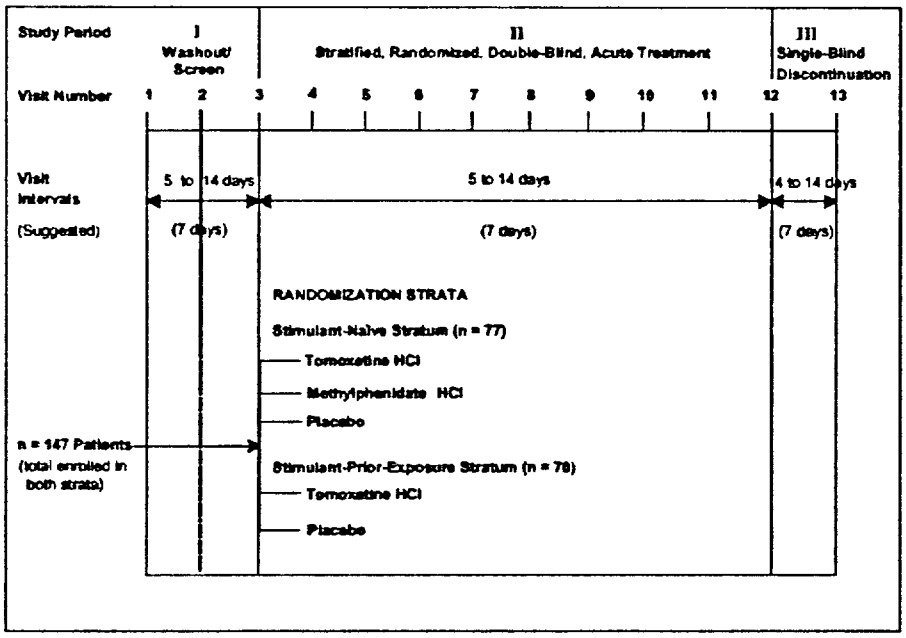
The study comprised 2 study periods: Study Period I –Screening and Study Period II–Acute Treatment, Single-Dose Pharmacokinetics and Steady-State Discontinuation Pharmacokinetics. These study periods are shown in the Figure below. The dose-titration schedule included doses ranging from 5 mg to 45 mg twice daily (10- to 90-mg total daily dose). The dose-titration schedule was not based on weight for this study. The mean final prescribed dose for all patients after adjusting for body weight was 1.6 mg/kg/day. The CYP2D6 genotype for each patient was determined at screening. Although PMs (poor metabolizers) were eligible to enroll, this study enrolled only EMs (extensive metabolizers).



Study HFBD

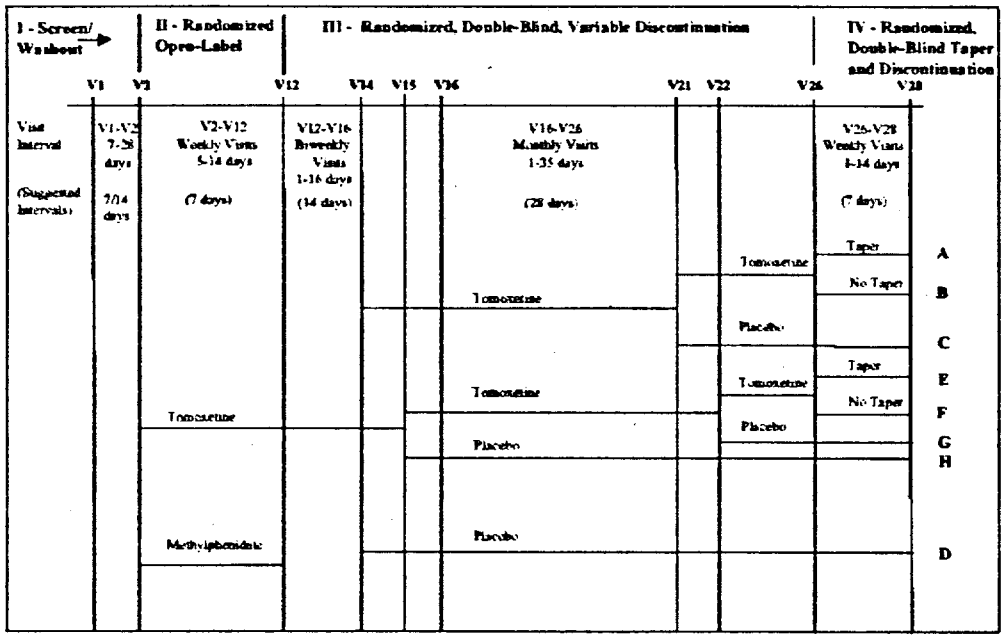
This was a Phase 2 stratified, randomized, double-blind, parallel, outpatient study of pediatric patients, aged 7 through 12 years, who met diagnostic criteria for DSM-IV ADHD.

The double-blind dose-titration schedule for patients randomized to atomoxetine allowed patients to be titrated to a maximum total daily dose of 2 mg/kg/day or 90 mg/day. The dose-titration schedule was based on weight, so that all patients on a given visit would receive similar mg/kg doses. Doses were administered twice a day as an evenly divided dose. The mean final prescribed atomoxetine dose for all patients was 1.6 mg/kg/day. The CYP2D6 genotype for each patient was determined at screening. Only EM patients were eligible for enrollment in this study. The study diagram is shown in the figure below.



Study HFBE

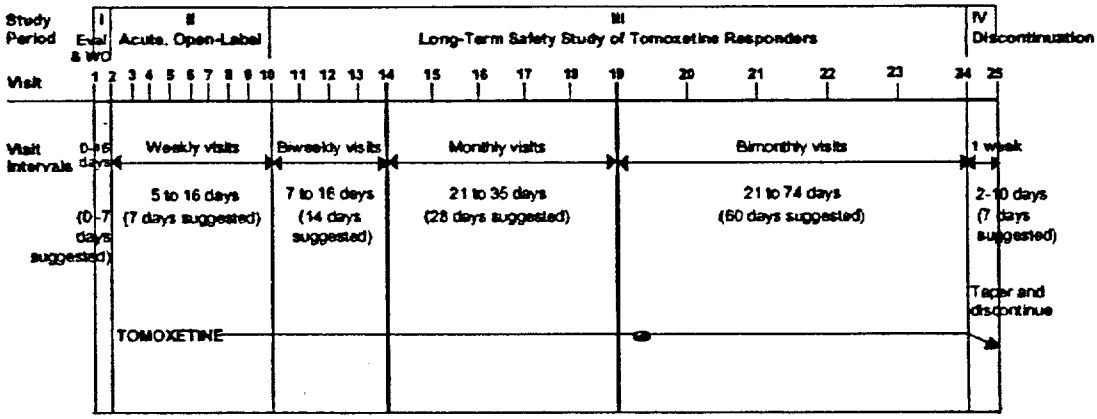
This was a Phase 2 study of patients (age 7-15, 184 patients) who met DSM-IV criteria for ADHD. The study design is illustrated in the figure below. Study Period II consisted of up to 10 weeks of active treatment in which eligible patients were randomized to open-label treatment with either atomoxetine hydrochloride or methylphenidate hydrochloride (administered as Ritalin). During Study Period II, the dose-titration schedule included doses ranging from 5 mg to 45 mg twice daily (10- to 90-mg total daily dose). The dose-titration schedule was based on weight, so that all patients on a given visit would receive similar mg/kg doses. Doses were typically administered twice a day as an evenly divided dose. The mean final prescribed atomoxetine dose for all patients was 1.35 mg/kg/day.



Study HFBF

This open-label study was an investigation of the long-term safety and tolerability of atomoxetine HCl of up to 80 weeks' duration in ADHD patients ages 6 years and older (but less than 18 years of age at the time of entry into their prior study). This long-term study was available to patients who completed HFBC, HFBD, HFBE, and HFBK and wanted to continue treatment, and was also available to patients who did not meet entry criteria for HFBD and HFBK due PM status.

The study design is illustrated in the figure below. During Study Period II, the dose-titration schedule included doses ranging from 5 mg to 45 mg twice daily (10- to 90-mg total daily dose). The dose-titration schedule was based on weight. This study is currently ongoing, although pharmacokinetic blood sampling has been discontinued since sufficient data were collected. Both EM and PM patients were eligible for enrollment in this study. Patients who were characterized as PMs were assigned different dosages (doses and dosing schedules) of atomoxetine than EMs.

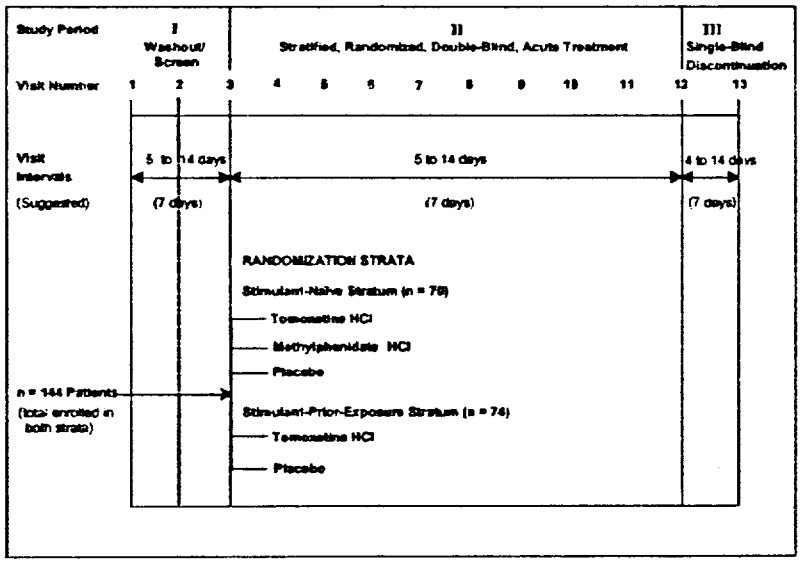


Abbreviations: Disc. = Discontinuation; Eval. & WO = Evaluation and washout

Study HFBK

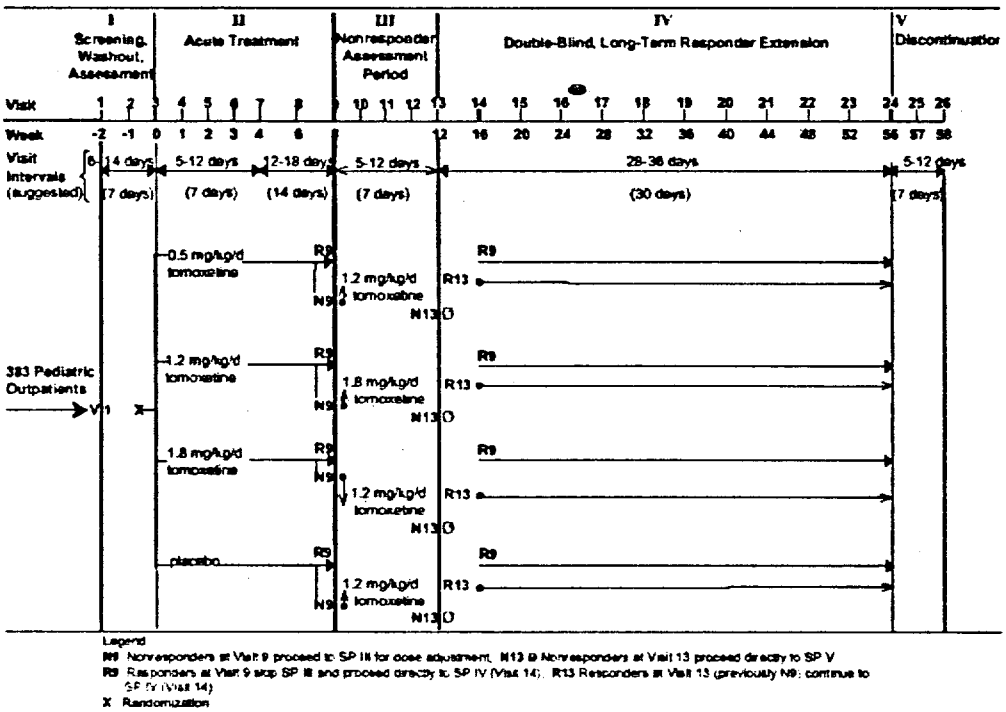
This was a Phase 2, stratified, randomized, double-blind, parallel, outpatient study of pediatric patients, aged 7 through 12 years, who met diagnostic criteria for DSM-IV ADHD.

The patients were titrated to a maximum total daily dose of 2 mg/kg/day or 90 mg/day. The dose-titration schedule was based on weight. Doses were administered twice a day as an evenly divided dose. The mean final prescribed atomoxetine dose for all patients was 1.5 mg/kg/day. The CYP2D6 genotype for each patient was determined at screening. Only EM patients were eligible for enrollment in this study. The study diagram is shown in the figure below.



Study LYAC:

This was a randomized, double-blind, placebo-controlled study. Atomoxetine hydrochloride capsules or placebo capsules were given twice daily for 8 weeks. Patients were randomized to placebo and three treatment groups with target doses of 0.5 mg/kg/day, 1.2 mg/kg/day and 1.8 mg/kg/day, respectively. The study flow chart is shown in the following figure.



Dose titration was utilized for the 1.2 mg/kg/day and 1.8 mg/kg/day groups, with the target doses achieved at Visit 5 for the 1.2 mg/kg/day group,. and Visit 6 for the 1.8 mg/kg/day group. The mean (range) final atomoxetine prescribed dose (in mg/kg/day) for the 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day treatment groups were 0.43 (0.37-0.50), 1.13 (0.52-1.33), and 1.57 (0.49-1.79) respectively.

Patients were at least 8 years of age but less than 18 years of age at Visit 1. At both Visit 2 and Visit 3, each patient's score from the ADHD Rating Scale-IV (ADHDRS-IV) was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype (predominantly inattentive or predominantly hyperactive-impulsive) or the total score for the combined subtype (if the child met DSM-IV criteria for the combined subtype) using published norms for the ADHDRS-IV-Parent Version: Investigator Administered and Scored (ADHDRS- IV-Parent:Inv). In addition, at both Visit 2 and Visit 3, each patient's score from the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale was at least 3.

Study LYAE:

This 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.

Data:

Population pharmacokinetic study:

Pharmacokinetics

Study HFBC

During Study Period II, patients were given the option to participate in a single-dose pharmacokinetic study (Visit 2) and/or in a steady-state discontinuation pharmacokinetic study (Visit 13). In addition to these optional pharmacokinetic studies, all patients had single blood samples drawn at several visits throughout the study (typically Visits 4, 7, and 10). Patients who did not elect to participate at Visit 13 in the steady-state discontinuation pharmacokinetic study also had a single blood sample drawn at their final visit.

At Visit 2, patients who elected to participate in the single-dose pharmacokinetic study prior to beginning treatment with atomoxetine were admitted to the Hospital for a 24-hour period. Blood samples were collected immediately prior to receiving a 10-mg dose of atomoxetine and 1, 2, 4, 8, 12, and 24 hours following the single dose. Following completion of the 24-hour single-dose study, each patient was discharged and began twice-daily treatment with atomoxetine in the outpatient setting.

At their final visit (Visit 13), patients were given the option to participate in a steady-state, 24-hour discontinuation pharmacokinetic study provided they were compliant with their prescribed daily dosage of atomoxetine for a minimum of 3 consecutive days. Patients had their dose held on the morning of their final visit and were admitted to the Hospital for 24 hours. Blood samples were collected immediately prior to receiving the prescribed morning dose of atomoxetine and 1, 2, 4, 8, 12, and 24 hours following the dose.

Study HFBD

A single sample was collected at Visits 5, 8, 10, 12, and early study discontinuation.

Study HFBE

A single sample was collected at Visits 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and early study discontinuation.

Study HFBF

A single sample was collected at Visits 5, 10, 11, 12, 14, 15, 16, 18, 20, 22, 24, 25, and early study discontinuation.

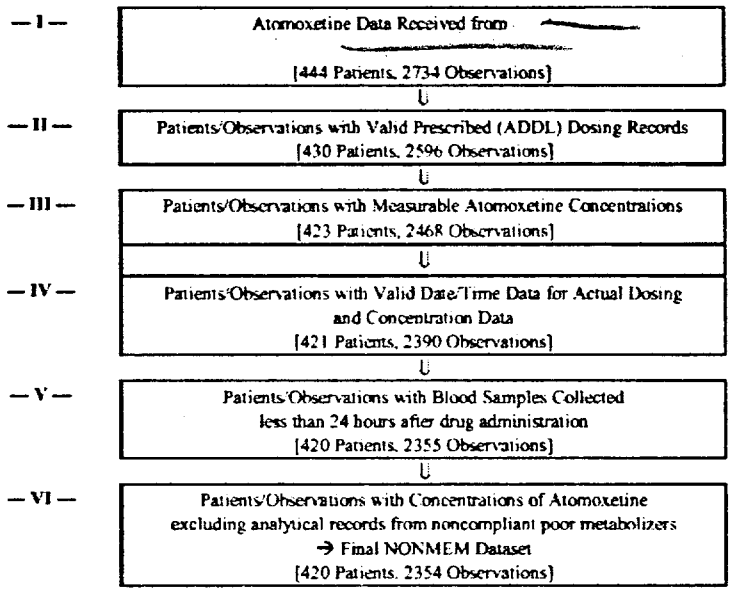
Study HFBK

A single pharmacokinetic sample was collected at Visits 5, 8, 10, 12, and early study discontinuation

The distribution of patients across the 5 studies included is shown in the following table.

	HFBC	HFBD	HFBE	HFBK	HFBF[a]	Total
Patients	25	60	163	60	112[b]	420
Concentrations	220	185	813	209	927	2354

The data from these studies included in the population pharmacokinetic analysis are shown in the following figure.



The demographic data for these studies are shown in the following tables.

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Demographic	Mean	Median	Min	Max	SD	SEM	%CV	n
Weight (kg)	39.3	35.3	22.7	124.5	13.9	0.286	35.3	2354
Age (yr)	10.2	9.9	7.0	15.8	1.9	0.039	18.5	2354
Height (cm)	140.8	139.0	107.0	188.0	11.9	0.249	8.5	2297
BMI (kg/m^2)	19.4	18.1	—	—	4.1	0.085	21.0	2297
Albumin (g/L)	42.8	43.0	—	—	2.56	0.053	6.0	2354
Bilirubin (µmol/L)	7.6	6.8	—	—	3.78	0.078	50.1	2353
ALT (U/L)	17.5	16.0			9.75	0.204	55.6	2282

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

PK/PD Study LYAC:

Pharmacokinetics

A blood sample was drawn from each patient on Visits 6, 7, 8, and 9 for measurement of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylatomoxetine in plasma for the pharmacokinetic assessment. Pharmacokinetic samples were taken at the time of the visit (not at a particular time after dosing).

Patients were identified by genotype as extensive or poor metabolizers of CYP2D6 substrates. There were 716 atomoxetine concentrations determined from blood samples collected from 190 patients. Thirty-four samples were excluded from the analysis primarily because the concentration was below the limit of quantitation. The final dataset 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 for atomoxetine concentration at all 4 scheduled sampling visits. There were 171 EM, 8 UM, and 10 PM patients included in this analysis. The demographic data are shown in the following tables.

Demographic	Mean	Median	Min	Max	SD	SEM	%CV	n
Weight (kg)	40.7	36.7	19.5	77.2	13.2	0.505	32.4	682
Age (yr)	11.3	10.9	8.0	17.5	2.3	0.089	20.5	682
Height (cm)	144.8	142.5	114.5	188.0	13.7	0.527	9.5	674
Albumin (g/L)	43.3	43.0			2.79	0.107	6.4	682

Demographic	Category	n	% Total
Genotype	EM	171	90.5
	UM	8	4.2
	PM	10	5.3
Gender	Male	131	69.3
	Female	58	30.7
Age Group	<12 yr	130	68.8
	≥12 yr	59	31.2
Ethnic Origin	Caucasian	150	79.4
	African	31	16.4
	Hispanic	4	2.1
	Other	4	2.1
Food within 1 hr of dose	No	153	22.4
	Yes	529	77.6

Pharmacodynamics

The primary efficacy variable was the ADHDRS-IV-Parent:Inv total score. The total score is the sum of the scores for each of the 18 items, with higher scores indicating greater severity of ADHD symptoms. Each item is scored on a 0 to 3 scale (total score ranges from 0 to 54) and each item corresponds to one of the 18 DSM-IV symptoms of ADHD.

Study LYAE:

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 [redacted] 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.

Data Checking

The number of observed concentrations were plotted against time to generate a distribution of samples over dosing interval.

Models

Population Pharmacokinetics

Structural Model

One and two-compartment structural models, with first-order appearance and elimination, were examined in the population analysis. These models were parameterized in terms of Ka, CL/F, and V/F, as well as Q and Vp for the two-compartment models.

Covariate Model

The effect of PM status was incorporated first and was structured to estimate CL/F separately for PMs, as shown in the following equation.

$$CL/F = (1\text{-}PM) \cdot \theta_1 + PM \cdot \theta_2$$

Where PM is an indicator variable having a value of either 1 (for poor metabolizers) or 0 (for all other patients), θ_1 is the typical value of CL/F for extensive or ultra-extensive metabolizers, and θ_2 is the typical value of CL/F for poor metabolizers.

Body weight was tested on both CL/F and V/F, using linear, exponential and power models, as shown in the following equations.

Linear Model	$P = \theta_1 + \theta_2 \cdot (WT/MED)$
Exponential Model	$P = \theta_1 \cdot EXP(\theta_2 \cdot (WT/MED))$
Power Model	$P = \theta_1 \cdot (WT/MED)\ \theta_2$

Where P is the individual's estimate of the parameter (for example, CL/F), θ_1 is the typical value for the parameter, θ_2 is the effect of the covariate (for example, weight), WT is the value for body weight, and MED is the population median for body weight.

Patient factors assessed as potential covariates in the analysis and the individual pharmacokinetic parameters to which they were applied are listed in the table below.

Continuous Covariates	Pharmacokinetic Parameters Tested	Model(s) Tested
Body Weight at Visit [a]	CL/F, V/F	linear, exponential, power
Albumin	CL/F, V/F	linear, exponential, power
Age at Study Entry	CL/F, V/F, Ka	linear, exponential, power
Alanine Transaminase	CL/F, V/F	linear, exponential, power
Body Mass Index	CL/F, V/F	linear, exponential, power
Total Bilirubin	CL/F, V/F	linear, exponential, power
Atomoxetine Dose	CL/F, V/F, Ka	linear, exponential, power
Categorical Covariates	**Pharmacokinetic Parameters Tested**	
CYP2D6 Genotype [a]	CL/F, V/F	EM vs PM vs UM
Age at Study Entry	CL/F, V/F, Ka	<12 yrs vs ≥12 yrs
Gender	CL/F, V/F, Ka	M vs F
Age/Gender Interaction	CL/F, V/F	M <12 vs M ≥12 vs F <12 vs F ≥12
Ethnic origin	CL/F, V/F, Ka	Caucasian vs Non-Caucasian; Caucasian vs. Hispanic vs. African
Caffeine (caffeine drinker at entry)	CL/F, V/F	Yes vs No
Food (food within 1 hr of dose)	Ka	Yes vs No

Continuous covariates were examined for their influence on atomoxetine pharmacokinetic parameters using linear, exponential, and power models as shown in the equations for body weight. All categorical factors were tested for their impact on atomoxetine parameters using a categorical model, as shown in the following equation.

Categorical Model $P = \theta_1 \cdot (1 + \theta_2 \cdot IND)$

Where P is the individual's estimate of the parameter (for example, CL/F), θ_1 is the typical value for the parameter, θ_2 is the effect of the covariate, and IND is an indicator variable having a value of 0 or 1.

Since very few patients reported any smoking and alcohol use, these were not evaluated.

Random Variance Models

A series of pharmacostatistical models were systematically evaluated. First-order conditional estimation (FOCE) with interaction was used in for estimation. Five inter-patient variability (η) models were assessed: 1) η on CL/F, 2) η on CL/F and V/F, 3) η on CL/F and V/F with covariance, 4)η on CL/F, V/F and Ka, 5) η on CL/F and V/F with covariance, η on Ka. For each inter-patient variability model assessed, 2 residual error models were examined: 1) proportional, and 2) combined proportional and additive.

PK/PD study LYAC

Pharmacokinetics model

The population pharmacokinetic approach was used to analyze the atomoxetine concentration data and calculate the individual atomoxetine clearance estimate for each patient (the empirical

Bayesian estimate of clearance). 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.

Individual clearance estimates were obtained for LYAC patients with at least 2 atomoxetine concentrations. The individual clearance estimates were then used to estimate AUC for each patient using the following equation: AUC = Dose/(CL/F). The dose (mg) which was associated with each patient's final plasma sample was used for this calculation. Since the dose titration was completed at Visit 6, the AUC was calculated when patients were taking their final mg/kg/day dose.

Pharmacodynamic model

For study LYAC, the relationship between AUC and the primary efficacy measure (ADHDRS-IV-Parent:Inv - Total) was evaluated by modeling improvements from baseline in ADHDRS-IV-Parent:Inv total score at visit 9 versus estimated atomoxetine AUC. For this analysis, the relationship between change from baseline total score and AUC for the ith patient was modeled using the relationship:

$$\Delta T_i = E_0 + E_{max}\left(\frac{AUC_i}{AUC_i + AUC_{50\%}}\right).$$

Here E_0 is defined to be the expected improvement seen with placebo, Emax the maximum expected benefit associated with atomoxetine dosing over placebo, and $AUC_{50\%}$ expected atomoxetine AUC value at which 50% of the maximum benefit is realized. 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 a minimal amount of PM data.

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.

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Model Selection

Initial Model Selection

For the population analysis, the base model was a one-compartment model with first order absorption and with genotype and body weight as covariates. Then potentially significant covariates were added to the base model in combination so that a full model containing all possible covariates was established. The significant covariates were identified as those which, when added to the base model individually, resulted in a decrease in the objective function of >3.841 points. The process was then reversed, with all potential covariates, including PM status and body weight, being removed individually from the full model. Covariates retained in the final model were those which resulted in a significant increase in MOF (minimum value of objective function; ≥10.828 points for 1 degree of freedom, $p<0.001$), when removed from the full model.

Final Model Selection

Parameter sensitivity analyses were used to assess both the base and final pharmacokinetic models. These analyses were used to examine the overall shape of the parameter space, confirm the absence of local minima, and identify 95% confidence intervals. The analysis was performed by fixing the parameter of interest to 5%, 10%, 15%, 20%, 30%, and 40% of the population estimate and allowing NONMEM to estimate all other parameters. Changes in the objective function were used to assess the effect of altering the parameter value on the overall fit of the plasma concentration versus time data. The curve produced by the objective function versus parameter value relationship was fit using polynomial regression to obtain a 95% confidence interval. Assuming a chi-square distribution, the values that produce a change in the objective function of 3.841 represent the 95% confidence limits for that parameter.

The leverage analysis technique was designed to evaluate the contribution or leverage of selected patients on the model. For each of 10 runs from a single leverage analysis, a subset of 10% of the patients was randomly omitted such that each patient was omitted from the analysis exactly once. The final model was run using the remaining 90% of the data. This procedure was performed twice with different subsets of the patients omitted. The parameter estimates from all runs were compared with the 95% confidence intervals calculated in the parameter sensitivity analysis. The reason for any marked difference in parameter estimates was investigated.

The final model was also evaluated using external qualification, which is the application of the developed model to a new dataset (validation dataset), from study LYAC. The final model parameters were held constant and used to predict the data for the validation dataset, and empirical Bayesian estimates of concentrations for each patient in the validation dataset were obtained. These empirical Bayesian predictions were compared to the actual observed concentrations. Agreement in the predicted and observed concentrations was evaluated to verify model predictive ability. In addition, model parameters were estimated by refitting the final model to the validation dataset, and the parameter estimates compared with those obtained previously. The reason for any marked difference in parameter estimates was investigated.

This population pharmacokinetic model was used to analyze the atomoxetine concentration data and calculate the individual atomoxetine clearance estimate for each patient (the empirical Bayesian estimate of clearance) in the PK/PD study LYAC.

This model was also used for pharmacokinetic analysis of study LYAE to investigate the relationship between concentrations and QTc interval prolongation.

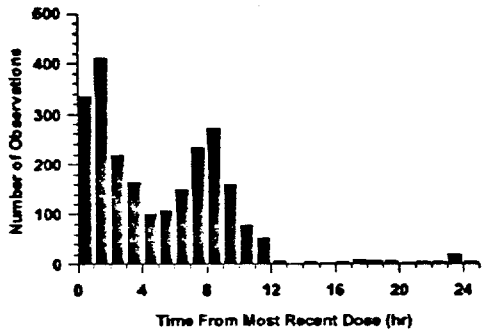
Software

The softwares used include SAS (version 6.12) for the data formatting, NONMEM (version V level 1.1) for modeling and simulation, S-PLUS (version 6) for graphing.

Results and Discussion

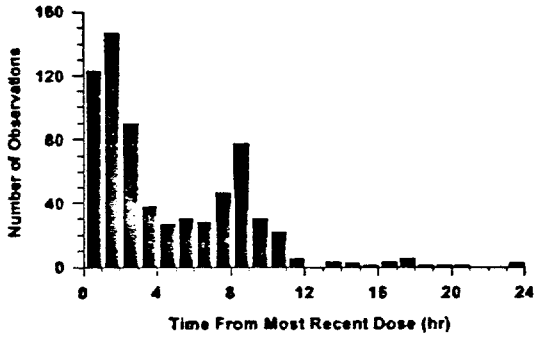
Data Checking

For the population analysis, a total of 2354 plasma samples collected from 420 patients was used in the population analysis. The number of blood samples collected per patient ranged from 2 to 19. The average number of samples per patient was 6.3. The following figure illustrates the



distribution of samples over the dosing interval. Approximately one-third of the samples were obtained during the absorption phase (up to 1 to 2 hours postdose) for atomoxetine. The remaining samples were well distributed across the remainder of the dosing interval. Therefore, the entire dosing interval is characterized. A small number of samples were collected between 12 and 24 hours postdose.

The following figure illustrates the distribution of blood samples over the dosing interval for study LYAC. Approximately 40% of the samples were obtained during the absorption phase (up to 1 to 2 hours post-dose) for atomoxetine. The remaining samples were distributed across the remainder of the dosing interval. Therefore, the entire dosing interval is characterized. A small number of samples were collected between 12 and 24 hours post-dose. Samples collected after more than 24 hours post-dose were not included in the pharmacokinetic analyses.



Model and Model Selection

Base Model

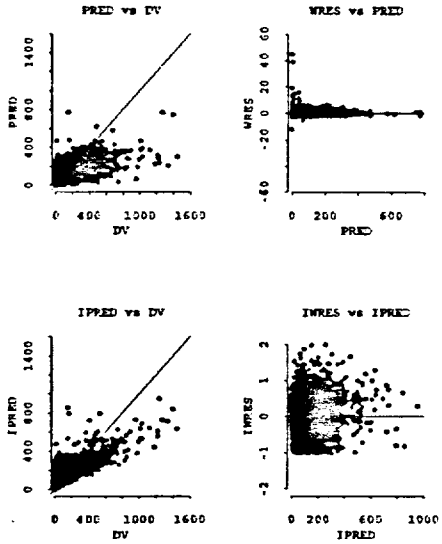
For the population analysis, the two-compartment models were very unstable, most not completing successfully. Those models that did complete successfully did not show noticeable improvement in goodness-of-fit when compared to similar one-compartment models.

The initial base model selected was a one-compartment model with η's on CL/F and V/F, and proportional residual error. The initial base model was unstable. Therefore, PM status and body weight were incorporated into the base model to stabilize the model before the evaluation of other covariates since these 2 patient factors are known to greatly influence atomoxetine pharmacokinetics based on previous analyses. The pharmacokinetic parameter estimates for the final base model are shown in the following table.

Parameter Description	Population Estimate (%SE)	Inter-Patient Variability (%SE)
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.710 (9.94)	—
Clearance [a]		
Parameter for CL/F for EM patients (L/hr)	17.7 (3.03)	45.4% (11.3)
Parameter for CL/F for PM patients (L/hr)	1.97 (5.05)	
Power model exponent for effect of body weight on CL/F	0.848 (10.6)	
Volume of Distribution [b]		
Parameter for V/F (L)	74.7 (6.91)	32.7% (26.6)
Power model exponent for effect of body weight on V/F	0.935 (12.1)	
Residual Error	56.4% (5.25)	

The final base 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. Addition of these factors to the model greatly reduced the inter-patient variability in CL/F (reduced from 76.0% to 45.4%) and V/F (reduced from 80.8% to 32.7%) and also stabilized the model.

The goodness of fit plots for the final base model is shown in the following figure.



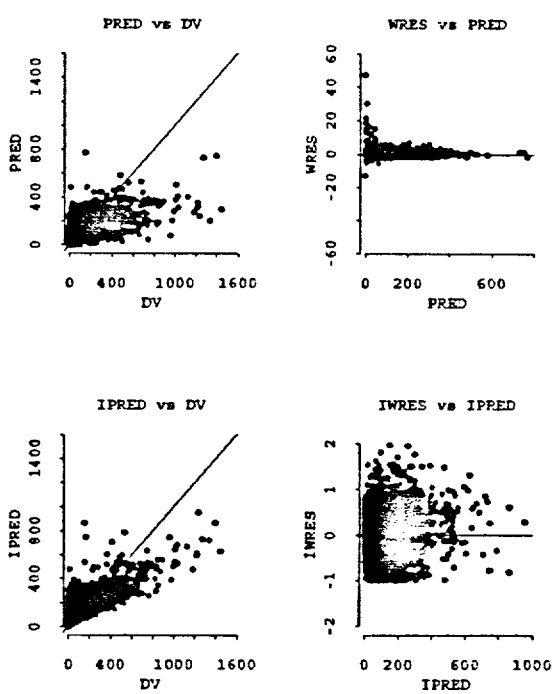
Final Model

Through the model development process, a final population pharmacokinetic model was developed and the parameter estimates are shown in the following table.

Parameter Description	Population Estimate (%SE)	Inter-Patient Variability (%SE)
Rate of Absorption		
Parameter for Ka with food (hr^{-1})	0.679 (7.29)	—
Parameter for Ka without food (hr^{-1})	0.926 (14.6)	—
Clearance [a]		
Parameter for CL/F for EM patients (L/hr)	17.4 (3.00)	44.5 % (11.4)
Parameter for CL/F for PM patients (L/hr)	1.96 (5.02)	
Parameter for CL/F for UM patients (L/hr)	31.8 (11.6)	
Effect of body weight on CL/F	0.834 (10.0)	
Effect of albumin on CL/F	-0.942 (35.4)	
Volume of Distribution [b]		
Parameter for V/F (L)	75.8 (6.06)	32.6 % (26.7)
Effect of body weight on V/F	0.947 (11.4)	

PM status and body weight were shown to greatly reduce the inter-patient variability and were retained in the final model. Three additional covariates were determined to be statistically significant and retained in the final model: UM status, albumin, and food intake. The effect of the UM genotype on CL/F could be distinguished from that of the PM and the EM. In addition, albumin was identified as having an effect on clearance. Atomoxetine clearance is decreased with increasing plasma albumin levels. Food within 1 hour of atomoxetine dosing was also identified as having an effect on the rate of atomoxetine absorption. The rate of atomoxetine absorption is reduced by prior food intake.

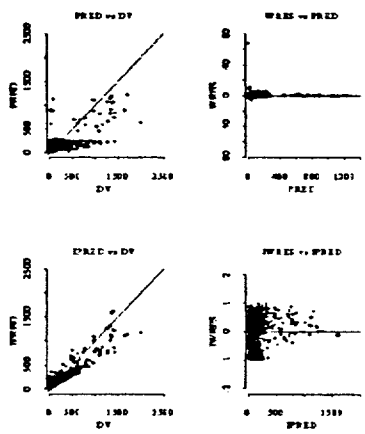
Although these 3 additional covariates were retained in the final model, they explained a minimal amount of inter-patient variability. The addition of these 3 covariates had essentially no effect on the residual error and resulted in no apparent improvement in the goodness of fit plots as shown in the following figure.



Study LYAC use the population pharmacokinetic model developed in the population analysis of combined studies. The following table summarizes the results obtained from the analysis.

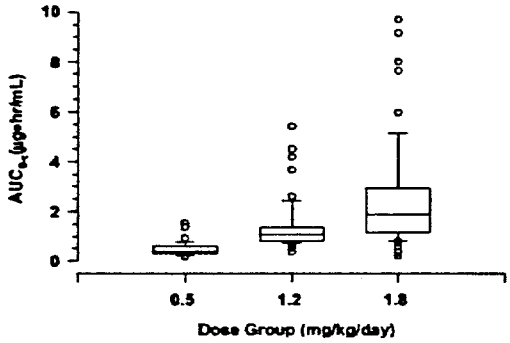
Parameter Description	Population Estimate (%SE)	Inter-Patient Variability (%SE)
Rate of Absorption		
Parameter for K_a with food (hr^{-1})	[illegible]	—
Parameter for K_a without food (hr^{-1})	[illegible]	—
Clearance [a]		
Parameter for CL/F for EM patients (L/hr)	[illegible]	[illegible]
Parameter for CL/F for PM patients (L/hr)	[illegible]	
Parameter for CL/F for UM patients (L/hr)	[illegible]	
Effect of body weight on CL/F	[illegible]	
Effect of albumin on CL/F	[illegible]	
Volume of Distribution [b]		
Parameter for V/F (L)	[illegible]	[illegible]
Effect of body weight on V/F	[illegible]	
Residual Error	[illegible]	

The following figure shows the goodness of fit plots for this analysis.



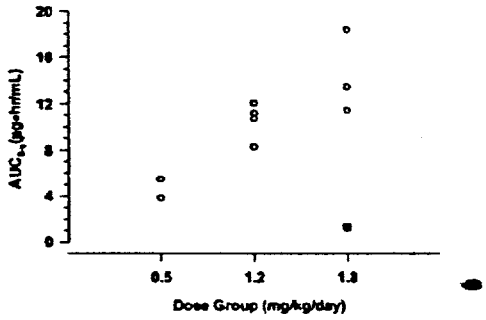
The AUC values in EM patients at different doses are shown in the following table and figure.

Dose Group (mg/kg/day)	Mean $AUC_{0-\tau}$ (µg•hr/mL)	Median	Min	Max	SD	SEM	%CV	n
0.5	0.47	0.39	[illegible]		0.30	0.050	63.91	36
1.2	1.39	1.08			0.97	0.124	70.04	61
1.8	2.46	1.88	[illegible]		1.99	0.243	81.13	67

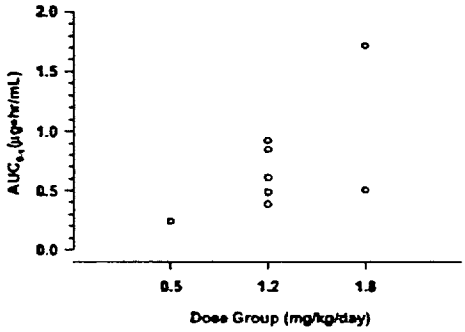


The following Figure shows the atomoxetine AUC values for PM patients with at least 2 atomoxetine concentrations included in the analysis. The PM patients displayed higher AUC

values compared to EM patients, which is consistent with the lower clearance in PM patients and also consistent with previous analyses.



The following Figure shows the atomoxetine AUC values for UM patients with at least 2 atomoxetine concentrations included in the analysis. The UM patients displayed slightly lower AUC0-□values compared to EM patients, which is consistent with the slightly higher clearance in UM patients and also consistent with previous analyses.

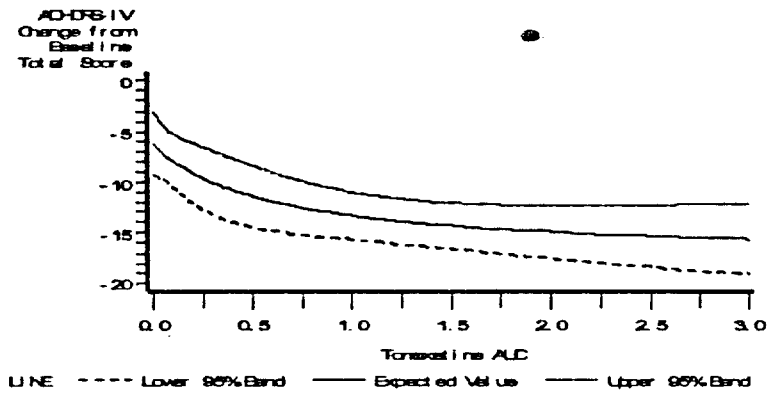


Pharmacodynamic Model

For study LYAC, scatter plots of the change from baseline in ADHDRS-IV-Parent:Inv total score and atomoxetine AUC for patients with at least 2 plasma levels showed that pearson's correlation coefficients between response and AUC was –.438 and -.068 for PMs and EMs, respectively. These low correlation values suggest that the relationship between AUC and efficacy cannot be explained by a simple linear relationship. A nonlinear model (inhibitory Emax model) was fit to the observed AUC and change from baseline ADHDRS-IV-Parent:Inv total scores data. All extensive metabolizer patients with a visit 9 total score value and a baseline total score value were included within this analysis. Patients receiving placebo were included assuming an AUC of zero. Poor metabolizer patients were excluded from this analysis. The following model estimates were obtained.

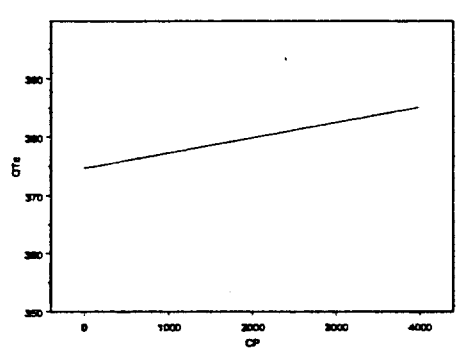
E_0	E_{max}	$AUC_{50\%}$
-6.2	-17.4	0.574 µg·hr/mL

The resulting fit of this model showed that the expected maximum improvement from baseline would be –17.4 (compared to –6.2 for 8 weeks of placebo dosing). This suggested an 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 from the model prediction. Therefore, there appears to be a relationship between systemic exposure and efficacy. The following figure shows model predicted mean change from baseline to endpoint in ADHDRS-IV-Parent:Inv total score and atomoxetine AUC for EM patients with confidence bounds.



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

Model	Obj. function	Alpha	Beta	Keo (h^{-1})	Slope (msec/ng/mL)
Without covariate	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).

The population model predicted steady state atomoxetine C_{max} and AUC for EM, UM and PM