AEs from Child and Adolescent Placebo Controlled BID ADHD Database where the relative risk was >2 in at least one of the origin (race) groups and there was at least a two fold difference when comparing the relative risks between origin (race) groups

Event	Risk in Caucasians		RR_C	Risk in Others		RR_O
	ATX (n=267)	PBO (n=163)		ATX (n=73)	PBO (n=44)	
Emotional Labil	6.0% (16)	1.2% (2)	5	2.7% (2)	6.8% (3)	0.4
Personality dis	3.7% (10)	0.6% (1)	6.2	1.4% (1)	6.8% (3)	0.2
Abdominal pain	21.7% (58)	20.2% (33)	1.1	15.1% (11)	6.8% (3)	2.2
Nausea	6.7% (18)	10.4% (17)	0.6	9.6% (7)	2.3% (1)	4.2
Pain	4.1% (11)	6.1% (10)	0.7	5.5% (4)	2.3% (1)	2.4
Constipation	3.0% (8)	1.2% (2)	2.5	2.7% (2)	2.3% (1)	1.2
Sleep disorder	1.9% (5)	0.6% (1)	3.2	1.4% (1)	2.3% (1)	0.6

From Sponsor's Table ISS.A10.8, pp.2270-2276.

Adult ADHD Placebo Controlled Studies

There were occasional differences in the RR for AEs in this stratified analysis. Using the criteria from above, the AEs with RRs that differed by origin are listed below. These results are based on a small number of non-Caucasians (atomoxetine=22, placebo=27).

AEs from Adult Placebo Controlled BID ADHD Database where the relative risk was >2 in at least one of the origin (race) groups and there was at least a two fold difference when comparing the relative risks between origin (race) groups

Event	Risk in Caucasians		RR_C	Risk in Others		RR_O
	ATX (n=247)	PBO (n=236)		ATX (n=22)	PBO (n=27)	
Nausea	13.0% (32)	4.2% (10)	3.1	4.5% (1)	11.1% (3)	0.4
Anorexia	12.1% (30)	3.4% (8)	3.6	4.5% (1)	3.7% (1)	1.2
Asthenia	4.9% (12)	3.0% (7)	1.6	18.2% (4)	3.7% (1)	4.9
Dizziness	6.5% (16)	1.7% (4)	3.8	4.5% (1)	3.7% (1)	1.2
Impotence*	9.9% (16)	0.7% (1)	14.1	8.3% (1)	5.3% (1)	1.6
Abnl Ejaculation*	6.8% (11)	1.3% (2)	5.2	0	10.5% (2)	0
Dysmenorrhea°	7.1% (6)	2.4% (2)	3.0	10.0% (1)	12.5% (1)	0.8

From Sponsor's Table ISS.A10.11, pp.2289-2298.
* In males, °In females

4.9.5 Lab Outliers by Origin (Race)

The sponsor found no statistically significant differences for lab outliers from Child and Adolescent Placebo Controlled BID ADHD studies or Adult placebo controlled studies when stratified by gender (ISS p.591, 599).

4.9.6 Vital Signs, Weight, and QTc by Origin (Race)

There were no notable differences in vitals sign changes when stratified by origin (race). The vital sign mean changes from baseline compared to placebo were similar for pediatric Caucasians compared to pediatric others and adult Caucasians compared to adult others (ISS p. 595, 602).

The data corrected QTc mean change from baseline compared to placebo for pediatric Caucasians was 0.62 compared to 4.0 for pediatric Others (ISS, p.598). The data corrected QTc mean change from baseline compared to placebo for adult Caucasians was 0.37 compared to –5.3 for adult Others (ISS, p.602).

4.9.7 Adverse Events by Age

Child and Adolescent Placebo Controlled BID ADHD Studies

There were few AEs with different relative risks when comparing pediatric subjects <12 years old (atomoxetine 258, placebo 172) to those >12 years old (atomoxetine 82, placebo 35). Only Hostility met the criteria used in these analyses. The relative risk for Hostility was 4.5 for pediatric subjects <12 (atomoxetine 2.7%, 7/258, placebo 0.6% 1/172), and no Hostility AEs were reported in subjects >12 (ISS, pp.2318-2325).

Adult ADHD Placebo Controlled Studies

There were occasional differences in the RRs for AEs in this stratified analysis. Using the criteria from above, the AEs with RRs that differed in adults by age are listed below.

AEs from Adult Placebo Controlled BID ADHD Database where the relative risk was >2 in at least one of the age groups and there was at least a two fold difference when comparing the relative risks between age groups

Event	Risk in Those<42		$RR_{<42}$	Risk in Those>42		$RR_{>42}$
	ATX (n=128)	PBO (n=146)		ATX (n=141)	PBO (n=117)	
Insomnia	21.9% (28)	5.5% (8)	4	19.9% (28)	12.8% (15)	1.6
Dry mouth	21.1% (27)	4.1% (6)	5.1	21.3% (30)	10.3% (12)	2.1
Nausea	8.6% (11)	6.8% (10)	1.3	15.6% (22)	2.6% (3)	6.0
Anorexia	14.8% (19)	2.7% (4)	5.5	8.5% (12)	4.3% (5)	2.0
Pain	4.7% (6)	4.8% (7)	1.0	9.9% (14)	4.3% (5)	2.3
Dyspepsia	4.7% (6)	6.2% (9)	0.8	7.1% (10)	3.4% (4)	2.1
Libido decreased	4.7% (6)	2.7% (4)	1.7	9.2% (13)	0.9% (1)	10.2
Dizziness	4.7% (6)	2.1% (3)	2.2	7.8% (11)	1.7% (2)	4.6
Abnormal dreams	6.3% (8)	0.7% (1)	9.0	4.3% (6)	5.1% (6)	0.8
Impotence*	5.4% (5)	1.1% (1)	4.9	14.6% (12)	1.3% (1)	11.2
Fever	3.9% (5)	5.5% (8)	0.7	2.8% (4)	0.9% (1)	3.1
Parasthesia	5.5% (7)	2.1% (3)	2.6	2.8% (4)	2.6% (3)	1.1
Abnormal ejaculation*	2.2% (2)	3.3% (3)	0.7	11.0% (9)	1.3% (1)	8.5
Vomiting	2.3% (3)	5.5% (8)	0.4	2.1% (3)	0	
Chest pain	2.3% (3)	0.7% (1)	3.3	3.5% (5)	2.6% (3)	1.3
Chills	1.6% (2)	2.1% (3)	0.8	4.3% (6)	0	
Menstrual disorder°	13.9% (5)	1.9% (1)	7.3	3.4% (2)	5.4% (2)	0.6
Weight loss	3.9% (5)	0		0.7% (1)	1.7% (2)	0.4

From Sponsor's Table ISS.A10.17, pp.2339-2348.

* In males, °In females

4.9.8 Lab Outliers by Age

The sponsor found a statistically significant difference only for low urine specific gravity lab outlier (higher odds ratio compared to placebo in the <12 year old group) from Child and Adolescent Placebo Controlled BID ADHD studies (ISS, p.609). In the Adult placebo controlled studies when stratified by age, the <42 year old group had a higher odds ratio compared to placebo for urinalysis occult blood (ISS p.618).

4.9.9 Vital Signs, Weight, and QTc by Age

There were no notable differences in vitals sign changes when stratified by age. The vital sign mean changes from baseline compared to placebo were similar for pediatric subjects <12 compared to pediatric subjects >12 and adult subjects <42 compared to adult subjects >42 (ISS p. 611, 619).

The data corrected QTc mean change from baseline compared to placebo for pediatric subjects <12 was 0.45 compared to 4.43 for pediatric subjects >12 (ISS, p.614). The data corrected QTc mean change from baseline compared to placebo for adult subjects <42 was –2.82 compared to –2.56 for adult subjects >42 (ISS, p.621).

4.10 Drug Interaction

The sponsor conducted drug interaction studies and results from those studies are summarized below.

HFBO- looked at atomoxetine given with salbutamol. The sponsor reported an increase in heart rate with the combination. For example, at 2 hours post dosing, single dose, the mean increase in heart rate for salbutamol alone was 19bpm, for atomoxetine alone was 2bpm, and for the combination was 46bpm. The sponsor did not find evidence of increase in blood pressure or SVR with the combination of salbutamol and atomoxetine compared to the either agent alone.

LYAP-looked at atomoxetine given with methyphenidate in EM subjects. The sponsor reported that there is no statistical difference in HR with methylphenidate in the presence or absence of atomoxetine.

E002 –looked at atomoxetine given with ethanol. This was a two period double blind cross over study in healthy volunteers. During the first study period subjects took either atomoxetine (40mg bid), or placebo for 5 days. Ethanol was administered (2ml/kg) on the 5th day followed by measurements of psychomotor function. Patients were crossed over after a 4-week washout. The sponsor reported that there was no evidence of a greater interaction with alcohol among PM subjects compared to EM subjects. Additionally, the sponsor reported "Following dosing with 40mg bid for 5 days, EM and PM subjects showed no difference in psychomotor performance in the absence of alcohol compared to placebo.

HFBL- looked at atomoxetine given with paroxetine to EM subjects. This single blind sequential study administered paroxetine 20mg qd with atomoxetine, and the sponsor reported a substantial effect on PK of atomoxetine. The combination also resulted in greater orthostatic tachycardia compared to paroxetine alone in EM subjects or atomoxetine alone in PM subjects (data from study LYAE). EM subjects taking the combination had a greater decrease in orthostatic systolic BP compared to EM subjects taking paroxetine alone. The decrease in orthostatic SBP in EM subjects taking paroxetine and atomoxetine was similar to the decrease in orthostatic SBP in PM subjects taking atomoxetine alone. The paroxetine-atomoxetine interaction vital sign results are summarized in the following table:

Table ISS.5.4.41. Comparison of Cardiovascular Variables (Least-Square Means) Averaged over Days 4 and 5 Between PM Subjects (Study LYAE) and EM Subjects on Paroxetine (Study HFBL)

	Least-Square Means			Least-Square Means		
	Paroxetine	Placebo		Paroxetine and Tomoxetine (20 mg BID)	Tomoxetine (30 mg BID)	
Variable	HFBL EM Subjects[a]	LYAE PM Subjects	p-Value[b] (baseline)	HFBL EM Subjects	LYAE PM Subjects	P-value[b] (atomoxetine)
SHR (bpm)	79.5	71.5	0.072	105.6	83.6	0.0001
OHR (bpm)	15.5	8.3	0.089	33.9	18.6	0.0006
OSBP (mm Hg)	-8.5	-1.0	0.068	-16.4	-15.5	0.82

Abbreviations: Standing Heart Rate (SHR); Orthostatic Heart Rate (OHR); Orthostatic Systolic BP (OSBP) BP = blood pressure, bpm = beats per minute. mmHg = millimeters of mercury. (Orthostatic refers to the difference between standing and supine measurements.)

[a] Before administration of tomoxetine in Period 2.

[b] P-value of the indicated difference.

Source Data: Data on file at Lilly Clinic.

The sponsor reported in Table ISS.5.4.42, p.469, that during the co-administration period, there were more dizziness events (3.81% 4/105*) compared to paroxetine alone (0.68%, 1/147*) or atomoxetine alone (0/175*).
*#events/#intervals

LYAJ- looked at atomoxetine given with midazolam. The sponsor reported that the combination did not result in more AEs than when atomoxetine was given alone.

4.11 Overdose

There were no large atomoxetine overdoses in human subjects in the ADHD development program. The sponsor identified 7 cases of overdose where patients took 2-5 times the recommended dose. Five cases were dispensing mistakes and two were intentional. The five who were mistakenly dispensed the wrong amount of atomoxetine finished their respective studies. None of the 7 cases resulted in an SAE. Commonly reported symptoms among overdose subjects were anorexia, abdominal pain, and headache. The sponsor reported increases in heart rate but no changes in blood pressure or QTc in atomoxetine overdose patients (ISS, pp. 626-9).

The sponsor described what appeared to be toxicity symptoms in a PM subject with the highest recorded serum concentration of atomoxetine in the NDA. That case was summarized above in the CP section and the summary is repeated here.

Subject **LYAE-1009** a 28-year-old PM male developed ataxia, myoclonic jerking, of his legs at night and dizziness and had hyperreflexia on neurologic exam. He had been receiving atomoxetine 75mg bid (2.44mg/kg/day) for five days and had a serum concentration of 5596ng/mL, the highest recorded serum concentration. His symptoms resolved off atomoxetine over the next 48 hours.

4.12 Human Pregnancy

There have been two pregnancies in subjects exposed to atomoxetine, both from the historical depression trials database. In one case, the subject was exposed for 6 weeks and when she had a positive pregnancy test, atomoxetine was stopped. The baby was born normal and healthy. The outcome of the second case is unknown (ISS, p.572)

4.13 Withdrawal

In the pediatric studies HFBD and HFBK, after 9 weeks of double blind treatment, the remaining atomoxetine subjects were observed on placebo for 1-week following abrupt atomoxetine discontinuation while placebo subjects continued their assigned treatment for that week. The sponsor compared AEs during this one-week discontinuation phase. There did not appear to be evidence of differences in the actual AEs or frequency of AEs reported during the discontinuation phase based on the small sample size (atomoxetine 102, PBO 92) (ISS, p.632). The atomoxetine discontinued group experienced decreases in DBP (-0.98mmHg), SBP (-0.43mmHg), and pulse (–3.8bpm) during the discontinuation phase compared to slight increases in these measurements in the placebo group (ISS, p.633). QTc, Fridericia and data corrected, decreased among atomoxetine withdrawn subjects (-0.157, -1.505, respectively) and increased among placebo subjects (3.859, 4.442, respectively) (ISS, p.634)

In the adult studies LYAA and LYAO, after the double blind treatment phase, 120mg/day and 90mg/day atomoxetine subjects were randomized to abrupt or tapered discontinuation and observed during a 4-week discontinuation phase. The taper reduced the dose by 30mg/week and then stopped atomoxetine once the subject reached 60mg/day. The sponsor observed 73 abrupt and 94 tapered discontinuation subjects. There were no differences in the reasons for discontinuation during the discontinuation phase. One tapered and no abrupt d/c subjects discontinued during this phase for an AE. The following table summarizes selected AE risks by d/c assignment.

Select AE risks following withdrawal of Atomoxetine, studies LYAA, LYAO

Event	Abrupt d/c (n=73)	Taper (n=94)	p-value
Dizziness	5.5% (4)	0	.035
Flu syndrome	4.1% (3)	2.1% (2)	.654
Somnolence	4.1% (3)	2.1% (2)	.654
Depression	2.7% (2)	1.1% (1)	.581
Insomnia	2.7% (2)	10.6% (10)	.069

During the discontinuation phase, both groups experienced decreases in SBP, DBP, and pulse with the declines in SBP and pulse greater among the abrupt d/c group. Both the abrupt d/c and the taper group experienced decreases in their data corrected QTc (-0.95, -1.25, respectively). (ISS, 636-43).

4.14 Drug Disease Interaction

The sponsor stated that hepatic impairment will have an impact on systemic exposure to atomoxetine since clearance is dependent on hepatic blood flow and hepatic function (482). Excretion of inactive metabolites in urine will not change the effects of atomoxetine in patients with end stage renal disease. The sponsor reported "Neither maximum serum concentrations nor total systemic exposure to atomoxetine parent differed significantly between patients with severe renal insufficiency and normal subjects" (p.482). Both the liver and hepatic insufficiency studies were single dose studies and therefore do not provide safety information about chronic dosing.

5. Review of Systems

5.1 Cardiovascular

There were no deaths due to cardiovascular causes in the atomoxetine development program.

The sponsor identified the following four CV SAEs in atomoxetine subjects: murmur (HFBE-023-0894), peripheral shutdown (LYAF-570-1882), unstable angina (LYAR-083-6419), and chest pain (LYAB-103-5786). A syncopal event (LYAB-063-5565) was listed under the neurological body system but will be considered here with the CV SAEs. A pediatric cardiologist evaluated the murmur SAE, and an echocardiogram documented a small patent foramen ovale not considered hemodynamically significant. The peripheral shutdown SAE narrative described symptoms of feeling cold ½-1 hour following atomoxetine dosing in a 9-year-old male. The subject was found to have "peripheral shutdown" in hands and feet and was admitted for observation. Atomoxetine was stopped with resolution of symptoms. The chest pain SAE involved a pediatric subject with a history of pulmonary artery stenosis and the patient improved following discontinuation. The unstable angina SAE was a 46 year old male with a history of hypertension, moderate obesity and a family history of CAD. He developed chest pain and was diagnosed with unstable angina. He discontinued from the study. The syncopal event occurred in a 7-year-old EM male and was incompletely described. Work up included a normal EEG, normal labs, negative drug screen, and normal ECG and head CT. Apparently the subject experienced two additional syncopal episodes after stopping atomoxetine. Atomoxetine was subsequently restarted with no additional syncopal episodes.

The historical database (depression, urinary incontinence trials) identified 22 CV SAEs in 1,275 subjects. Extrasystole, hypertension, and tachycardia occurred in 3 subjects each. Atrial arrhythmia, bundle branch block, and syncope occurred in 2 subjects each. The following CV events were reported for one subject: angina, arrhythmia, ECG abnormal, hemorrhage, myocardial infarction, ST elevated, and vascular disorder. The narratives for these events provided little information about the events.

CV AEs did not commonly lead to discontinuation from the pediatric or adult ADHD studies. Palpitation and tachycardia were the only CV AEs leading to discontinuation of more than two subjects in the pediatric phase II/III ADHD trials. The narratives for these events did not suggest an association with dizziness or syncope. One pediatric subject discontinued for hypertension and had a baseline BP of 117/81mmHg and a highest recorded BP of 120/94mmHg. In the adult placebo controlled trials, chest pain (n=2) and palpitations (n=2) were the events leading to discontinuation of more that 1 subject. Neither palpitation event was associated with dizziness or syncope, but one case was associated with parasthesias. One adult discontinued for hypertension (baseline BP 153/94mmHg, highest on study 141/99mmHg) and one for hypotension (baseline BP 129/81mmHg, on day of d/c 120/80mmHg).

Four atomoxetine subjects discontinued from clinical pharmacology trials for syncope. Narrative descriptions for these events were summarized in the clinical pharmacology section of this review (n=2) and in the QT review section (n=2). All four subjects who experienced syncope were EMs and the range of atomoxetine doses was 10-60mg. Two subjects were also taking fluoxetine, a CYP2D6 inhibitor, at the time of the event. Although there was insufficient evidence to be certain of the causes of these syncope events, the sponsor's narratives suggested orthostatic blood pressure and vasovagal etiologies. In one case, the event occurred while standing for morning VS and was associated with bradycardia and the subject felt faint prior to the event. One syncope event followed rising from a squatting position in a subject who may have been dehydrated from vomiting and diarrhea. Another syncope event occurred after voiding and was preceded by lightheadedness. The last event occurred during a fast and after sitting up for a blood draw. The sponsor identified 5 subjects (1.6%, 5/316) with syncope AEs within 12 hours of an atomoxetine dose in CP studies (ISS p.417). Although no events coded as postural hypotension led to discontinuation, 10 subjects (3.2%, 10/316) had a postural hypotension AE within 12 hours of an atomoxetine dose in CP studies (ISS p.417).

In a post hoc analysis using a case definition for symptomatic orthostatic hypotension (SOH), 8 clinical pharmacology subjects experienced 17 SOH events. The sponsor reported that SOH was more common among PM subjects (13.3%, 4/30) than EM subjects (2.7%, 4/150). None of the SOH events occurred within 24 hours of first atomoxetine dose. Four subjects had events 48-60 hours after their first atomoxetine dose. Seven of the subjects had an SOH event at the 40-60mg dose range.

In the historical depression placebo controlled trials, vasodilatation and tachycardia were the only CV AEs leading to discontinuation of at least 3 atomoxetine subjects and at least twice as frequent compared to placebo. In these studies, the risk for vasodilatation leading to d/c was 0.8% (9/1153) in the atomoxetine group compared to 0 in the placebo group (n=654). The risk for tachycardia leading to d/c was 0.3% (4/1153) in the atomoxetine group compared to 0 in the placebo group (n=654). One atomoxetine subject (0.1%, 1/1153) and no placebo subjects discontinued for syncope.

In the pediatric ADHD studies, no CV AEs occurred in at least 5% of subjects. Tachycardia was reported in 2.5% (n=49) subjects, chest pain in 2.3% (n=44) subjects, postural hypotension in 1.2% (n=23) subjects, hypertension in 0.7% (n=13) subjects and syncope in 0.4% (n=7) subjects. The following table summarizes the risks for these events in the placebo controlled pediatric ADHD bid trials allowing a comparison of risk by treatment.

Risks for CV AEs reported in Pediatric and Adolescent Placebo Controlled ADHD studies using BID Dosing

CV AE	ATX N=340	PBO N=207
Postural Hypotension	1.8% (6)	0.5% (1)
Tachycardia	1.5% (5)	0.5% (1)
Chest Pain	1.2% (4)	0
Hypertension	0.6% (2)	0
Palpitation	0.6% (2)	0.5% (1)

Syncope was not reported in this safety sub-group

The risks for tachycardia (2.2% PM, 1.1% EM), syncope (1.1% PM, 0.2% EM), and hypertension (0.6% PM, 0.2% EM) were greater among pediatric PM subjects than EM subjects, suggesting a potential exposure level response relationship.

In the Adult ADHD studies, no CV AEs occurred in at least 5% of subjects. Vasodilitation and palpitation were reported in 4.1% (n=11) of subjects, chest pain in 3% (n=8) of subjects, tachycardia in 3% (n=8) subjects, hypertension in 0.7% (n=2) subjects, and postural hypotension in 0.4% (n=1). Each of these CV events occurred at least twice as

commonly among atomoxetine subjects compared to placebo subjects except for hypertension which occurred more frequently among placebo subjects. Syncope was not reported as a treatment emergent AE in these studies.

The sponsor's analyses of vital sign data support an atomoxetine-related increase in systolic blood pressure, diastolic blood pressure and pulse. The following tables summarize the mean changes from the pediatric and adult ADHD placebo controlled BID groups.

Diastolic Blood Pressure, Systolic Blood Pressure and Pulse Mean Change from Baseline to Endpoint, Child and Adolescent acute placebo controlled ADHD studies and Adult acute placebo controlled ADHD studies using BID dosing

Parameter	Treatment (n)	Mean Change	p-value
Child and Adolescent acute placebo controlled ADHD studies using BID dosing			
Diastolic BP	Atomoxetine (335) Placebo (204)	2.060 -0.453	.002
Systolic BP	Atomoxetine (335) Placebo (204)	2.791 1.184	.148
Pulse	Atomoxetine (335) Placebo (204)	7.816 1.532	<.001
Adult acute placebo controlled ADHD studies using BID dosing			
Diastolic BP	Atomoxetine (258) Placebo (258)	1.771 0.525	.083
Systolic BP	Atomoxetine (258) Placebo (258)	2.868 -0.002	.002
Pulse	Atomoxetine (258) Placebo (258)	5.262 -0.328	<.001

The SBP, DBP and pulse mean changes observed in the once daily dose study were comparable to the changes illustrated above. The mean increases in diastolic blood pressure, systolic blood pressure, and pulse were higher among PM subjects compared to EM subjects suggesting a potential exposure level response relationship.

The vital sign outlier analyses were consistent with the mean change analyses. In pediatric ADHD BID subjects, 19% of atomoxetine subjects had a DBP high outlier compared to 11% of placebo subjects (RR=1.7) and 18% of atomoxetine subjects had a SBP high outlier compared to 9% of placebo subjects (RR=2). Nine percent of atomoxetine subjects had a high pulse outlier compared to 4% of placebo subjects (RR=2.25).

The relative risks for DBP and SBP outliers in the pediatric ADHD QD studies were similar to the risks in the pediatric BID studies. The data demonstrated a higher relative risk for high pulse outliers in the once daily dosed pediatric studies compared to the BID studies. In the QD studies, the risk for a high pulse outlier was 7.1% in the atomoxetine group and 1.2% in the placebo group, RR=5.9. In the pediatric BID studies the high pulse outlier RR was 2.25.

In the adult studies, there was little difference in risk for high DBP between atomoxetine and PBO but 5% of atomoxetine and 3.5% of placebo subjects had a SBP high outlier (RR=1.4). Almost 11% of atomoxetine subjects had a high pulse outlier compared to 3% of placebo subjects (RR=3.7).

PM subjects had higher mean increases in DBP, SBP, and pulse compared to EM subjects, although the high outlier risks were similar for both groups.

Orthostatic blood pressure data were not collected during phase II/III ADHD trials. The sponsor examined orthostatic blood pressure changes in CP multi-dose studies. At most of the doses and time points for PM subjects the orthostatic systolic blood pressure changes were more negative than placebo with the greatest difference –29.4mmHg, 75mg dose pre dose. The orthostatic systolic blood pressure change differences between EM and placebo subjects were smaller with the greatest difference -12.6mmHg, 40mg at 1-hour post dose (Table ISS.5.4.27, p.445). At most of the doses and time points for PM subjects the orthostatic diastolic blood pressure changes were more negative than placebo (greatest difference –18.2mmHg, 60mg dose at time 0). The orthostatic systolic blood pressure change differences between EM and placebo subjects were smaller with the greatest difference –9.2mmHg, 20mg at pre dose (Table ISS.5.4.31, p.449).

The ECG data from a clinical pharmacology study demonstrated QTc prolongation in PM subjects at the 60 BID and 75 BID dosages with the greatest increases at the pre-dose time point for the 75mg BID dose. A second clinical pharmacology study that used fluoxetine to create "phenotypic" PM subjects did not demonstrate QTc prolongation. The ECG data collected during the phase II/III studies did not find atomoxetine related QTc prolongation although the ECGs were not collected in the same careful manner used in the clinical pharmacology studies. Considering clinical events that could be potentially related to arrhythmia, there were no sudden deaths or documented adverse events of torsades de pointes, ventricular tachycardia or ventricular fibrillation in the development program. There were six atomoxetine subjects with convulsions and there were occasional syncopal episodes in atomoxetine subjects. Atomoxetine was associated with increased risk of dizziness and palpitations compared to placebo but any relationship between these events and effect on QTc is speculative. Pre-clinical data demonstrate that atomoxetine blocks I_{Kr} providing a potential mechanism for the QTc results observed in the clinical pharmacology study.

5.2 Digestive System

There were no deaths due to digestive causes in the atomoxetine development program.

The sponsor identified 14 subjects with digestive system SAEs. Nine of these events were cases coded as appendicitis, two were acute abdominal pain, one was a GI infection, one was increased LFTs and the last was vomiting in a subject who took an atomoxetine overdose. The appendicitis cases were summarized above. One of the abdominal pain cases (LYAI-055-5048) occurred in an 11-year-old male who had a prior history of abdominal pain. The pain stopped after discontinuing atomoxetine but then later recurred off drug. The second abdominal pain SAE occurred in a 49-year-old female (LYAR-081-5952) and was attributed to diverticulitis although the subject was not treated with antibiotics making this diagnosis suspect. The GI infection case (LYAF-601-7009) was an 8-year-old male who developed vomiting and diarrhea and was admitted to work up a possible diagnosis of celiac disease. The increased LFT case (LYAF-652-9053) was discussed above and was notable for hives, confusion and ALT of 169 and AST of 136. LFTs improved off drug and hepatitis serology was reportedly negative. Subject 004-1125 a 13 year old male with a history of thalassemia minor took twice the prescribed amount of atomoxetine for 3 weeks and developed lightheadedness and intermittent vomiting that persisted for 1 week following atomoxetine discontinuation.

Liver function test abnormal (n=5) and nausea (n=2) were the only digestive SAE occurring in more than 1 atomoxetine subject enrolled in depression and urinary incontinence trials in the Historical database.

Digestive AEs did not commonly lead to discontinuation from clinical trials for atomoxetine subjects. Nausea led to the discontinuation of 3 subjects in the pediatric ADHD trials using BID dosing. Pediatric subject LYAB-084-4924 discontinued for abnormal LFTs. The highest recorded ALT for this subject was 87U and highest total bilirubin was 0.3mg/dL. In the adult ADHD studies, no atomoxetine subjects discontinued for digestive AEs. Subject LYAT-023-3409 discontinued from the once daily dosed pediatric ADHD study for vomiting. This 6-year-old male developed nausea and vomiting after 14 days of atomoxetine. The sponsor did not provide an outcome in this subject's narrative.

In the historical data base depression trials, nausea (0.5%, 6/1,153) and constipation (0.3%, 3/1,153), were the only AEs leading to discontinuation of more than 1 atomoxetine subject.

Digestive AEs were commonly reported by atomoxetine subjects in the ADHD development program and data from placebo controlled trials suggest a relationship between atomoxetine and these AEs. Abdominal pain (21%, 411/1,933) anorexia (15%, 282/1,933), vomiting (14%, 272/1,933) nausea (11%, 212/1,933), diarrhea (6%, 123/1,933) and constipation (5%, 96/1,933) were the most commonly reported digestive AEs in the pediatric and adolescent BID ADHD studies. Anorexia, dyspepsia, constipation, weight loss, and gastroenteritis occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo on the pediatric ADHD BID placebo controlled trials. In the adult ADHD BID placebo controlled trials, nausea, anorexia, constipation, flatulence, and rectal disorder occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo. In the pediatric once daily ADHD study, anorexia, abdominal pain, vomiting, nausea, dyspepsia, and diarrhea occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo. Data from study LYAC, the pediatric ADHD BID study that randomized to fixed doses suggests a dose response for 3 digestive AEs. Those data are provided below.

Selected LYAC Adverse Events by Dose (mg/kg/day)*

Event	ATX 0.5 (n=44)	ATX 1.2 (n=84)	ATX1.8 (n=83)	PBO (n=83)
Abdominal Pain	11.4% (n=5)	14.3% (n=12)	14.5% (n=5)	10.8% (n=9)
Anorexia	6.8% (n=3)	11.9% (n=10)	12% (n=10)	4.8% (n=4)
Vomiting	6.8% (n=3)	7.1% (n=6)	10.8% (n=9)	6% (n=5)

The analyses of lab data did not suggest a relationship between atomoxetine and increases in transaminases or total bilirubin.

5.3 Hemic and Lymphatic System

There were no deaths due to hemic or lymphatic causes in the atomoxetine development program. There were no hemic or lymphatic SAEs in the ADHD database. In the historical database there was one leukopenia SAE and one leukemia SAE. Hemic and Lymphatic System AEs did not commonly lead to discontinuations from ADHD trials. One pediatric subject (LYAB-064-5616) discontinued for lymphocytosis, which was diagnosed as mononucleosis. No adult subjects discontinued for hemic or lymphatic system AEs. No subjects discontinued for hemic or lymphatic system AEs in the historical database depression trials.

Ecchymosis (2.6%, 51/1,933) was the only Hemic and Lymphatic System AEs occurring in more than 1% of pediatric ADHD subjects from BID trials. Anemia (0.5%, 10/1,933) and leukopenia (0.5%, 10/1,933) were rarely reported in these studies. Data from placebo controlled pediatric trials did not suggest increased risks for hemic and lymphatic system AEs among atomoxetine subjects.

Aside from small mean increases in platelet counts in atomoxetine subjects but not present in placebo subjects, lab data analyses did not suggest atomoxetine-related changes in hematologic parameters.

5.4 Metabolic and Nutritional

There were no deaths due to Metabolic and Nutritional causes in the atomoxetine development program. There was one SAE in the Metabolic and Nutritional body system in the ADHD database. Subject LYAR-081-5953, a 35-year-old male with a baseline glucose of 105mg/dL, was hospitalized for newly diagnosed diabetes mellitus (blood glucose 451mg/dL). In the historical database, the only Metabolic and Nutritional SAE was hypoglycemia.

Weight loss led to the discontinuation of one pediatric subject from the ADHD studies. No adults discontinued from placebo controlled ADHD trials for a metabolic or nutritional AE. Two subjects from the historical database depression trials discontinued for weight loss, the only Metabolic and Nutritional AEs leading to discontinuation.

Weight loss was the only metabolic and nutritional AE reported by more than 1% of atomoxetine subjects (2.6%, 51/1,933) in pediatric ADHD trials. In the placebo controlled pediatric ADHD trials, weight loss was reported by 2.4% (8/340) of atomoxetine subjects compared to 0 placebo subjects. Similarly, 2.2% (6/269) of adult ADHD subjects had a weight loss AE compared to 0.8% (2/263) of placebo subjects. In study LYAC, a pediatric ADHD study where subjects were randomized to 3 fixed doses of atomoxetine or placebo, there were no weight loss AEs in the placebo (n=83) or 0.5mg/kg/day (n=44) groups. In the 1.2mg/kg/day group 1.2% (1/84) reported a weight loss AE compared to 2.4% (2/83) of the 1.8mg/kg/day group (LYAC Study report, p.346).

Recorded weight data from adolescent and pediatric placebo controlled trials support an atomoxetine related risk of weight loss. In the pediatric ADHD placebo controlled trials, atomoxetine subjects had a mean decrease in weight (-0.381kg) compared to an increase (1.545kg) among placebo subjects. In these studies, the risk for loss of at least 3.5% of baseline body weight was 32.3% (108/334) in atomoxetine subjects compared to 5.9% (12/204) in placebo subjects (RR=5.5). In study LYAC, a pediatric ADHD study where subjects were randomized to 3 fixed doses of atomoxetine or placebo, the risk for losing at least 3.5% of body weight demonstrated dose response. The sponsor reported that 1.3% (1/83) of placebo subjects, 7.1% (3/43) of 0.5mg/kg/day subjects, 19.3% (16/84) of 1.2mg/kg/day subjects, and 29.1% (23/81) of 1.8mg/kg/day subjects lost at least 3.5% of their body weight at the end of the study. Additionally, The risk of losing at least 3.5% of body weight for poor metabolizers receiving at least 1.2mg/kg/day atomoxetine was 64% compared to 44.5% for extensive metabolizers receiving at least 1.2mg/kg/day atomoxetine (p=.002).

Adult subjects in placebo controlled ADHD trials also had mean decreases in weight (-1.21kg) while the placebo group had a mean increase in weight (0.36kg). Atomoxetine exposed adults also had a greater risk of losing at least 7% of their body weight (4.7%, 12/258) compared to placebo subjects (0.4%,1/258).

Since there were no long-term placebo controlled data, the sponsor explored atomoxetine effects on weight and height by comparing the observed growth data to expected growth from the general population based growth tables and z scores (see above). While atomoxetine subjects had a mean increase in weight for one year (4 kg) and 1.5 years (6.5kg) there was a mean decrease in z scores of .25 and a mean decrease in weight percentile of 7.1 at one year. The sponsor also noted a mean decrease in weight z score of .28 and a mean decrease in weight percentile of 7.3 at 1.5 years (Safety update, p.115). This indicated that compared to the general population, the observed weight gain was less than predicted.

Using data for subjects exposed to atomoxetine for at least 1 year, the mean increase in height was 6.4cm with a decrease in mean z score of 0.16. Percentile for height decreased from 52 at baseline to 47 at endpoint (Safety update, p.121). Using data for subjects exposed to atomoxetine for at least 1.5 years, the mean increase in height was 9.3cm with a decrease in mean z score of 0.14. Percentile for height decreased from 54 at baseline to 49.5 at endpoint (Safety update, p.121).

The sponsor noted that those in the lowest height and weight quartiles at baseline had the smallest decrease in percentile/z scores.

5.5 Musculoskeletal System

There were no deaths from musculoskeletal causes in the development program. The musculoskeletal SAEs in the ADHD database included fractures and limb injuries. In the historical depression trial database, 4 subjects had an SAE of CPK increased and 1 had a bone disorder SAE. Musculoskeletal AEs did not commonly lead to discontinuation from the pediatric or adult ADHD trials or from the depression trials in the historical database.

Myalgia (2.7%, 52/1,933) and twitching (1.8%, 34/1,933) were the two AEs occurring in at least 1% of subjects in the overall child and adolescent ADHD database. In the child and adolescent placebo controlled ADHD trials, twitching occurred at a similar frequency in the atomoxetine and PBO groups and myalgia occurred more frequently in the placebo group. In the adult placebo controlled ADHD trials, myalgia was the only musculoskeletal AE reported more frequently among atomoxetine subjects (5.6%, 15/269) than placebo subjects (2.7%, 7/263).

The lab data suggested that atomoxetine exposure was associated with decreases in CPK. The CPK decreases were more negative in PM subjects compared to EM subjects.

5.6 Nervous System/Psychiatric

There were no deaths from nervous system causes in the development program. Nervous system/Psychiatric SAEs were among the more common SAEs in atomoxetine subjects. Subjects LYAB-057-5333 and LYAI-088-8570 had convulsion SAEs. One atomoxetine subject had meningitis (HFBE-012-0451). There were five depression SAEs (HFBF-015-1586, HFBF-017-1659, LYAB-051-5098, LYAI-089-8602, and LYBB-056-7442) and one SAE coded to Intentional self injury (LYAI-015-1745) that involved a suicidal gesture. The depression SAEs were hospitalizations for suicide ideation or gestures. Four of these subjects were males, the age range for these subjects was 10-14yrs, and the range of duration of atomoxetine use was 51 days to 461 days. There was one psychotic disorder SAE (LYAC-017-7267) with verbatim terms of hallucinations and delusions. The narrative noted that after 7 months of atomoxetine treatment, this 9-year-old male was "acting strangely...obsessed with genitalia". The narrative noted sexual abuse by classmates at school. In addition to the above nervous system SAEs, there were two hostility SAEs, one agitation SAE, and one bipolar disorder SAE. Depression was the only nervous system SAE reported by more than 2 subjects in the historical depression database.

Nervous system/psychiatric AEs were among the most common AEs leading to discontinuation from pediatric and adolescent ADHD trials. Nervousness (n=8), somnolence (n=6), emotional lability (n=5), depression (n=4), twitching (n=4), agitation (n=3), anxiety (n=3), and hostility (n=2) were the nervous system/psychiatric AEs leading to discontinuation of at least 2 subjects in the child and adolescent ADHD trials. In the child and adolescent ADHD placebo controlled trials, nervousness was the only nervous system/psychiatric AE leading to discontinuation of more than one subject (0.6%, 2/340) in the atomoxetine group and more frequently led to discontinuation compared to the placebo group (n=0/207). In the adult ADHD placebo controlled BID trials, insomnia was the only nervous system/psychiatric AE leading to discontinuation of more than one subject (1.1%, 3/270) in the atomoxetine group and more frequently led to discontinuation compared to the placebo group (0.4%, 1/266). In the pediatric ADHD trial once daily trial, one atomoxetine subject discontinued for emotional lability and one for somnolence.

Nervous system/psychiatric AEs reported by more than 5% of subjects in the child and adolescent ADHD BID trial overall database included insomnia (10.6%, 205/1933), somnolence (10.6%, 204/1933), nervousness (10%, 193/1933), dizziness (6.1%, 117/1933) and emotional lability (6.1%, 117/1933). In the child and pediatric placebo controlled ADHD BID trials, Emotional lability and hostility were the only nervous system/psychiatric AEs that occurred in at least 2% of atomoxetine subjects and at least twice as frequently compared to placebo. The risks for select nervous system AEs from these trials are included in the following table.

Risks for Selected Nervous System/Psychiatric AEs from Child and Pediatric Placebo Controlled ADHD BID trials

AE	ATX (n=340)	Placebo (n=207)
Nervousness	8.8% (30)	5.8% (12)
Somnolence	8.5% (29)	6.3% (13)
Emotional Lability	5.3% (18)	2.4% (5)
Dizziness	4.4% (15)	2.9% (6)
Depression	2.6% (9)	3.9% (8)
Hostility	2.1% (7)	0.5% (1)

In addition to the common events reported above, the sponsor reported that 4 subjects (0.2%, 4/1933) in the overall pediatric ADHD database had AEs coded as convulsions. In general there was limited information provided about these cases. None of these events were listed as the reason for discontinuation from a trial and none met the criteria for a serious AE.

In the adult ADHD placebo controlled trials, insomnia, libido decreased, dizziness, and nervousness occurred in at least 2% of atomoxetine subjects and at least twice as frequently compared to placebo. In the child and pediatric placebo controlled ADHD once daily trial, dizziness, depression, and hostility were the nervous system AEs that occurred in at least 2% of atomoxetine subjects and at least twice as frequently compared to placebo.

In study LYAC, a pediatric ADHD study where subjects were randomized to 3 fixed doses of atomoxetine or placebo, there appeared to be evidence of dose response for somnolence. In this study, 3.6% (n=3) of placebo subjects reported somnolence compared to 4.5% (n=2) in the atomoxetine 0.5mg/kg/day group, 7.1% (n=6) in the atomoxetine 1.2mg/kg/day group, and 10.8% (n=9) in the 1.8mg/kg/day group. Mood swings, sedation, hypersomnia, depressed mood, tremor, and feeling jittery all occurred in at least 1%of PM subjects and at least twice as frequently when compared to EM subjects.

5.7 Respiratory System

There were no deaths from respiratory system causes in the development program. There were 5 respiratory SAEs in the ADHD development program with two cases of pneumonia (LYBB-035-6560, LYAI-042-7006), one asthma exacerbation (LYAI-021-4009), one sinusitis (LYAI-012-4507), and one respiratory disorder (LYAB-044-4827). The respiratory disorder case involved a 10 year old male with a history of asthma who had been taking atomoxetine for 11 months when he developed acute respiratory distress and mild facial swelling. He was treated with epinephrine, dexamethasone, and ceftriaxone. He re-started atomoxetine following the event and had no additional episodes of respiratory distress during those 6 months of treatment.

No respiratory system AEs led to discontinuation of more than 1 subject in the child and adolescent ADHD BID overall studies or the adult placebo controlled ADHD trials databases.

The Respiratory system AEs reported by more than 5% of subjects in the child and adolescent ADHD BID overall studies database were rhinitis (27%, n=518), pharyngitis (15%, n=292), cough increased (12%, n=234), and sinusitis (5.3%, n=103). In the child and adolescent placebo controlled ADHD BID trials, no respiratory AEs occurred in at least 1% of the atomoxetine group and at least twice as frequently compared to the placebo group. In the adult placebo controlled ADHD trials, epistaxis (atomoxetine 1.1% 3/269, placebo 0.4%,1/263) and laryngitis (atomoxetine 1.1% 3/269, placebo 0.4%,1/263) were the respiratory AEs occurred in at least 1% of the atomoxetine group and at least twice as frequently than in the placebo group.

5.8 Skin and Appendages

No subjects died from skin related disorders in the development program. Six skin-related SAEs were reported from ADHD studies. The skin SAEs included 4 subjects with burn injuries (LYAC-001-7012, LYAI-001-4046, LYAI-067-5005, and LYAF-541-1404), a case of basal cell carcinoma (LYAA-72-2186), and a case of angioneurotic edema/urticaria (LYAB-096-6164). The angioedema event was summarized above and was notable for the fact that the subject had a history of angioedema (x2) prior to taking atomoxetine and that the subject had been taking the atomoxetine for almost 7 months when the event occurred. The historical depression trials database included one rash SAE and one urticaria SAE.

Rash led to discontinuation of two subjects (HFBE-015-0556 and LYAB-090-6023), urticaria one subject (LYAB-041-4642), and allergic reaction one subject (LYAC-019-7806) from the child and adolescent ADHD overall BID database. The events coded as rash occurred in a 14-year-old male and a 9-year-old male and neither narrative provided a detailed description of the rash or information about outcome. The urticaria event occurred in a 16-year-old male after 48 days of atomoxetine treatment. This subject was treated with antihistamines and methylprednisolone. The allergic reaction event occurred in a 15-year-old male and the narrative described edema, pruritis and rash that were graded as severe and that occurred after 2 days of atomoxetine treatment. The subject was treated with prednisone and symptoms resolved 1 week later.

The allergic reaction AE described above was the only skin event leading to discontinuation of an atomoxetine subject from the child and adolescent placebo controlled ADHD BID trials. In the adult placebo controlled ADHD trials, one atomoxetine subject (LYAA-106-1114) and no placebo subjects discontinued for urticaria. The adult with urticaria was a 35-year-old male with a history of hives triggered by stress who developed hives which fluctuated in severity during the study. In the historical depression trials database, rash led to discontinuation of 0.3% (3/1153) atomoxetine subjects and 0.2% (1/654) placebo subjects and urticaria led to the discontinuation of 0.1% (1/1153) atomoxetine subjects and 0.2% (1/654) placebo subjects.

Rash (6.3%, 121/1933) was the only skin AE reported by more than 5% of the atomoxetine subjects in the child and adolescent ADHD overall BID database. Pruritis was reported by 1.1% (22/1933) of atomoxetine subjects and urticaria by 0.5% (10/1933) of atomoxetine subjects in this group. In the child and adolescent ADHD placebo controlled BID database, the risk for rash was 6.2% (21/340) in the atomoxetine group and 5.8% in the placebo group. Pruritis occurred in 1.8% (6/340) of atomoxetine subjects and no placebo subjects. Urticaria occurred in 0.6% (2/340) of atomoxetine subjects and 0.5% (1/207) of PBO subjects in these studies. In the adult placebo controlled ADHD trials, sweating was reported by 5.2% (14/269) of atomoxetine subjects and 0.8% (2/263) of placebo subjects. Rash was reported by 3% (8/269) of adult atomoxetine subjects and 1.9% (5/263) of placebo subjects. Pruritis was reported by 1.5% (4/269) of adult atomoxetine subjects and no placebo subjects. Urticaria was reported by 0.7% (2/269) of adult atomoxetine subjects and no placebo subjects.

In study LYAC, a pediatric ADHD study where subjects were randomized to 3 fixed doses of atomoxetine or placebo, there was evidence of dose response for pruritis. Pruritis was reported by no subjects in the placebo or 0.5mg/kg/day groups. In the 1.2mg/kg/day group, 1.2% (1/84) and in the 1.8mg/kg/day group 6% (5/83) of atomoxetine subjects reported pruritis. Urticaria was more common among PM subjects (1.1%, 2/181) than EM subjects (0.6%, 12/1974) while the risk for pruritis was similar for PM (1.1%, 2/184) and EM (1%, 19/1974) subjects. Using the sponsor's AE data sets, I identified no events of unexplained facial swelling, tongue swelling or throat swelling/tightness.

5.9 Special Senses

There were no deaths and no SAEs related to special senses in the development program. In the historical depression-trials database, 2 subjects had cataract SAEs and one subject had each of the following SAEs: chorioretinitis, eye disorder, and glaucoma.

No subjects in the child and adolescent ADHD overall BID database discontinued for a special senses AE. One subject (LYAO-081-3261) in the adult ADHD placebo controlled trials database discontinued for taste perversion. The narrative for this event noted that a 42-year-old female developed a severe bitter taste that began 48 days after starting atomoxetine. The event did not resolve at the time of discontinuation.

In the child and adolescent ADHD overall BID database, ear pain (2.2%, 43/1933), otitis media (1.8%, 35/1933) and conjunctivitis (1.1%, 21/1933) were the AEs reported by more than 1% of atomoxetine subjects. Mydriasis was reported for 0.6% (12/1933) subjects in these studies. One atomoxetine subject (LYAB-065-5661) had an AE coded to deafness. The verbatim term for this event was "decreased hearing left ear" and occurred in a subject with a history of intermittent tinnitus. In the child and adolescent ADHD placebo controlled BID trials database, only mydriasis occurred in at least 1% of atomoxetine subjects (1.2%, 4/340) and at least twice as frequently when compared to placebo (0/207). In the adult ADHD placebo controlled BID trials database, no AEs occurred in at least 1% of atomoxetine subjects and at least twice as frequently when compared to placebo. In the child and adolescent ADHD placebo controlled once daily database, mydriasis occurred in 1 atomoxetine subject (1.2%, 1/85) and no PBO subjects (0/85). In study LYAC, a pediatric ADHD study where subjects were randomized to 3 fixed doses of atomoxetine or placebo, mydriasis was not reported for the placebo group (n=83) or the 0.5mg/kg/day group (n=44) but was reported by 3.6% (3/84) of the 1.2mg/kg/day group and 1.2% (1/83) of the 1.8mg/kg/day group. Mydriasis was reported more frequently among PM subjects (2.2%, 4/181) than EM subjects (0.6%, 11/1974). There were no glaucoma AEs in the pediatric or adult ADHD trials.

5.10 Urogenital System

There were no deaths in the development program from urogenital causes. In the ADHD database, there were three urogenital SAEs in atomoxetine subjects, LYAC-068-7753 and LYAR-081-5967 had urinary tract infections and HFBF-023-1889 had epididymitis. The historical depression trials database listed the following urogenital SAEs: breast carcinoma (n=2), unintended pregnancy (n=2), kidney calculus (n=1) and urination impaired (n=1).

In the child and adolescent ADHD overall BID database, no subjects discontinued for urogenital AEs. In the adult ADHD placebo controlled trials, urinary retention was the only urogenital AE leading to the discontinuation of more than one atomoxetine subject (0.7%, 2/270 vs. 0/266 PBO subjects). Subject LYAO-021-3578, a 50-year-old male who discontinued for urinary retention developed urinary fullness and a urinary stream that was less forceful on atomoxetine and these symptoms resolved 14 days after stopping the drug. Subject LYAO-082-3312, a 45-year-old male developed urinary retention and discomfort that was associated with decreased urinary flow on atomoxetine and was present at the time of discontinuation. In the historical depression-trials database, no urogenital AEs led to discontinuation of at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo.

In the child and adolescent ADHD overall BID database, urinary incontinence was the only AE reported by more than 1% of atomoxetine subjects (1.1%, 21/1933). In the child and adolescent ADHD placebo controlled trials BID database, dysmenorrhea occurred in 1.1% (n=1) of atomoxetine females and no placebo females. In these studies no other urogenital AE occurred in at least 1% of atomoxetine subject and at least twice as frequently compared to placebo.

In the adult placebo controlled ADHD trials, several urogenital AEs occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo. The adverse event data suggested increased risk for AEs potentially related to bladder outlet restriction or obstruction, particularly urinary retention and urination impaired (subsumed verbatim terms related to urinary hesitation). Those events are listed in the following table.

Urogenital Treatment Emergent AEs Occurring in at least 1% of Atomoxetine Subjects and at least Twice as Frequently Compared to Placebo Subjects, Adult Placebo Controlled ADHD Studies

Event	ATX (n=269)	PBO (n=263)
Impotence**	9.8% (17)	1.2% (2)
Dysuria	4.8% (13)	0.4% (1)
Abnormal Ejaculation**	6.3% (11)	2.3% (4)
Dysmenorrhea*	7.4% (7)	3.3% (3)
Menstrual disorder*	7.4% (7)	3.3% (3)
Urinary retention	2.6% (7)	0
Urination impaired	2.6% (7)	0
Prostatic disorder**	3.4% (6)	0
Oliguria	1.1% (3)	0

*Based on females only; ATX n=95, PBO n=91
**Based on males only; ATX n=174, PBO n=172

In addition to the increased risk of impotence among adult atomoxetine subjects depicted above, five atomoxetine and no placebo subjects in adult study LYAA recorded concomitant use of sildenafil (Viagra) (LYAA Study Report, p.323). This finding was not replicated in adult study LYAO, where 1 atomoxetine and 2 placebo subjects used sildenafil (LYAO Study Report, p.300).

Lab data from the child and adolescent ADHD BID placebo controlled trials demonstrated a slight but statistically significant mean increase in creatinine in the atomoxetine group (1.575umol/L) compared to placebo (0umol/L). This finding was not observed in the adult ADHD placebo controlled trials database, the child and adolescent placebo controlled ADHD once daily trials, or the historical depression trials. There was no statistically significant difference in creatinine mean change from baseline when comparing EM and PM subjects. There were no statistically significant differences in creatinine outliers in the child and adolescent placebo controlled ADHD BID controlled trials, the adult ADHD placebo controlled trials, the child and adolescent placebo controlled ADHD once daily trials, or the historical depression trials.

5.11 Body as a Whole

There were no deaths from the Body as a Whole category in the ADHD development program. Two atomoxetine subjects in the historical database died, one from complications of AIDS, and the second from cancer. There were two atomoxetine subjects in the ADHD database with overdose SAEs. Subject HFBF-004-1125, a 14-year-old male, developed intermittent lightheadedness and vomiting after taking a double dose (3.26mg/kg/day) for 10 days. Subject LYAB-053-5167, a 17-year-old female overdosed on her mother's prescription trazodone. In the CP studies, there was a non-serious symptomatic toxicity case. The event was summarized above (LYAE-1009) and was notable for ataxia, myoclonic jerking of the legs at night, dizziness and had hyperreflexia on neurologic exam. This PM subject had been receiving atomoxetine

75mg bid (2.44mg/kg/day) and had a serum concentration of 5,596ng/mL, the highest recorded serum concentration. This subject's symptoms resolved over the next 48 hours. The historical depression trials database included the following SAEs: surgical procedure (n=6), intentional overdose (n=5), infection (n=2), injury accident (n=2), abdominal pain (n=1), back pain (n=1), carcinoma (n=1), headache (n=1), and neoplasm (n=1).

No Body as a Whole category AE led to discontinuation of at least 1% of subjects in the child and adolescent ADHD overall BID database. No body as a whole AEs led to discontinuation of at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo in the child and adolescent placebo controlled ADHD BID trials or the adult ADHD placebo controlled trials.

In the child and adolescent ADHD overall BID database, headache (32%, 617/1933), abdominal pain (21%, 411/1933), fever (11%, 209/1933) accidental injury (9%, 181/1933), asthenia (9%, 177/1933), flu syndrome (9%, 164/1933), pain (7%, 134/1933), infection (7%, 127/1933) and allergic reaction (5%, 94/1933) were the AEs occurring in at least 5% of atomoxetine subjects. In the child and adolescent placebo controlled ADHD BID trials none of the body as a whole AEs occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo. In the adult ADHD placebo controlled trials chest pain (atomoxetine 3%, 8/269, placebo 1.5%, 4/263), chills (atomxetine 3%, 8/269, placebo 1.1%, 3/263), and surgical procedure (atomoxetine 3%, 8/269, placebo 1.5%, 4/263) occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo. In the child and adolescent placebo controlled ADHD once daily trial, asthenia (atomoxetine 11%, 9/85, placebo 1.2%, 1/85), fever (atomoxetine 7%, 6/85, placebo 3.5%, 3/85), allergic reaction (atomoxetine 2%, 2/85, placebo 0/85), and flu syndrome (atomoxetine 1%, 1/85, placebo 0) occurred in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo.

6. Discussion

The sponsor adequately described the safety data collected in the atomoxetine ADHD development program. The ADHD studies appear to have been appropriately designed to capture treatment emergent adverse events and other safety data. The overall number of individuals exposed to atomoxetine exceeds ICH guidelines. As with most NDA safety databases, based on the number exposed, there is limited power to detect infrequent drug related adverse events.

The number of individuals exposed to atomoxetine in selected sub-populations was small. The ADHD database is predominately comprised of pediatric patients and extensive metabolizers. A small number of adults were exposed to atomoxetine in ADHD studies. The sponsor's additional adult safety data from depression and urinary incontinence trials had limited value because this historical database included less detail than the ADHD trial safety database. In particular, the SAE and discontinuation for AE narratives from the depression trials provided little detail about the events that they summarized. The ADHD database included safety data for a small number of atomoxetine poor metabolizers.

The coding of adverse events generally appeared appropriate, although the sponsor's use of two different coding dictionaries complicated this review. The sponsor used COSTART for ISS safety analyses and MedDRA for labeling and Safety Update analyses. The different coding methods resulted in the use of slightly different adverse event terms but did not appear to meaningfully alter conclusions about atomoxetine's adverse event profile.

Atomoxetine was not associated with increased mortality risk and there were relatively few SAEs in this NDA. There were no deaths in the ADHD development program and SAEs were infrequently reported, with few SAEs reported by more than one atomoxetine subject.

Appendicitis was the most commonly reported SAE with 8 cases in atomoxetine subjects but the exact relationship between this event and atomoxetine has not been established. All appendicitis cases in the NDA occurred in pediatric patients. Since these appendicitis cases occurred during open-label and uncontrolled trials, comparisons of risks within controlled trials were not possible. The pediatric appendicitis rate in the NDA was 2.5 times higher than the pediatric general population rate estimates derived from Hospital Discharge Survey data (pooled 1995-1999). There did not appear to be any common risk factors among the atomoxetine subjects with appendicitis such as dose of atomoxetine or time to event. While the finding of an increased risk for appendicitis among atomoxetine subjects compared to background is interesting, the data do not allow firm conclusions about the relationship between atomoxetine and appendicitis. If approved, the sponsor's reporting of post marketing appendicitis cases should be expedited to allow close monitoring of this event.

The common atomoxetine treatment emergent adverse events that occurred more frequently compared to placebo included abdominal pain, nausea, vomiting, constipation, anorexia, dry mouth, insomnia, palpitations, decreased appetite, and dizziness. There appeared to be evidence of dose response for some of these events. In general, these events rarely led to discontinuation from a trial. In addition to the events noted above, data from adult atomoxetine subjects demonstrated higher risks of sexual side effects for atomoxetine subjects compared to placebo subjects.

Several atomoxetine subjects had AEs coded as convulsions but these events were not adequately described in the NDA. Two subjects had SAEs classified as convulsions although one case was not definitively diagnosed and there were potentially confounding circumstances in both cases. In addition, there were four cases coded as convulsions in open-label trials with insufficient details about the events to determine if these were seizures or represent another diagnosis such as syncope, or if there were obvious non-drug related etiologies. We asked the sponsor to provide additional data for these cases.

The atomoxetine NDA included cases of angioedema and urticaria in subjects exposed to atomoxetine. There was one SAE of angioedema in an atomoxetine subject, without mention of respiratory compromise. This subject had a history of angioedema events prior to enrolling in the atomoxetine study and the reported event occurred 8 months after starting atomoxetine making it difficult to determine whether atomoxetine contributed to the event. Cases of urticaria were reported among atomoxetine subjects. Within the placebo-controlled trials urticaria, angioedema, and allergic reaction events were infrequent and also occurred in placebo subjects, thus there was limited power to detect and accurately describe differences in risk by treatment. The sponsor has included a statement about angioedema, urticaria, and allergic reactions in a warning in the proposed atomoxetine labeling. If approved, the sponsor's reporting of urticaria and angioedema post marketing cases should be expedited to allow close monitoring for these events.

Atomoxetine use appeared to be associated with an increased risk for urinary bladder outlet restriction related adverse events, not a surprising finding since it was being developed at one time as a treatment for urinary incontinence. In the adult trials, two subjects discontinued for urinary retention symptoms that began after starting atomoxetine. In addition, the risk for urinary retention AEs and urination impaired AEs (mainly urinary hesitation) were both 2.6% in adult atomoxetine subjects and zero among placebo subjects. Risk for dysuria, which included AEs of difficulty urinating and trouble initiating urination, was also increased in atomoxetine adult subjects compared to placebo. The atomoxetine labeling should include information about the potential for bladder outlet related AEs.

There was one SAE of elevated liver function tests and one discontinuation for elevated transaminases but no cases of acute liver failure in the NDA database. There was no evidence in the safety database of an atomoxetine associated increased risk for elevated transaminases or increased bilirubin.

Although I did not identify any studies where pupil size was measured, the controlled clinical trial data suggested an increased risk for mydriasis among atomoxetine exposed subjects, with some suggestion of dose response. There were no AEs of glaucoma in the pediatric or adult ADHD trials. Mydriasis was observed in animal studies. The atomoxetine labeling should mention these findings and recommend avoiding use of atomoxetine in patients with narrow angle glaucoma.

The data presented by the sponsor support a relationship between atomoxetine and orthostatic blood pressure decreases and events potentially related to these changes. The vital sign data from multi-dose clinical pharmacology trials suggested orthostatic blood pressure decreases for atomoxetine subjects and greater declines among PM subjects compared to EM subjects. The sponsor identified 8 clinical pharmacology subjects with evidence of symptomatic orthostatic hypotension and four clinical pharmacology subjects who discontinued for syncope. While there were no syncope AEs in the pediatric or adult ADHD controlled trials, seven pediatric subjects had syncope AEs in open label trials. We do not have orthostatic blood pressure data for these individuals since it was not collected in these trials. In the pediatric placebo controlled trials, the risk for postural hypotension AEs was higher among atomoxetine subjects (1.8%, 6/340) compared to placebo subjects (0.5%, 1/207). In adult trials one atomoxetine subject (0.4%, 1/269) and no placebo subjects had postural hypotension AEs. The risk for dizziness AEs was increased among atomoxetine subjects although the link between this event and postural hypotension is admittedly speculative. Taken together, the evidence suggests that exposure to atomoxetine is associated with orthostatic blood pressure changes and higher risks for postural hypotension and perhaps related dizziness and syncope. These data should be presented in labeling if atomoxetine is approved.

The vital sign data support that atomoxetine is associated with increases in heart rate and blood pressure. The observed mean changes were relatively small. No subjects had SAEs related to increase in blood pressure or pulse and few subjects discontinued or had AEs related to such changes. Furthermore there were no events suggestive of acute hypertensive related sequelae such as renal dysfunction, stroke, encephalopathy, myocardial infarction or congestive heart failure. The atomoxetine development program included children and relatively healthy adults. The sponsor has not studied the magnitude or impact of atomoxetine blood pressure and pulse changes in a population with a greater burden of underlying cardiovascular disease. Atomoxetine use should be restricted in patients with symptomatic cardiovascular disease and moderate to severe hypertension. These restrictions are currently mentioned in the labeling of the approved ADHD treatments and appear appropriate for atomoxetine as well. The vital sign data from the methylphenidate subjects in controlled trials and a clinical pharmacology trial suggest that the treatment-related increases in pulse and BP were comparable.

Atomoxetine use was associated with weight loss in the short-term controlled trials. Atomoxetine's effect on height is less clear since there were no long-term controlled trials to allow an assessment of this parameter. The sponsor found that gain in height in pediatric atomoxetine subjects was less than what would be predicted using general population data. These data do not allow us to determine whether this finding illustrates an effect of atomoxetine restricting growth or merely reflects an underlying difference between ADHD patients and the general population, a hypothesis raised in the medical literature[1]. Atomoxetine labeling should carry a description of the height and weight data, and mention the lack of long term controlled data resulting in uncertainties about effects on growth.

The sponsor provided their interpretation of atomoxetine effect on cardiac repolarization in several places across their submissions. They state that for the doses examined in clinical trials, atomoxetine did not prolong cardiac repolarization in either EM or PM subjects (ISS, p.515). Although statistically significant prolongation was observed in study LYAE, they note that study LYAY did not find evidence of QT prolongation (ISS, p.518). They also comment that no dose or plasma concentration relationship to QT was observed in clinical trials (ISS, p.545). They feel that within the dose range assessed, atomoxetine is unlikely to be associated with an increased risk of cardiac arrhythmias related to the effects on cardiac repolarization (Safety Update, p.139).

While the sponsor is assured by their data, it does not appear that the relationship between exposure to atomoxetine and prolongation of the QTc interval has been completely described, particularly in the PM sub-population of users. Study LYAE raises concerns about a relationship between QTc prolongation and atomoxetine exposure. The results do not appear to support an atomoxetine-QTc prolonging relationship among EM subjects with little change in QTc from baseline across the doses studied. In PM subjects, the mean changes observed were unremarkable at lower atomoxetine doses but at higher doses the observed changes are concerning with a statistically significant increase in QTc despite the small sample size studied. The finding of greatest QTc increase from baseline at a pre-dose time point and the apparent lack of a consistent linear plasma concentration relationship do not appear to support a plasma concentration/QTc relationship, yet the evidence appears to suggest some relationship to exposure level. The statistically significant increased QTc mean changes were observed in PM subjects, who have greater exposure because of metabolic deficiencies, and occurred at the highest administered doses.

[1] Spencer T, Bierderman J, Wilens T,. Growth Deficits in Children with Attention Deficit Disorder. Pediatrics, 1998; 102: 501-506.

While the sponsor feels the results from study LYAY, which used fluoxetine as a CYP 2D6 inhibitor in EM subjects, dismiss an atomoxetine-QTc lengthening relationship, there are several important points to note about this study. The sponsor's interpretation requires the assumption that administration of fluoxetine is the same as having a PM genotype. The sponsor demonstrated that the plasma levels of atomoxetine increased when given with fluoxetine to EM subjects although it is not clear that resulted in the same exposure experienced by PM patients. To accept the sponsor's conclusions, another required assumption is that the presence of fluoxetine does not modify the effect of atomoxetine on the QTc interval. Without fully understanding the effect of fluoxetine and atomoxetine on the QTc interval, one cannot assess this assumption. This study did characterize the effect of atomoxetine on QTc when given concomitantly with fluoxetine to EMs but is of unknown value when considering the effect of atomoxetine on QTc in PMs.

Beyond the data from the two studies considered above, there are additional data that raise concern about atomoxetine's effect on cardiac repolarization. Prolonged mean QTc was observed among PM subjects for some of the tested doses in single dose study HFBJ. The sponsor demonstrated increased risk for QTc outliers among PM subjects exposed to a maximal atomoxetine dose of at least 1.2mg/kg/day compared to EM subjects exposed to a maximal atomoxetine dose of at least 1.2mg/kg/day.

The phase III controlled trial mean change and outlier data did not support an atomoxetine effect on cardiac repolarization, although the methods used to collect and analyze these data were not as rigorous as the methods used in the clinical pharmacology studies.

Although atomoxetine will be used in a pediatric population, the effect of atomoxetine on cardiac repolarization in pediatric patients has not been carefully studied. The pediatric QTc data from the development program come from phase III trials where the methodology used was not optimal for evaluating atomoxetine's effect on QTc.

The atomoxetine safety database includes several ECG tracings with short PR intervals and a few ECG tracings consistent with WPW but the evidence does not suggest that these findings are due to atomoxetine. In most cases of short PR interval, the findings were present at baseline arguing against an atomoxetine etiology. In one case, the shortened PR was treatment emergent but was intermittent and resolved with continued atomoxetine treatment. For the cases with ECG findings consistent with WPW, several had these findings on baseline ECGs. For one of the treatment emergent cases, the ECG findings did not develop until one year after beginning atomoxetine. In the other case, the subject had a short PR at baseline and the findings consistent with WPW persisted after discontinuation of atomoxetine. Given the estimates of prevalence of WPW in the general population, it is not surprising to observe cases in this database. Without accurate background estimates it is difficult to assess the prevalence of short PR intervals in this database. Since most of the short PR interval cases were present at baseline, the evidence does not appear to suggest an association with atomoxetine.

The sponsor's analyses of clinical trial data suggest a similar AE profile for EM and PM subjects, who were dosed without considering metabolic status. The sponsor concluded that the AE profiles for EM and PM subjects were similar and therefore, despite differences in plasma levels, CYP2D6 status need not be considered when dosing atomoxetine. While the sponsor identified higher increases in heart rate and greater weight loss among PM subjects compared to EM subjects, there did not appear to be meaningful differences in SAE risk, discontinuation due to AE risk, or risk for many treatment emergent AEs. For selected potentially important treatment emergent AEs such as syncope and vasovagal attacks, the data suggested an increased risk in PM subjects with too few events to allow firm conclusions.

The sponsor's AE risk comparisons by metabolic status relied on the experience in a relatively small number of PM subjects. Furthermore, not all subjects classified as PM had genetic deficiencies in CYP2D6. Some were classified as phenotypic PMs because of concomitant use of a CYP2D6 inhibitor and resulting increased plasma levels. While this approach provides safety information for CYP2D6 inhibited subjects, it is not clear if phenotypic and genotypic PM subjects have similar exposure and a similar AE profile. Even if one accepts similarity for these two groups, the number of PM subjects exposed in the development program is small. The sponsor provided information for 181 PMs (genotypic + phenotypic) with 61PY, and for 112 PMs exposed to a maximum atomoxetine dose of least 1.2mg/kg/day with 28 PY. Furthermore, the exposure in the group that had a maximum atomoxetine dose of least 1.2mg/kg/day is likely overestimated since the subjects exposed to that maximum dose did not necessarily remain on that dose throughout their entire observation period. While the sponsor demonstrated safe atomoxetine use without considering metabolic status for dosing during closely monitored clinical trials, one must note the limitations of the data used to support the sponsor's conclusion that metabolic status need not be considered in dosing.

There is inadequate information to fully evaluate the sponsor's labeling proposal that suggests that atomoxetine dose adjustment with a CYP2D6 inhibitor is unnecessary. In the studies mentioned above that included phenotypic PMs, the study design had EM patients take a metabolic inhibitor first and then atomoxetine was administered, and titrated per protocol in the presence of the inhibitor. We have no information about what happened to EM subjects who took atomoxetine and then added a CYP2D6 inhibitor. In these cases, atomoxetine is not being titrated to tolerance and it possible that the safety profile under these circumstances may be different. We should request analyses from the sponsor that review the experience of EM subjects that were on stable doses of atomoxetine and then started a CYP2D6 inhibitor, to examine whether this circumstance was associated with AEs, or important vital sign changes.

The sponsor's proposed labeling suggests that atomoxetine can be administered either once daily or in divided doses twice daily, but the once daily dosing trial used a lower dose than what the sponsor suggests in labeling. The sponsor conducted one small pediatric ADHD study where atomoxetine was dosed QD. In that study there were no SAEs. The absolute and relative risks for many of the common treatment emergent AEs was increased in the QD study compared to the BID study. Despite this finding, the absolute discontinuation due to AE risk was similar to the risk observed in atomoxetine subjects in the BID studies (QD 2.4%, 2/85, BID 3.8%, 13/340). The relative risks for discontinuation for AEs were similar for the two dosing regimens as well (QD RR=2.0, BID RR=2.7). The sponsor's proposed labeling would allow single daily doses up to 1.8mg/kg/day, but the highest dose allowed in this controlled trial was 1.5mg/kg/day. The dosage and administration section of labeling may need revision to reflect the absence of safety data for atomoxetine dosing above1.5mg/kg/day as a single dose.

Attachments
Studies

Name of Company: Eli Lilly and Company Name of Active Ingredient: Atomoxetine hydrochloride	SUMMARY OF CLINICAL TRIALS PLACEBO-CONTROLLED, PEDIATRIC STUDIES

Study Investigator / Coordinating center / Number of center(s) / Report number	Design	Number of Subjects With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product / Dosage / Regimen	Reference Therapy / Dosage / Regimen
Dr. Christopher Kratochvil University of Nebraska Medical Center Omaha, NE 13 Centers B4Z-MC-LYAC	Double-Blind, Stratified, Randomized, Parallel	Acute phase: N = 297 M = 212 F = 85 Ages 8–18 yr Mean age = 11.2 yr	ADHD (DSM-IV), K-SADS-PL:Behavioral, ADHDRS-IV-Parent:Inv, CGI-ADHD-S	8 weeks acute treatment; followed by 50 weeks extension phase	Atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day, or a maximum of 120 mg TDD, given BID	Placebo
Dr. David Michelson Eli Lilly and Company Indianapolis, IN 9 Centers B4Z-MC-LYAT	Double-Blind, Randomized, Parallel	N = 171 M = 119 F = 52 Ages 6-16 yr Mean age = 10.3 yr	ADHD (DSM-IV), K-SADS-PL:Behavioral, ADHDRS-IV-Parent:Inv	6 weeks	Atomoxetine titrated from 0.5 to 1.5 mg/kg/day, given QD	Placebo
Dr. Thomas Spencer Massachusetts General Hospital Boston, MA 7 Centers B4Z-MC-HFBD	Double-blind, Stratified, Randomized, Parallel	N = 147 M = 119 F = 28 Ages 7-13 yr Mean age = 9.7 yr	ADHD (DSM-IV), K-SADS-E: ADHD, DICA-IV-C, ADHDRS-IV-Parent:Inv	9 weeks	Atomoxetine 5 mg/day titrated to a maximum of 90 mg/day, given BID	Placebo, Methylphenidate 5 mg/day titrated to a maximum of 60 mg/day, given BID
Dr. Keith Connors Duke University Medical Center Durham, North Carolina 10 Centers B4Z-MC-HFBK	Double-blind, Stratified, Randomized, Parallel	N =144 M = 117 F = 27 Ages 7-13 yr Mean age = 9.9 yr	ADHD (DSM-IV), K-SADS-E: ADHD, DICA-IV-C, ADHDRS-IV-Parent:Inv	9 weeks	Atomoxetine 5 mg/day titrated to a maximum of 90 mg/day, given BID	Placebo, Methylphenidate 5 mg/day titrated to a maximum of 60 mg/day, given BID
Dr. Joseph Biederman Massachusetts General Hospital Boston, MA 23 Centers B4Z-MC-HFBE	Open-Label followed by Double-Blind, Randomized, Variable Discontinuation of Responders	N= 228 M= 211 F=17 Ages 7-15 yr Mean age =10.4 yr	ADHD (*DSM-IV*), K-SADS-E: ADHD, ADHDRS-IV-Parent:Inv	58 weeks	Atomoxetine *5 mg/day* titrated to a maximum of 90 mg/day, given BID	Placebo, *Methylphenidate* 5 mg/day titrated to a maximum of 60 mg/day, given TID

Name of Company: Eli Lilly and Company Name of Active Ingredient: Atomoxetine hydrochloride	SUMMARY OF CLINICAL TRIALS PLACEBO-CONTROLLED, ADULT STUDIES

	Study Investigator / Coordinating center / Number of center(s) / Report number	Design	Number of Subjects With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product / Dosage / Regimen	Reference Therapy / Dosage/ Regimen
	[redacted]	Double-Blind, Stratified, Randomized, Parallel	N = 280 M = 178 F = 102 Ages 18 yr and older Mean age = 40.3 yr	ADHD (DSM-IV), CAAR-D, CAARS-Inv:SV, CGI-ADHD-S	10 weeks	Atomoxetine 30 mg/dose titrated up to 60 mg/dose, given BID	Placebo
	[redacted]	Double-Blind, Stratified, Randomized, Parallel	N = 256 M = 170 F = 86 Ages 18 yr and older Mean age = 42.1 yr	ADHD (DSM-IV), CAAR-D, CAARS-Inv:SV, CGI-ADHD-S	10 weeks	Atomoxetine 30 mg/dose titrated up to 60 mg/dose, given BID	Placebo

Name of Company: Eli Lilly and Company Name of Active Ingredient: Atomoxetine hydrochloride	SUMMARY OF CLINICAL TRIALS UNCONTROLLED PEDIATRIC STUDIES

	Study Investigator / Coordinating center / Number of center(s) / Report number	Design	Number of Subjects With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product / Dosage / Regimen
	Dr. Joseph Biederman Massachusetts General Hospital Boston, MA 1 Center B4Z-MC-HFBC	Open-Label	N = 30 M = 25 F = 5 Ages 7-13 yr Mean age = 10.1 yr	ADHD (DSM-IV), K-SADS:E ADHD	up to 17 weeks	Atomoxetine 10 mg/day titrated to a maximum of 90 mg/day, given BID
	Dr. Christopher Kratochvil University of Nebraska Medical Center Omaha, NE 57 Centers B4Z-MC-LYAB	Open-Label	N = 914 M=696 F=218 Ages 6-17 yr Mean age = 11.0 yr	ADHD (DSM-IV), K-SADS-PL:Behavioral, ADHDRS-IV-Parent:Inv	up to 2 years	Atomoxetine 0.5 mg/kg/day titrated to a maximum of 1.8 mg/kg/day or 120 mg TDD, given BID

		Open-Label	N=357 M=270 F=87 Ages 6-18 yr Mean age =11.3 yr	ADHD (DSM-IV), K-SADS- PL:Behavioral, ADHDRS-IV- Parent:Inv	11 weeks	Atomoxetine 0.5 mg/kg/day titrated to a maximum of 1.8 mg/kg/day, or 120 mg TDD, given BID
	Dr. Thomas Spencer Massachusetts General Hospital Boston, MA 22 Centers B4Z-MC-HFBF	Open-Label Extension	N = 325 M=266 F=59 Ages 6-17 yr Mean age = 10.4 yr	ADHD (DSM-IV), met criteria for previous study	up to 95 weeks	Atomoxetine 5 mg/day titrated to a maximum of 90 mg/day, given BID

Name of Company: Eli Lilly and Company Name of Active Ingredient: Atomoxetine hydrochloride	SUMMARY OF CLINICAL TRIALS OTHER ONGOING STUDIES

Study Investigator / Coordinating center / Number of center(s) / Report number	Design	Number of Subjects With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product / Dosage / Regimen	
Dr. David Michelson Eli Lilly and Company Indianapolis, IN 31 Centers B4Z-MC-LYAI	Open-Label, Extension	N = 296 M=229 F=67 Ages 6-18 yr	ADHD (DSM-IV), ADHDRS-IV- Parent:Inv, CGI-ADHD-S at entry into previous study	Up to 260 weeks	Atomoxetine 0.5 mg/kg/day titrated up to 1.8 mg/kg/day or a maximum of 120 mg TDD, given QD or BID	
Dr. David Michelson Eli Lilly and Company Indianapolis, IN 18 Centers B4Z-MC-LYAF	Open-Label followed by Double-Blind, Randomized, Discontinuation of Responders	N=60 M=58 F=2 Ages 6-15 yr	ADHD (DSM-IV), ADHDRS-IV- Parent:Inv	Up to 78 weeks	Atomoxetine 0.5 mg/kg/day titrated to a maximum of 1.8 mg/kg/day, or 120 mg TDD, given BID	
Dr. David Michelson Eli Lilly and Company Indianapolis, IN 30 Centers B4Z-MC-LYAR	Open-Label Extension	N=84 M=51 F=33 Ages 18 yr and older	ADHD (DSM-IV) and enrolled in previous study	up to 3 years	Atomoxetine 25 mg/day to 60 mg/day, given BID	
Warren K. Bickel, PhD University of Vermont Burlington, Vermont 1 center B4Z-MC-LYAD	Double-blind, Randomized, 6-treatment, 6-period, crossover study utilizing balanced Latin square design	N = 16 M = 5 F = 11 Ages 18-36 yr Mean age = 22.3 yr	Volunteers with a history of recreational drug use, but no DSM-IV substance abuse diagnosis or ADHD diagnosis	Single doses, separated by 2 to 10 days	Atomoxetine 20, 45, and 90 mg	Methylphenidate 20 and 40 mg, placebo

	Study Investigator/ Coordinating center/ Number of center(s)/ Report number	Design	Number of Subjects With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product/ Dosage/ Regimen/ Route of Administration
CLINICAL PHARMACOLOGY-BIOAVAILABILITY/BIOEQUIVALENCE STUDIES						
		Part A Open-label Part B Open-label, 4 period, Randomized, Latin Square	Part A N=2 M=1 F=1 Part B N=20 M=9 F=11 19-54yr, inclusive	Healthy EM subjects	Part A 2 single ATX doses with 4d between (iv dose/po) Part B 4 single ATX doses with 4d between (1-iv dose/3-po); 2 single doses of O; 1 single dose of Maalox®	Part A ATX iv dose 5-mg; 40-mg dose as capsule po Part B ATX 40-mg dose (1x40-mg capsule) iv dose 20 mg O 80-mg dose capsule po Maalox® 20 mL dose po
		Part A: Open-label Part B: Open-label, 3 period, Randomized, Latin Square	Part A n=2 M=1 F=1 Part B n= 8 M=5 F=3 20-52yr. inclusive	Healthy PM subjects	Part A Single iv ATX dose Part B 3 single ATX doses (1 - iv, 2 - po)	Part A ATX iv dose 20 mg Part B ATX Market Image capsules 40-mg dose (1x40-mg capsule) po, 40-mg dose (2x20-mg capsule) po, ATX iv dose 20 mg
	Dr. Holly R. Thomasson Lilly Laboratory for Clinical Research Indianapolis, Indiana USA 1 center B4Z-LC-HFBG	Open-label, 5 period, Randomized, Constrained, Latin Square	n = 25 M = 14 F = 11 18 - 55 yr. inclusive	Healthy EM subjects	5 single ATX doses	ATX 40-mg dose (2x20-mg capsule), 40-mg tablet, 40-mg aq solution, 5-mg capsule, 5-mg dose (2x2.5-mg tablet) po

		Open-label, 3 period, Randomized, Latin Square Fed/Fasted	n=25 M= 17 F= 8 19-54 yr, inclusive	Healthy EM Subjects	3 single ATX doses with 4d between	ATX Market Image capsule 40-mg dose (1x40-mg capsule) po fed/fasting. ATX 40-mg dose (2x20- mg capsule) po fasting
		Open-label, 3 period, Randomized, Latin Square Fed/Fasted	n=58 M=26 F=32 18-55yr, inclusive	Healthy EM subjects	3 single ATX doses with 4d between	ATX Market Image capsule 60-mg dose (1x60-mg capsule) po fed/fasting, ATX 60-mg dose (1-40- mg and 1-20-mg capsule) po fasting

	Study Investigator / Coordinating center / Number of center(s) / Report number	Design	Number of Subjects With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product / Dosage / Regimen / Route of Administration
CLINICAL PHARMACOLOGY-PHARMACOKINETICS (PK) STUDIES						
	Dr. Holly R. Thomasson Lilly Laboratory for Clinical Research Indianapolis, Indiana USA 1 center B4Z-LC-HFBH	Open-label, Sequential, atomoxetine and radiolabeled atomoxetine	n = 7 4 = EM 3 = PM M = 7 19 – 54 yr, inclusive	Healthy EM and PM male subjects	ATX 5d; ^{14}C- ATX Single dose	ATX 20-mg capsule po BID; ATX 20-mg capsule labeled with ~100 µCi ^{14}C po
		Part A: Single-blind, Placebo controlled, Single dose escalation Part B: EM and PM Subjects Single-blind, EM Subjects only: Placebo controlled, Randomized, Multiple dose	n=27 M=14 F=13 Part A n=15 EM n=10 PM Part B n=14 EM n=6 PM 19-40 yr, inclusive	Healthy EM and PM subjects	Part A: 5 Single ATX doses Part B: 7 d	Part A: P or ATX 10, 30, 60, 90, 120-mg dose as capsules po Part B: P or ATX 40-mg dose as capsules po BID

		Single-blind, Placebo controlled, Multiple dose escalation	n=16 EM =10 PM=6 M= 11 F= 5 22-60 yr, inclusive	Healthy EM and PM subjects	20d	P, ATX 30-, 45-, 60- and 75-mg dose as capsules po BID
	Dr. Joseph Biederman Massachusetts General Hospital Boston, MA 1 Center B4Z-MC-HFBC	Open-Label	N = 30 M = 25 F = 5 Ages 7-13 yr Mean age = 10.1 yr	ADHD (DSM-IV), K-SADS:E ADHD	up to 17 weeks	Atomoxetine 10 mg/day titrated to a maximum of 90 mg/day, given BID
	Dr. Holly R. Thomasson Lilly Laboratory for Clinical Research Indianapolis, Indiana USA 1 center B4Z-LC-HFBM	Open-label, Single dose	n=13 6 ESRD subjects; 7 healthy matched; M=4 F=9 35-50 yr, inclusive	EM ESRD subjects with matched healthy EM subjects	Single ATX dose	ATX 20-mg capsule po
		Open-label, 2 period, *Parallel group*	n=22 11 hepatic *subjects* 11 healthy matched M=14 F=8 34-63 yr *inclusive*	Liver impaired subjects (Child Pugh B or C) with matched healthy EM subjects	Periods 1 Single doses Sorbitol iv x 3hr; Single dose DEB po Period 2 Single ATX dose	40% Sorbitol (7.5 mL/hr) DEB 10 mg ATX 20-mg capsule po
		Part A: Single-blind, Placebo controlled, Single dose escalation Part B: Single-blind, Placebo controlled, Randomized, Multiple dose	Part A n=23 Part B n=26 M=26 20-31 yr, inclusive	Healthy EM and PM subjects	Part A: P and 4 Single ATX doses *Part B:* 7d	Part A: P or ATX 10, 40, 90, 120-mg dose as capsules po Part B: P, ATX 40-mg dose as capsules po BID or ATX 60-mg dose as capsule po BID

		Part A: Single-blind, Placebo controlled, Single dose escalation Part B: Single-blind, Placebo controlled, Randomized, Multiple dose	Part A n=23 Part B n=26 M=26 20-31 yr. inclusive	Healthy EM and PM subjects	Part A: P and 4 Single ATX doses Part B: 7d	Part A: P or ATX 10, 40, 90, 120-mg dose as capsules po Part B: P, ATX 40-mg dose as capsules po BID or ATX 60-mg dose as capsule po BID
	Dr. Holly R. Thomasson Lilly Laboratory for Clinical Research Indianapolis, Indiana USA 1 center B4Z-LC-HFBP	Open label, Sequential, 2-period DI	n= 22 M=11 F=11 26-55 yr. inclusive	Healthy EM subjects	ATX 13d; DE 2 single doses	Period 1 ATX 30-(initial dose) followed by 40-mg ATX as capsule po; BID; Period 2 ATX 40-(initial dose) followed by 60-mg ATX as capsule po BID; Period 1 & 2 DE 50-mg as tablet po
		Open label, 2 period DI	n = 8 M=4 F=4 20-35yr, inclusive	Healthy PM subjects	ATX 12d MID 4 single doses	Period 1 & 2 MID 5-mg as syrup po Period 2 ATX 60-mg dose (2x10-mg & 1x40-mg capsule) po BID
	Dr. Holly R. Thomasson Lilly Laboratory for Clinical Research Indianapolis, Indiana USA 1 center B4Z-LC-HFBL	Single-blind, Sequential, 2 periods DI	n=22 M=17 F=5 20-49 yr. inclusive	Healthy EM subjects	ATX 11 d; Par 17 d;	P, ATX 20-mg capsule po BID; Par 20-mg tablet po QD
		Single blind, 4 period, Sequential	n=20 EM=19 PM =1 M=15 F=5 19-53 yr. inclusive	Healthy PM and EM subjects	Flu Bw ATX 15d	P, ATX 10-, 45-, 75-mg dose as capsule po BID; Flu 60-, 20-mg dose as capsule po QD

	Dr. Stephen D. Wise Lilly-NUS Centre for Clinical Pharmacology Singapore 1 center B4Z-FW-HFBO	Double-blind, Placebo controlled, Randomized, 2 period Latin Square Crossover Double-dummy DI	n=13 M = 13 22-25 yr, inclusive	Healthy EM male subjects	10d ATX 5d Sa 3 single doses	P po and iv, ATX 60 mg dose as capsule po BID, Sa 3 single iv doses of 5μg/min for 2 hours, 5% Dextrose
	Dr. Stephen D. Wise Lilly-NUS Centre for Clinical Pharmacology Singapore 1 center B4Z-FW-LYAP	Double-blind, Randomized, Placebo controlled, 3 period DI	n=12 M=12 22–27 yr, inclusive	Healthy EM subjects	ATX 5d Met 5d	P Met 60 mg po QD ATX 60-mg dose (3x20-mg) as capsule po BID
	Dr. R. A. Lucas Lilly Research Center, UK 1 center B4Z-EW-E002	2 Period, Double-blind, Cross-over, Randomized	n=12 6= EM 6 =PM M = 6 F = 6 19-43 yr, inclusive	Healthy subjects; EM and PM of debrisoquine	5d	ATX 40-mg BID po or P, plus 2 mL/kg ethanol
	Dr. Christopher Kratochvil University of Nebraska Medical Center Omaha, NE 13 Centers B4Z-MC-LYAC	Double-Blind, Stratified, Randomized, Parallel	Acute phase: N = 297 M = 212 F = 85 Ages 8–18 yr Mean age = 11.2 yr	ADHD (DSM-IV), K-SADS-PL:Behavioral, ADHDRS-IV-Parent:Inv, CGI-ADHD-S	8 weeks acute treatment; followed by 50 weeks extension phase	Atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day, or a maximum of 120 mg TDD, given BID

Vital Sign Outlier Cutoffs, Pediatric

TABLE 2. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Boys Aged 1 to 17 Years by Percentiles of Height

Age, y	Blood Pressure Percentile*	Systolic Blood Pressure by Percentile of Height, mm Hg†							Diastolic Blood Pressure by Percentile of Height, mm Hg†						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	90th	94	95	97	98	100	102	102	50	51	52	53	54	54	55
	95th	98	99	101	102	104	106	106	55	55	56	57	58	59	59
2	90th	98	99	100	102	104	105	106	55	55	56	57	58	59	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	108	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	111	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	62	63	64	65	66	66
	95th	106	107	109	111	113	114	115	66	67	67	68	69	70	71
5	90th	104	105	106	108	110	112	112	65	65	66	67	68	69	69
	95th	108	109	110	112	114	115	116	69	70	70	71	72	73	74
6	90th	105	106	108	110	111	113	114	67	68	69	70	70	71	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	69	70	71	72	72	73	74
	95th	110	111	113	115	115	118	119	74	74	75	76	77	78	78
8	90th	107	108	110	112	114	115	116	71	71	72	73	74	75	75
	95th	111	112	114	116	118	119	120	75	76	76	77	78	79	80
9	90th	109	110	112	113	115	117	117	72	73	73	74	75	76	77
	95th	113	114	116	117	119	121	121	76	77	78	79	80	80	81
10	90th	110	112	113	115.	117	118	119	73	74	74	75	76	77	78
	95th	114	115	117	119	121	122	123	77	78	79	80	80	81	82
11	90th	112	113	115	117	119	120	121	74	74	75	76	77	78	78
	95th	116	117	119	121	123	124	125	78	79	79	80	81	82	83
12	90th	115	116	117	119	121	123	123	75	75	76	77	78	78	79
	95th	119	120	121	123	125	126	127	79	79	80	81	82	83	83
13	90th	117	118	120	122	124	125	126	75	76	76	77	78	79	80
	95th	121	122	124	126	128	129	130	79	80	81	82	83	83	84
14	90th	120	121	123	125	126	128	128	76	76	77	78	79	80	80
	95th	124	125	127	128	130	132	132	80	81	81	82	83	84	85
15	90th	123	124	125	127	129	131	131	77	77	78	79	80	81	81
	95th	127	128	129	131	133	134	135	81	82	83	83	84	85	86
16	90th	125	126	128	130	132	133	134	79	79	80	81	82	82	83
	95th	129	130	132	134	136	137	138	83	83	84	85	86	87	87
17	90th	128	129	131	133	134	136	136	81	81	82	83	84	85	85
	95th	132	133	135	136	138	140	140	85	85	86	87	88	89	89

* Blood pressure percentile was determined by a single measurement.
† Height percentile was determined by standard growth curves.

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TABLE 3. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Girls Aged 1 to 17 Years by Percentiles of Height

Age, y	Blood Pressure Percentile*	Systolic Blood Pressure by Percentile of Height, mm Hg†							Diastolic Blood Pressure by Percentile of Height, mm Hg†						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	90th	97	98	99	100	102	103	104	53	53	53	54	55	56	56
	95th	101	102	103	104	105	107	107	57	57	57	58	59	60	60
2	90th	99	99	100	102	103	104	105	57	57	58	58	59	60	61
	95th	102	103	104	105	107	108	109	61	61	62	62	63	64	65
3	90th	100	100	102	103	104	105	106	61	61	61	62	63	63	64
	95th	104	104	105	107	108	109	110	65	65	65	66	67	67	68
4	90th	101	102	103	104	106	107	108	63	63	64	65	65	66	67
	95th	105	106	107	108	109	111	111	67	67	68	69	69	70	71
5	90th	103	103	104	106	107	108	109	65	66	66	67	68	68	69
	95th	107	107	108	110	111	112	113	69	70	70	71	72	72	73
6	90th	104	105	106	107	109	110	111	67	67	68	69	69	70	71
	95th	108	109	110	111	112	114	114	71	71	72	73	73	74	75
7	90th	106	107	108	109	110	112	112	69	69	69	70	71	72	72
	95th	110	110	112	113	114	115	116	73	73	73	74	75	76	76
8	90th	108	109	110	111	112	113	114	70	70	71	71	72	73	74
	95th	112	112	113	115	116	117	118	74	74	75	75	76	77	78
9	90th	110	110	112	113	114	115	116	71	72	72	73	74	74	75
	95th	114	114	115	117	118	119	120	75	76	76	77	78	78	79
10	90th	112	112	114	115	116	117	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	90th	114	114	116	117	118	119	120	74	74	75	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	79	79	80	81	81
12	90th	116	116	118	119	120	121	122	75	75	76	76	77	78	78
	95th	120	120	121	123	124	125	126	79	79	80	80	81	82	82
13	90th	118	118	119	121	122	123	124	76	76	77	78	78	79	80
	95th	121	122	123	125	126	127	128	80	80	81	82	82	83	84
14	90th	119	120	121	122	124	125	126	77	77	78	79	79	80	81
	95th	123	124	125	126	128	129	130	81	81	82	83	83	84	85
15	90th	121	121	122	124	125	126	127	78	78	79	79	80	81	82
	95th	124	125	126	128	129	130	131	82	82	83	83	84	85	86
16	90th	122	122	123	125	126	127	128	79	79	79	80	81	82	82
	95th	125	126	127	128	130	131	132	83	83	83	84	85	86	86
17	90th	122	123	124	125	126	128	128	79	79	79	80	81	82	82
	95th	126	126	127	129	130	131	132	83	83	83	84	85	86	86

* Blood pressure percentile was determined by a single reading.
† Height percentile was determined by standard growth curves.

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Vital Sign Outlier Cutoffs, Adult

Table ISS.4.3.1. Criteria for Categorical Analysis of Changes in Vital Signs and Weight
Adult Acute Placebo-Controlled ADHD Analysis Group

Parameter	Low	High
Diastolic Blood Pressure (mm Hg)	Decrease of at least 15 to a value of at most 50	Increase of at least 15 to a value of at least 105
Systolic Blood Pressure (mm Hg)	Decrease of at least 20 to a value of at most 90	Increase of at least 20 to a value of at least 180
Pulse (bpm)	Decrease of at least 15 to a value less than 50	Increase of at least 15 to a value of more than 120
Temperature (degrees F)		Increase of at least 2.0 to a value of at least 101
Weight (kg)	Decrease of at least 7%	Increase of at least 7%

Source: Olanzapine NDA (NDA No: 20-592).

Serious Adverse Events, ADHD Trials

Table ISS.4.4.1. Patients with ADHD Who Experienced Serious Adverse Events in Atomoxetine Clinical Trials Through July 31, 2001

Patient Number	COSTART or MedDRA Preferred Term [a] (actual term)	ISS/Date	ATX	PBO/ND
HFBD-005-2186	FLU SYNDROME [b] (GI viral syndrome)	4.1, 4.2		X
HFBD-017-2665	DEPRESSION [b] (suicidal ideation)	4.1, 4.2		X
HFBE-012-0451	MENINGITIS [b] (meningitis)	4.2	X	
HFBE-015-0568	HOSTILITY [b] (physical aggression)	4.2		X
HFBE-023-0887	HOSTILITY [b] (physical aggression)	4.2	X	
HFBE-023-0894	CARDIOVASCULAR DISORDER [b] (systolic ejection murmer grade 2-3/6)	4.2	X	
HFBF-001-1086	ACCIDENTAL INJURY [b] (knee injury)	4.2	X	
HFBF-001-1100	ABDOMINAL SYNDROME ACUTE [b] (appendicitis)	4.2	X	
HFBF-004-1125	OVERDOSE [b] (overdose) DIZZINESS [b] (intermittent lightheadedness) VOMITING [b] (intermittent vomiting)	4.2	X	
HFBF-012-1454	ACCIDENTAL INJURY [b] (auto accident)	4.2	X	
HFBF-015-1586	DEPRESSION [b] (depression with suicidal ideation)	4.2	X	
HFBF-015-1597	ABDOMINAL SYNDROME ACUTE [b] (appendicitis)	4.2	X	
HFBF-017-1659	DEPRESSION [b] (suicidal threat)	4.2	X	
HFBF-023-1889	EPDIDYMITIS [b] (acute epididymitis left testicle)	4.2	X	
HFBK-012-3442	ENCEPHALOPATHY [b] (toxic encephalopathy)	4.1, 4.2		X
LYAA-72-2156	SKIN CARCINOMA [b] (basal cell carcinoma)	4.3		X
LYAA-72-2186	SKIN CARCINOMA [b] (basal cell carcinoma)	4.3	X	
LYAB-037-4482	SKULL FRACTURE NOS [c] (skull fracture)	5/31/2001		
LYAB-044-4827	RESPIRATORY DISORDER NOS [c] (acute respiratory disorder)	6/4/2001		
LYAB-045-4873	HOSTILITY [b] (oppositional defiance)	4.2	X	
LYAB-051-5098	DEPRESSION [b] (suicidal ideation) INTENTIONAL INJURY [b] (scratches self, cutting self)	4.2	X	
LYAB-057-5333 [d]	GRAND MAL CONVULSION [c] (grand mal seizure)	5/20/2001	X	
LYAB-057-5333 [d]	GRAND MAL CONVULSION [c] (grand mal seizure)	5/20/2001		X
LYAB-096-6164	ANGIONEUROTIC OEDEMA [c] (angioedema) URTICARIA NOS [c] (hives)	5/29/2001	X	
LYAB-102-5742	INSOMNIA NEC [c] (insomnia) FATIGUE [c] (tiredness)	6/13/2001	X	
LYAB-103-5786	CHEST PAIN NEC [c] (chest pain)	3/28/2001	X	
LYAC-001-7012	RASH [b] (second degree burns)	4.1, 4.2	X	
LYAC-017-7267	PSYCHOTIC DISORDER NOS [c] (psychosis not otherwise specified)	4/2/2001	X	

Table ISS.4.4.1. **Patients with ADHD Who Experienced Serious Adverse Events in Atomoxetine Clinical Trials Through July 31, 2001**

Patient Number	COSTART or MedDRA Preferred Term [a] (actual term)	ISS/Date	ATX	PBO/ ND
HFBD-005-2186	FLU SYNDROME [b] (GI viral syndrome)	4.1, 4.2		X
HFBD-017-2665	DEPRESSION [b] (suicidal ideation)	4.1, 4.2		X
HFBE-012-0451	MENINGITIS [b] (meningitis)	4.2	X	
HFBE-015-0568	HOSTILITY [b] (physical aggression)	4.2		X
HFBE-023-0887	HOSTILITY [b] (physical aggression)	4.2	X	
HFBE-023-0894	CARDIOVASCULAR DISORDER [b] (systolic ejection murmer grade 2-3/6)	4.2	X	
HFBF-001-1086	ACCIDENTAL INJURY [b] (knee injury)	4.2	X	
HFBF-001-1100	ABDOMINAL SYNDROME ACUTE [b] (appendicitis)	4.2	X	
HFBF-004-1125	OVERDOSE [b] (overdose) DIZZINESS [b] (intermittent lightheadedness) VOMITING [b] (intermittent vomiting)	4.2	X	
HFBF-012-1454	ACCIDENTAL INJURY [b] (auto accident)	4.2	X	
HFBF-015-1586	DEPRESSION [b] (depression with suicidal ideation)	4.2	X	
HFBF-015-1597	ABDOMINAL SYNDROME ACUTE [b] (appendicitis)	4.2	X	
HFBF-017-1659	DEPRESSION [b] (suicidal threat)	4.2	X	
HFBF-023-1889	EPDIDYMITIS [b] (acute epididymitis left testicle)	4.2	X	
HFBK-012-3442	ENCEPHALOPATHY [b] (toxic encephalopathy)	4.1, 4.2		X
LYAA-72-2156	SKIN CARCINOMA [b] (basal cell carcinoma)	4.3		X
LYAA-72-2186	SKIN CARCINOMA [b] (basal cell carcinoma)	4.3	X	
LYAB-037-4482	SKULL FRACTURE NOS [c] (skull fracture)	5/31/2001		
LYAB-044-4827	RESPIRATORY DISORDER NOS [c] (acute respiratory disorder)	6/4/2001		
LYAB-045-4873	HOSTILITY [b] (oppositional defiance)	4.2	X	
LYAB-051-5098	DEPRESSION [b] (suicidal ideation) INTENTIONAL INJURY [b] (scratches self, cutting self)	4.2	X	
LYAB-057-5333 [d]	GRAND MAL CONVULSION [c] (grand mal seizure)	5/20/2001	X	
LYAB-057-5333 [d]	GRAND MAL CONVULSION [c] (grand mal seizure)	5/20/2001		X
LYAB-096-6164	ANGIONEUROTIC OEDEMA [c] (angioedema) URTICARIA NOS [c] (hives)	5/29/2001	X	
LYAB-102-5742	INSOMNIA NEC [c] (insomnia) FATIGUE [c] (tiredness)	6/13/2001	X	
LYAB-103-5786	CHEST PAIN NEC [c] (chest pain)	3/28/2001	X	
LYAC-001-7012	RASH [b] (second degree burns)	4.1, 4.2	X	
LYAC-017-7267	PSYCHOTIC DISORDER NOS [c] (psychosis not otherwise specified)	4/2/2001	X	

Table ISS.4.4.1. **Patients with ADHD Who Experienced Serious Adverse Events in Atomoxetine Clinical Trials Through July 31, 2001 (continued)**

Patient Number	COSTART or MedDRA Preferred Term [a] (actual term)	ISS/Date	ATX	PBO/ND
LYAC-017-7269	CONSTIPATION [c] (constipation) ABDOMINAL PAIN LOWER [c] (stomach pain in right lower quadrant)	1/9/2001		X
LYAC-025-7469	APPENDICITIS [c] (appendicitis) UMBILICAL HERNIA NOS [c] (umbilical hernia)	11/3/2000	X	
LYAC-068-7753	URINARY TRACT INFECTION [b] (urinary tract infection), NEPHRITIS [b] (nephritis)	4.1, 4.2	X	
LYAF-541-1405	APPENDICITIS [c] (acute appendicitis)	6/14/2001	X	
LYAF-570-1882	PERIPHERAL SHUTDOWN [c] (peripheral shut down)	7/19/2001	X	
LYAF-640-8051	CONCUSSION [c] (concussion)	4/18/2001	X	
LYAI-001-4046	BURNS NOS [c] (burns) FOOT FRACTURE [c] (fractured 2,3,4 metatarsals on right foot)	4/23/2001	X	
LYAI-007-4283	APPENDICITIS PERFORATED [c] (ruptured appendix)	6/7/2001	X	
LYAI-012-4507	SINUSITIS NOS [c] (sinusitis)	7/9/2001	X	
LYAI-021-4009	ASTHMA NOS [c] (exacerbation of asthma)	12/18/2000	X	
LYAI-053-7411	AGITATION [c] (agitation)	6/1/2001	X	
LYAI-055-5048	ABDOMINAL PAIN NOS [c] (abdominal pain)	11/27/2000	X	
LYAI-067-5005	APPENDICITIS [c] (acute appendicitis)	6/14/2001	X	
LYAI-067-5010	BURNING SENSATION NOS [c] (skin burns)	3/13/2001	X	
LYAI-071-7925	APPENDICITIS [c] (appendicitis) PNEUMONIA NOS [c] (pneumonia)	6/20/2001	X	
LYAI-089-8602	MAJOR DEPRESSIVE DISORDER NOS [c] (major depressive disorder) POST-TRAUMATIC STRESS DISORDER [c] (post traumatic stress disorder)	7/10/2001	X	
LYAO-61-3406	ACCIDENTAL INJURY [b] (motor vehicle accident) LUNG DISORDER [b] (contused left lung)	4.3	X	
LYAO-92-3616	PANCREATITIS NOS [c] (pancreatitis) PANCREATIC CYST [c] (pseudocyst in the pancreas) DRUG INDUCED PSYCHOSIS [c] (drug induced psychosis)	4.3 2/6/2001		X
LYAO-92-3617	CORONARY OCCLUSION [b] (left coronary artery blockage)	4.3		X
LYAR-072-5115	ACCIDENTAL INJURY [b] (fractured ankle)	5/19/2001	X	
LYAR-081-5952	ABDOMINAL PAIN NOS [c] (acute abdominal pain)	2/22/2001	X	
LYAR-081-5953	DIABETES MELLITUS NOS [c] (diabetes)	4/14/2001	X	

Table ISS.4.4.1. **Patients with ADHD Who Experienced Serious Adverse Events in Atomoxetine Clinical Trials Through July 31, 2001 (concluded)**

Patient Number	COSTART or MedDRA Preferred Term [a] (actual term)	ISS/Date	ATX	PBO/ ND
LYAR-083-6419	CHEST PAIN NEC [c] (chest pain) DYSPNEA NOS [c] (shortness of breath) ANGINA UNSTABLE [c] (unstable angina)	6/7/2001	X	
LYBB-035-6545	PATHOLOGICAL FRACTURE [b] (compound fracture)	4.2	X	
LYBB-035-6560	PNEUMONIA NOS [c] (pneumonia)	2/20/2001	X	
LYBB-056-7442	DEPRESSION [b] (depression) DEPRESSION SUICIDAL [c] (depression suicidal ideation)	4.2	X	
LYBB-095-8522	NON-ACCIDENTAL INJURY [c] (chest and thigh trauma due to stab wounds)	5/23/2001	X	
LYBB-206-8583	BIPOLAR DISORDER NEC [c] (bipolar disorder)	2/6/2001	X	
LYBB-206-8588	ACCIDENTAL INJURY [b] (injury to the left hand, chest trauma, injury to the left eye, ruptured eardrums)	4.2	X	

[a] Prior to 1 June 2001, events were coded with COSTART, after that with MedDRA.
[b] COSTART term
[c] MedDRA term
[d] Patient is listed twice because seizures continued several weeks after drug discontinuation
Abbreviations: ATX = atomoxetine; ISS = Integrated Safety Summary, PBO/ND = placebo or no drug
Data Source: Clintrace

Two Serious AEs were reported between 7/31/01 and the safety update:
LYAF-551-1809- Meningitis- Placebo
LYAB-063-5565-Syncope- Atomoxetine

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Table SU.6.1. Patients with ADHD Who Experienced Serious Adverse Events in Atomoxetine Clinical Trials from 1 September up to 15 November 2001

Patient Number	MedDRA [a] Preferred Term (actual term)	Date Reported	ATX	PBO/ ND
LYAB-053-5167	NON-ACCIDENTAL OVERDOSE (drug overdose)	10/25/2001	X	
LYAF-541-1404	BURNS SECOND DEGREE (burns second degree)	11/6/2001	X	
LYAF-590-3063	APPENDICITIS (appendicitis), OESOPHAGEAL DISORDER NOS (oesophageal swelling)	9/10/2001	X	
LYAF-601-7009	GASTROINTESTINAL INFECTION NOS (severe gastrointestinal tract infection)	10/26/2001	X	
LYAF-622-6008	FOREARM FRACTURE (fracture of left forearm)	10/12/2001	X	
LYAF-652-9052	RIGORS (chills), PYREXIA (fever)	8/15/2001	X	
LYAF-652-9053	CONFUSIONAL STATE (acute confusional state), LIVER FUNCTION TEST NOS ABNORMAL (elevated liver function tests)	10/2/2001	X	
LYAI-015-1745[b]	INTENTIONAL SELF-INJURY (suicidal ideation/gesture)	10/25/2001	X	
LYAI-018-3325	DIABETES MELLITUS INSULIN-DEPENDENT (juvenile onset diabetes)	10/15/2001	X	
LYAI-042-7006	PNEUMONIA NOS (pneumonia)	9/21/2001	X	
LYAI-088-8570	CONVULSIONS NOS (possible seizure)	11/7/2001	X	
LYAI-521-5561	APPENDICITIS (appendicitis)	9/21/2001	X	
LYAR-081-5967	KIDNEY INFECTION NOS (kidney infection)	10/1/2001	X	

[a] Prior to 1 June 2001, events were coded with COSTART, after that with MedDRA.

[b] The number for this patient (LYAI-015-1745) is incorrect. The correct patient number is LYAI-15-4625. The incorrect number was retained in this table because the same number appears on the patient summary and the Clintrace report.

Abbreviations: ATX = atomoxetine, MedDRA = Medical Dictionary for Regulatory Activity; PBO/ND = placebo or no drug (no events reported during this time period for patients receiving placebo or no drug)

Source: Clintrace database

Table 5. **All Serious Adverse Events by Body System from Completed Clinical Studies of Tomoxetine Hydrochloride in Adults with Depression**

	Tomoxetine (N=1275)	
Event Classification	n	%
Body System as a Whole		
Surgical Procedure	6	0.47
Intentional Overdose	5	0.39
Infection	2	0.16
Injury, accident	2	0.16
Abdominal pain	1	0.08
Back pain	1	0.08
Carcinoma	1	0.08
Headache	1	0.08
Neoplasm	1	0.08
Reaction Unevaluable	1	0.08
Cardiovascular System		
Extrasystole	3	0.24
Hypertension	3	0.24
Tachycardia	3	0.24
Atrial Arrhythmia	2	0.16
Bundle Branch Block	2	0.16
Syncope	2	0.16
Angina Pectoris	1	0.08
Arrhythmia	1	0.08
Electrocardiogram Abnormal	1	0.08
Hemorrhage	1	0.08
Myocardial Infarct	1	0.08
ST Elevated	1	0.08
Vascular Disorder	1	0.08
Digestive System		
Liver Function Tests Abnormal	5	0.39
Nausea	2	0.16
Anorexia	1	0.08
Duodenal Ulcer	1	0.08
Gastrointestinal Hemorrhage	1	0.08
Rectal Hemorrhage	1	0.08
Salivary Gland Enlargement	1	0.08
Vomiting	1	0.08

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Table 5. All Serious Adverse Events by Body System from Completed Clinical Studies of Tomoxetine Hydrochloride ir Adults with Depression (Concluded)

	Tomoxetine (N=1275)	
Event Classification	n	%
Metabolic and Nutritional Disorders		
Hypoglycemia	1	0.08
Hemic and Lymphatic System		
Leukemia	1	0.08
Leukopenia	1	0.08
Musculoskeletal System		
CPK Increased	4	0.31
Bone Disorder	1	0.08
Nervous System		
Depression	5	0.39
Anxiety	2	0.16
Agitation	1	0.08
Dizziness	1	0.08
Insomnia	1	0.08
Paralysis	1	0.08
Parasthesia	1	0.08
Urogenital System		
Breast Carcinoma	2	0.16
Unintended Pregnancy	2	0.16
Kidney Calculus	1	0.08
Urination Impaired	1	0.08
Skin and Appendages		
Maculopapular Rash	1	0.08
Urticaria	1	0.08
Special Senses		
Cataract	2	0.16
Chorioretinitis	1	0.08
Eye Disorder	1	0.08
Glaucoma	1	0.08

Source Data: ClinTrace Database and Lilly Drug Experience Network (project team files).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jerry Boehm
7/16/02 12:58:01 PM
MEDICAL OFFICER

Judith Racoosin
7/24/02 01:05:42 PM
MEDICAL OFFICER
See additional comment on the need for dose adjustment for CYP2D6 poor metabolizers, as well as recommendations for additional labeling changes in my supervisory review-JAR