NDA:	21-411
Drug Name:	Generic Name: Atomoxetine Proposed Trade Name: Strattera™
Sponsor:	Eli Lilly and Company
Reviewer:	Gerard Boehm, MD, MPH
Completed:	7/16/02

The Executive Summary-Safety Review

Atomoxetine (Strattera) is a presynaptic norepinephrine transporter inhibitor that is administered orally. During development, the sponsor changed the generic name of this drug from tomoxetine to atomoxetine, and recently changed the proposed trade name from [redacted] to Strattera. These names appear in this review and refer to the same drug.

The NDA development program included safety data from 17 clinical pharmacology trials and 14 trials in ADHD patients. The sponsor also submitted limited historical safety data from urinary incontinence and major depression (MDD) trials, two abandoned indications.

The ADHD development program included 350 atomoxetine subjects in clinical pharmacology trials and 2,337 atomoxetine subjects in ADHD trials. The urinary incontinence and MDD trials included 1,324 atomoxetine subjects.

The safety testing, capture of adverse events, and analyses of safety data were generally adequate. One exception was the incomplete assessment of the effect of atomoxetine on QTc in CYP2D6 poor metabolizers (PM) at high atomoxetine doses. The NDA lacked long-term controlled data for the assessment of the effect of atomoxetine on growth but this information is often not available in applications. The number of patients exposed in the ADHD development program exceeds ICH guidelines. There were a limited number of adults and PM subjects exposed in the development program. Follow up was generally adequate.

There were no deaths in the ADHD database. With the exception of appendicitis reports, there did not appear to be clusters of unexpected SAEs in atomoxetine exposed

individuals. The appendicitis rate in the database is 2.5 times the background rate from Hospital Discharge Survey Data (1995-1999). No appendicitis cases occurred in controlled trials, so risk comparisons within the database were not possible. There is insufficient evidence to conclude that atomoxetine increases the risk of appendicitis. If approved, post-marketing reports for appendicitis should be expedited to allow close follow up for this event.

Infrequent serious adverse events (SAEs) of potential concern in the NDA database include two seizure cases, one case of angioedema, and one case of elevated LFTs. There were no SAEs of liver failure, renal failure, rhabdomyolysis, ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, aplastic anemia, Stevens Johnson Syndrome, or toxic epidermal necrolysis.

Common side effects that occurred more frequently among atomoxetine subjects and in some cases that exhibited evidence of dose response included anorexia, dizziness, nausea, weight loss, insomnia, sweating, constipation and palpitations. Adults exposed to atomoxetine experienced increased risk of urinary bladder outlet symptoms and adverse sexual side effects including decreased libido, impotence, and abnormal ejaculation.

Infrequent side effects of potential concern included syncope, urticaria, and convulsions. Since these either occurred infrequently in the controlled trials or only in open label trials, it is difficult to assess the relationship between these events and atomoxetine.

Atomoxetine was observed to increase resting blood pressure and pulse and result in orthostatic blood pressure and pulse changes.

As alluded to above, atomoxetine is metabolized by CYP2D6 and its pharmacokinetics differ in genetic poor metabolizers and those who concomitantly take drugs that inhibit CYP2D6. For the small number of poor metabolizer subjects observed in the development program, there did not appear to be increased risk for serious AEs or even many of the common AEs. These subjects did appear to have higher increases in blood pressure and pulse and greater weight loss than non-inhibited extensive metabolizers. While the NDA summarized data from patients who were taking CYP2D6 inhibitor and then started atomoxetine, there was no summary of the experience for patients taking atomoxetine and then started on a CYP2D6 inhibitor.

The relationship between atomoxetine and cardiac repolarization, particularly in CYP450 2D6 poor metabolizers exposed to high doses, has not been fully characterized. This relationship should be clarified prior to approval. There are no carefully conducted studies of the effect of atomoxetine on QTc in pediatric subjects.

Recommendations
I recommend including information about the effect of atomoxetine on growth in the Warnings section of labeling.

I recommend stronger wording about restricting the use of atomoxetine in patients with moderate to severe hypertension or symptomatic cardiovascular disease. I also recommend adding information about the increased risk of orthostatic blood pressure changes and related symptoms.

I recommend adding a statement to labeling addressing atomoxetine and increased risk for urinary bladder outlet restriction symptoms.

Unresolved safety issues
I consider the effect of atomoxetine on the QTc for poor metabolizers at high doses to be an unresolved safety issue.

The sponsor has been asked to submit additional information for several subjects with convulsion adverse events. The division has not yet received that information.

The sponsor should provide analyses of the safety experience of the EM subjects who were on stable doses of atomoxetine and then had a CYP2D6 inhibitor added to their regimen.

Clinical Review-Safety

1. Materials Used In This Review

This safety review was based on the information included in the following submissions:

- October 10, 2001; NDA Integrated Summary of Safety (ISS), Study reports for individual studies, electronic data sets, electronic Case Report Forms (CRFs)
- December 13, 2001; Two month Safety Update, updated electronic data sets
- March 28, 2002 submission, April 25, 2002 e-mail; responses to reviewer questions

2. Background

2.1 Name, Drug Class, Proposed Indications

The sponsor classifies atomoxetine [benzenepropanamine, *N*-methyl-γ-(2-methylphenoxy), hydrochloride, (-)] or Strattera™as an inhibitor of the presynaptic norepinephrine transporter and states that atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. The sponsor seeks approval for atomoxetine use in the treatment of attention deficit hyperactivity disorder (ADHD) in those ages 6 and older.

2.2 State of the Armamentarium, Safety

The PDR includes the following drugs with an indication for treatment of attention deficit disorders with hyperactivity:

Adderall (Mixed Salts of a Single entity amphetamine)
Ritalin, Concerta, Metadate, Methylin, (methylphenidate)
Cylert (pemoline)
Desoxyn (methamphetamine),
Dexedrine, DextroStat (dextroamphetamine)

The following section summarizes major safety issues identified in the product labeling of selected approved ADHD drugs.

Adderall-CNS Stimulant

Boxed Warning- abuse potential
Contraindications- advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity, glaucoma, agitated states, hx drug abuse, during w/in14 days of MAO use

Warnings- may exacerbate behavior disorder or thought disturbance. Insufficient data to determine if chronic use inhibits growth. Appears in breast milk.
Precautions- mild hypertension, Prescribe the least amount feasible to minimize the possibility of overdose. May impair the ability to operate machinery or vehicles. Exacerbation of motor and phonic tics.

Desoxyn-CNS Stimulant

Boxed Warning Abuse Potential
Contraindications-Use within 14d of MAOI use. Glaucoma, advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity, agitation.
Warnings-Decrements in predicted growth
Precautions-Mild hypertension, not for fatigue, smallest amount to minimize overdose risk, could impair ability to operate machinery/vehicle, list of interactions, long-term effects have not been established. May exacerbate behavior disturbances, thought disorders, motor and phonic tics.

Dexedrine-CNS Stimulant

Boxed Warning Abuse Potential
Contraindications-Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity, glaucoma, agitated states, history of drug abuse, use within 14d of MAOI use.
Precautions-mild hypertension, limit amount dispensed, impair ability to operate machinery/vehicle, may worsen behavior or thought disturbances, exacerbate tics, inadequate data to assess long term growth
Schedule II

Ritalin-CNS Stimulant

Boxed Warning- Abuse Potential
Contraindications-anxiety, tension, agitation, hypersensitivity, glaucoma, tics/Tourette's MAOI use within the last 14 days
Warnings-Long term data not available suppression of growth has been reported
Not for severe depression, may exacerbate psychoses, not for normal fatigue
May lower seizure threshold, use cautiously in patients with hypertension, visual disturbances- accommodation/blurring of vision
Precautions-agitation may react adversely
Periodic CBC, differential, and platelet counts during prolonged therapy

Cylert-CNS stimulant

Boxed Warning-Liver failure- recommended as second line use, abuse potential
Contraindications-hypersensitivity, impaired hepatic function
Warnings-decrements in predicted growth (weight gain and or height)
Precautions-Exacerbation of behavior disturbance or thought disorder, administer with caution if renally impaired. Labs- monitor LFTs

2.3 Proposed Atomoxetine Labeling with Respect to Safety

The sponsor proposes that atomoxetine be contraindicated in those patients with hypersensitivity to atomoxetine or other constituents of the product. They also propose contraindicating atomoxetine use in those patients who are also taking a MAO inhibitor or have discontinued a MAO inhibitor within the previous 2 weeks.

In the ***Warnings*** section of proposed labeling, the sponsor states that allergic reactions including rash, angioneurotic edema and urticaria have been reported in patients taking atomoxetine.

In the ***Precautions*** section of the proposed labeling, the sponsor discusses atomoxetine-associated increases in heart rate (mean <10bpm) and/or blood pressure (mean <5mm Hg). They also note that orthostatic hypotension has been reported. Under information for patients in the ***Precautions*** section, the sponsor would recommend consulting a physician before using atomoxetine with other prescription drugs, over the counter medicines, vitamins, supplements, herbal remedies, or alcohol. The sponsor proposes that patients should consult a physician if they are nursing, pregnant or thinking about becoming pregnant. The sponsor would advise patients that they can take atomoxetine with or without food and that they should not take more than the prescribed amount in cases where they miss a dose. The sponsor proposes that patients should use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine. The sponsor states that routine laboratory requests are not required. The sponsor identifies interactions with MAO inhibitors, paroxetine, pressor agents, and drugs that affect norepinephrine. The sponsor would state that there is no evidence of carcinogenesis, mutagenesis, or impairment of fertility with atomoxetine, and atomoxetine is Pregnancy category C.

In the Adverse Reactions section of labeling, the sponsor states that atomoxetine was administered to over 2,000 children with ADHD and over 260 adults with ADHD. They propose an Adverse Event table that summarizes the experience in the child and adolescent placebo controlled trials (BID and q day regimens pooled) with events reported by at least 2% of atomoxetine subjects and at least twice the risk with placebo. This table is provided below.

Table 1.

Common Treatment-Emergent Adverse Events Associated with the Use of ——— in Acute (up to 9 weeks) Child and Adolescent Trials		
Adverse Event[1]	Percentage of Patients Reporting Event	
System Organ Class/Adverse Event	———	Placebo
Gastrointestinal Disorders		
Constipation		
Dyspepsia		
General Disorders		
Psychiatric Disorders		
Mood swings		

[1] Events reported by at least 2% of patients treated with atomoxetine, and ——— placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: ——— , anorexia, blood pressure increased, early morning awakenin ——— , mydria

In addition to the above table, the sponsor proposes a second adverse event table in labeling for the adult ADHD trials. The adult ADHD adverse event table would also include events that occurred in at least 2% of atomoxetine subjects and that had twice the risk observed in the placebo subjects. The sponsor did not include a listing of all adverse events observed during the atomoxetine clinical development program in their proposed labeling.

The sponsor would state in labeling that atomoxetine is not a controlled substance, is not a stimulant, is not associated with diversion, rebound, or withdrawal.

The sponsor would state that the effects of overdosage greater than twice the maximum recommend daily dose in humans are unknown. The sponsor would state that there is no specific information available about treatment of overdosage, but that overdose patients should be monitored and receive supportive care. They state that gastric emptying and activated charcoal with/without cathartics may prevent systemic absorption.

The proposed dosage and administration section of the atomoxetine labeling suggests dosing patients <70kg initially at 0.5mg/kg and increasing the dose after 3 ' days to a target dose of 1.2mg/kg/day administered as either a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. The dosage

may be increased to 1.8mg/kg/day in patients who have not achieved an optimal response. The maximum recommended dose for patients <70kg is 1.8mg/kg/day or 120mg, whichever is less. Patients >70kg and adults should start at 40mg/day and after 3 — days increase the dose to 80mg/day administered as either a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. The proposed labeling suggests that the dose can go up to 120mg/day in two divided doses. The maximum recommended dose for patients >70kg and adults is 120mg.

2.4 Animal Pharmacology and Toxicology

The sponsor summarized their findings from animal studies in section 12 (pp. 658-61) of the ISS. The sponsor conducted single dose studies in mice, rats, dogs and cats and repeated dose studies in mice, rats, and dogs. The sponsor also conducted in vitro and in vivo genotoxicity studies, oncogenicity studies in mice and rats, and reproductive and development studies in rats and rabbits.

The sponsor reported that in single dose oral toxicity studies, the median lethal dose was 25mg/kg in cats, greater than 37mg/kg in dogs, and greater than or equal to 190mg/kg in rats and 274mg/kg in mice. The sponsor observed mydriasis, reduced pupillary light reflex, mucoid stools, salivation, emesis, lethargy, weak legs, tremors, myoclonic jerking, and convulsions at sublethal doses in animals.

The sponsor reported that data on the single dose effects of atomoxetine in rodents, dogs, and monkeys indicate that the compound produces an acute behavioral profile that is distinctly different from the behavioral profile for psychomotor stimulants with known abuse profiles.

The sponsor reported that single doses of atomoxetine did not produce important changes in renal function, respiration, gastrointestinal motility, or immune function in animals.

Decreased body weight and mild hepatotoxicity were noted in repeated dose studies (3 month in mice and 12 month in rats). Hepatotoxicity was described as mottling and pallor of the liver, increased liver weight, hepatocellular vacuolization and increased ALT values. The sponsor reported no hepatotoxicity was observed in dogs administered up to 16mg/kg/day for 3 or 12 months. The sponsor noted tremors and emesis, in young dogs but no neurological or persistent ophthalmologic findings, no effects on body weight gain, and no major organ toxicity attributable to atomoxetine.

In multiple dose rat studies, the sponsor observed normal bone growth and normal physical, behavioral, and sexual maturation with no major organ toxicity but found minor delays in the onset of sexual maturation. The sponsor reported that neither reproductive performance nor fertility was compromised in a focused rat reproduction fertility study.

The sponsor reported that embryo-fetal developmental toxicity studies in rats and rabbits indicate that atomoxetine is not teratogenic or embryotoxic. The sponsor found no evidence to support that atomoxetine was carcinogenic in 2-year oncogenicity trials in both mice and rats.

The animal data related to QT interval are presented in a separate section of this review.

2.5 Human Pharmacokinetics

The sponsor reported that atomoxetine is primarily cleared from the body by oxidative metabolism with nearly all of its metabolites eliminated by excretion into the urine (HPSUM, p.14). Atomoxetine's pharmacokinetics are influenced by the cytochrome P450 2D6 (CYP2D6) polymorphism. While most individuals are extensive metabolizers (EM) of atomoxetine, 5-10% of Caucasians are poor metabolizers (PM) due to mutations or deletions of the CYP2D6 gene. Poor metabolizers have higher steady state plasma concentrations of atomoxetine and the *N*-desmethylatomoxetine metabolite (NDA, BIOSUM Report, p.7). In addition, drugs that inhibit CYP2D6 can result in increased steady state plasma concentrations of atomoxetine and the *N*-desmethylatomoxetine metabolite in exposed EM patients.

The major oxidative metabolite of atomoxetine regardless of CYP2D6 status is 4-hydroxyatomoxetine, which is rapidly glucuronidated. 4-hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at lower concentrations. In individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine is formed by other cytochrome P450 enzymes, at a slower rate.

The mean half-life of atomoxetine in adult extensive metabolizers is 3.6 hours and in poor metabolizers is 21 hours. At steady state, the AUC of atomoxetine is approximately 10-fold higher and the $C_{ss,max}$ is about 5-fold higher in CYP2D6 poor metabolizers than extensive metabolizers. Atomoxetine is rapidly and completely absorbed following oral administration (NDA, BIOSUM Report, p.10). In vitro protein binding in human plasma was 99% (NDA, Application Summary, p.65). The sponsor reported a modest effect of food on the rate of absorption of atomoxetine with approximately a 37% decrease in C_{max} and an approximate 2-hour delay in T_{max}. Food had no effect on the extent of absorption, with no significant difference in AUC (NDA, BIOSUM, p.14).

3. Approach to Safety Review/Methods

Using the electronic version of the NDA, the two-month Safety Update, and responses to specific questions, I reviewed treatment emergent events identified from the atomoxetine development program. To verify the accuracy of the primary data for all deaths and serious adverse events summarized by the sponsor, I cross checked data from the sponsor's listings, case report forms (CRFs), narrative summaries, and electronic data sets. To evaluate the adverse event (AE) coding procedures, I compared investigator verbatim terms with the corresponding preferred terms assigned by the sponsor. For selected events (ex. liver related abnormalities, rashes), I reviewed the coding in more detail by examining the CRF, electronic data sets, narrative summaries, and study report listings to determine if the coded terms accurately reflected the described events. I reviewed the death narratives, for all study subjects who died and summarized each death. In addition, I reviewed the CRFs, narrative summaries, data sets and study reports for serious adverse events (SAEs), selected AEs leading to discontinuation from a study, and any AE preferred terms suggestive of events of interest such as angioedema, urticaria, syncope, and appendicitis.

I reviewed the results of the sponsor's AE risk calculations. For the pediatric and adult placebo controlled data the distribution of person time by treatment was proportionate to the number of subjects assigned each treatment. Therefore, regardless of whether one uses person time or number of people in the denominator of risk calculations, the relative risks for events were similar and so I did not calculate AE rates using person time. For the analyses comparing the AE profiles between EM and PM subjects, the

mean exposure time for subjects in these two groups were similar so I did not calculate AE rates using person time. For the analyses comparing EM and PM subjects receiving a maximum atomoxetine dose of at least 1.2mg/kg/day, mean duration of exposure was greater among EM subjects. For these analyses, I calculated rates using person time in the denominator of risk calculations to account for this difference in exposure duration.

I reviewed the sponsor's lab and vital sign data analyses. I conducted additional analyses of extreme lab outliers, blood pressure outliers, and QTc data.

4. Review Findings

4.1 Description of Data Sources

The sponsor described their presentation of the safety data in the ISS in Sections 3.1 and 3.4 of the ISS.

The NDA includes safety data from 14 Phase II/III trials in ADHD patients. The sponsor summarized all available safety data from 11 ADHD clinical studies in the ISS (HFBD, HFBK, LYAC, HFBE, HFBC, LYAB, LYBB, HFBF, LYAT, LYAA, LYAO). The sponsor provided limited safety data (SAEs) for three trials (LYAF, LYAI, LYAR), which were ongoing at the time of the NDA submission (ISS, p.57).

The sponsor included safety data from 17 clinical pharmacology studies and one abuse potential study (LYAD). The sponsor provided a summary of safety data from 10 historical studies, where atomoxetine was tested for treatment of depression and urinary incontinence, indications abandoned by the sponsor due to lack of demonstrated efficacy.

In the NDA, the sponsor provided summaries of all SAEs from the entire development program through 8/01. The remaining safety data were analyzed and summarized using various groupings with different cutoff dates. The data were grouped based on study population and design characteristics and the groupings are described below.

The two-month Safety Update updated SAEs through 11/15/01. The two-month safety update also included safety data from study LYAQ, which evaluated atomoxetine tolerability in phenotypic PM subjects and summarized additional safety data from studies LYAB and LYAC, which were ongoing at the time of submission (Safety Update p.16).

Atomoxetine is not approved anywhere in the world so there are no post marketing data.

4.1.1 Primary Safety Analysis Groups

Child and Adolescent acute placebo controlled ADHD studies using BID dosing

The sponsor provided comparative analyses from Child and Adolescent acute placebo controlled ADHD studies using BID dosing (3 trials HFBD, HFBK, LYAC N=342 atomoxetine, 208 placebo). Study LYAC randomized subjects to placebo or fixed doses of atomoxetine (0.5, 1.2, or 1.8mg/kg/day) and included an 8-week acute treatment period. Studies HFBD and HFBK had a stratified randomization based on prior stimulant exposure. Subjects received their initial dosage based on their weight and the protocols allowed up or down dose titration based on response and adverse events. Studies HFBD and HFBK had 9-week acute treatment periods. The sponsor provided

comparisons of SAEs, discontinuations due to AEs, common AEs, laboratory results, and other testing using the data from these trials. Cutoff date 3/1/01.

Child and Adolescent Overall ADHD studies BID dosing
In order to provide a complete picture of events occurring in pediatric ADHD subjects exposed to BID atomoxetine the sponsor summarized the experience from Child and Adolescent overall ADHD studies using BID dosing. The data summarized in this analysis group came from 8 trials (HFBC, HFBD, HFBK, LYAC, HFBE, HFBF, LYAB, LYBB N=1,982 atomoxetine). This group includes the safety data from atomoxetine subjects enrolled in placebo and active controlled trials and open label trials. These data include absolute risks for events among atomoxetine exposed subjects but do not allow for comparisons of observed risks. Cutoff date 3/1/01.

Adult acute placebo controlled ADHD studies using BID dosing
The sponsor provided separate comparative analyses using data from Adult acute placebo controlled ADHD studies using BID dosing (2 trials LYAA N= 141 atomoxetine, 139 placebo, LYAO n=129 atomoxetine, n=127 placebo). Both studies had a 10-week acute treatment phase, with atomoxetine subjects initially dosed at 30mg BID and allowed titration to a maximum dose of 60 mg BID based on efficacy. Subjects could be titrated down to the previously tolerated dose if they developed intolerable AEs following a dose increase. Subjects were discontinued if they required a dose decrease below a previously tolerated dose or if they were unable to tolerate the 30mg BID dose. These analyses allow comparisons between adult placebo treated subjects and adult atomoxetine subjects. Cutoff date 4/30/01.

4.1.2 Secondary Safety Analysis Groups
The sponsor provided analyses based on additional groupings of data.

Poor Metabolizers from Child and Adolescent ADHD Studies
Approximately ten percent of the general population are poor metabolizers (PM) of atomoxetine (based on CYP2D6 genotype) and therefore can have higher plasma atomoxetine exposures than the remaining population of extensive metabolizers (EM). In trials HFBE, HFBF, LYAB, LYAC, and LYBB, subjects were classified based on their CYP2D6 genotype. To assess whether PM subjects have a different adverse event profile, given their higher plasma exposure, the sponsor provided a separate analysis of the risks in this group of subjects (n=125). Cutoff date 3/1/01.

In their two-month safety update, the sponsor provided additional information and updated analyses for PM vs. EM subjects. The sponsor identified 182 enrolled PM subjects (Safety update, p.17). Of the 57 new PM subjects added since the NDA, the sponsor identified 46 as *phenotypic* PM subjects. These subjects did not have a PM genotype but were given a CYP2D6 inhibitor and had peak atomoxetine plasma levels within 2 SD of the mean or >2 SD above the mean expected plasma concentrations for PMs (Safety Update, pp. 18-19). Since it is not clear if it is reasonable to pool data from *genotypic* and *phenotypic* PM subjects, the results of both the NDA and safety update analyses will be reviewed and then summarized separately.

Child and adolescent QD
The sponsor conducted a single study (LYAT) using a QD dosing regimen and the safety data from this trial are presented separately. Investigators titrated subjects to a maximum dose of 1.5mg/kg/day (or 100mg/day) based on efficacy and tolerability and

the acute treatment phase lasted 6 weeks. These analyses include 85 subjects exposed to atomoxetine and 86 exposed to placebo. Cutoff date 6/14/01.

Methylphenidate comparison
The sponsor provided a comparison of risk between atomoxetine and methylphenidate from the controlled trials that included a methylphenidate treatment arm (HFBD, HFBE, and HFBK). These analyses include 313 subjects exposed to atomoxetine and 82 exposed to methylphenidate. Cutoff date 3/1/01.

Adult volunteer data-Clinical Pharmacology Studies
The sponsor stated in multiple places in the Introduction section of the NDA that they summarized safety data from an abuse potential trial and 17 clinical pharmacology trials. This pooling was to include 350 subjects exposed to atomoxetine. However, when I reviewed the Adult volunteer data section, it identified only the 17 CP studies (322 subjects) but not the abuse potential study, LYAD (ISS, p.399). Therefore, I reviewed the LYAD study report and present results in the section reviewing Clinical Pharmacology Studies. Cutoff date 3/1/01.

Historical Data- Depression and Urinary Incontinence Trials
The sponsor provided a summary of safety data collected from depression and urinary incontinence trials. This includes 1,324 subjects exposed to atomoxetine and 710 subjects exposed to placebo. Cutoff date 3/1/01.

4.2 Exposure

4.2.1 Number of Subjects Exposed

In the NDA, the sponsor provided data for 4,011 subjects assigned to receive atomoxetine with 2,337 assigned atomoxetine in ADHD studies and the remainder assigned atomoxetine in clinical pharmacology studies (n=350) and historical studies (n=1,324). The following table provides a summary of enrollment by treatment, grouped by study design.

Exposure in the Atomoxetine NDA analysis groups, enrolled population

Analysis group	Atomoxetine	Methylphenidate	Placebo
ADHD Studies			
Child and adolescent Overall BID	1,982	82	233
Acute placebo controlled	342	-	208
Acute Methylphenidate controlled	313	82	-
CYP2D6 Poor Metabolizers	125	3	8
Child and adolescent QD placebo controlled	85	-	86
Adult Acute BID placebo controlled	270	-	266
Total ADHD Studies	2,337	82	585
Non-ADHD Studies			
Adult Clin Pharm and Special Studies	350	28	-
Adult MDD/UI Historical Studies	1,324	-	710
Total Non-ADHD Studies	1,674	28	710

From Sponsor's table 3.2.1, ISS p. 69.

There were slight differences between the number of subjects assigned atomoxetine treatment and the number actually exposed. The sponsor explained on p.139 of the ISS that 1,929/1,982 atomoxetine subjects enrolled in Child and adolescent overall BID studies received at least 1 dose of atomoxetine. For the remaining 53 subjects, 6 were recorded as taking no drug, 43 had no post baseline information, and for 4 subjects, the study sites were uncertain whether the subjects took any study drug. The sponsor's exposure table summary (ISS.A7.2, p.1,400) identified 338/342 pediatric subjects exposed to atomoxetine from the Child and adolescent acute placebo controlled ADHD studies. The sponsor's exposure table reported that 269/270 subjects assigned atomoxetine in the adult acute ADHD trials were exposed (Table ISS.3.2.3, p.72).

The sponsor did not provide an updated exposure section in the two-month safety update, but did identify 2,218 child and adolescent ADHD subjects from BID studies, an increase from the 1,982 subjects identified above (Safety Update, p.18).

4.2.2 Person Years Exposure

The following table summarizes the person time exposure in selected safety analysis groups through the ISS and through the 2-month safety update.

Person years Exposure for Selected Safety Analysis Groups

Analysis Group	Treatment	ISS	Safety Update, Cumulative
Acute child and adolescent*	Atomoxetine	75	75
	Placebo	35	35
Overall Child and Adolescent*	Atomoxetine	796	1,795
Acute Adult*	Atomoxetine	58	58
	Placebo	60	60
Overall Adult*	Atomoxetine	58	205
Overall Child and Adolescent°	EM Overall	N/A	762
EM vs. PM	PM Overall	N/A	61
	EM≥ 1.2mg/kg/day	N/A	679
	PM≥ 1.2 mg/kg/day	N/A	28

*From sponsor's table 4.1, 3/28/02 submission, p.133.
°From Safety Update, p.26. Calculated by: (mean duration in days x number exposed)/365

4.2.3 Exposure by Dose and Duration

The sponsor submitted exposure data that exceeds ICH guidelines. The sponsor reported that 526 pediatric subjects were exposed to atomoxetine for at least 6 months and 169 pediatric subjects were exposed to atomoxetine for at least one year. The proposed labeling suggests the effective dose for atomoxetine is 1.2mg/kg/day (for those <70kg). The sponsor provided a summary of exposure by modal dose and duration in pediatric studies in ISS table 3.2.2. In this table, 428 pediatric subjects were exposed to a modal dose of at least 1.2mg/kg/day for at least 6 months and 129 subjects were exposed to a modal dose of at least 1.2mg/kg/day for at least 1 year.

In the NDA, the sponsor provided safety data for 67 PM subjects exposed to maximum atomoxetine dose of 1.2mg/kg/day (ISS p.249). In the two month safety update, the sponsor identified 112 PM subjects exposed to a maximum atomoxetine dose of 1.2mg/kg/day (Safety Update, p.18). In the NDA, 13 PM subjects were exposed to a maximum daily prescribed dose of at least 1.2mg/kg/day for at least six months and one was exposed to that dose for at least one year (Table ISS.5.1.4, p.252). These 6 month

and 1 year exposure numbers were unchanged in the safety update (Safety Update, p. 24).

4.2.4 Exposure by Age

A majority of the subjects (88%, 2037/2337) exposed to atomoxetine in the phase II/III ADHD trials were in the pediatric age group. In the Child and Adolescent Overall ADHD BID trials analysis group, the mean age of subjects exposed to atomoxetine was 10.9 years with a range of 6 to 18 years. The sponsor reported that 68% (1353/1982) of these subjects were <12 years old (Table ISS.4.2.1, p.137). In the pediatric trial LYAT using QD dosing, the mean age (10 years) and age range (6 to 15 years) were similar to the Child and Adolescent Overall ADHD BID trials group (Table.ISS.5.2.1, p.332).

4.2.5 Exposure by Sex

Pediatric ADHD subjects

In the NDA, the sponsor reported that in pediatric ADHD trials, 23% (448/1,982) of those assigned to atomoxetine were female and 77% (1,534/1,982) were male. The gender distribution was similar for the placebo group where 20% (46/233) were female and 80% (187/233) were male. The methylphenidate group was shifted to an even greater male preponderance with 96% (79/82) males and 4% (3/82) females.

Adult ADHD subjects

The sponsor reported that in adult ADHD trials, 36% (96/270) of those assigned to atomoxetine were female and 64% (174/270) were male. The gender distribution was similar for the placebo group where 35% (92/266) were female and 65% (174/266) were male.

4.3 Review of the Sponsor's AE Surveillance, Coding of AEs and Approach to Evaluating the Safety of Atomoxetine in Phase II/III Trials

The sponsor summarized the SAEs, AEs leading to discontinuation and treatment emergent AEs from the atomoxetine development program. SAEs were defined in study reports as deaths, initial or prolonged inpatient hospitalizations, life-threatening events, severe or permanent disabilities, cancers, congenital anomalies, or events significant for another reason. An AE was defined in study reports as any undesirable experience, unanticipated benefit or pregnancy. Subjects discontinuing for both AEs and other reasons had the adverse event recorded as the reason for discontinuation. Investigators were to select the most important AE as the reason for discontinuation in cases where more than one AE was present at discontinuation (ISS, p.82). Investigators identified AEs by open-ended questions and questionnaires (Barkley Behavior and Adverse Events Questionnaire-Modified, BBAEQ-M in pediatric studies and Association for Methodology and Documentation in Psychiatry-5, AMDP-5 in adult studies). The sponsor analyzed AEs captured by open-ended questions separately from those captured by questionnaires.

AE investigator verbatim terms were mapped to COSTART classification terms and subsequently also mapped to MedDRA terms. The ISS presents the results using COSTART as the main analyses and in a separate section the sponsor compared the observed risks using COSTART and MedDRA. The sponsor calculated AE risks by dividing the number of subjects in the treatment group with an AE by the total number of subjects in that treatment group for the particular safety database analysis group.

In addition to AE data, investigators collected vital sign data, laboratory data and ECGs during atomoxetine studies. In phase II/III trials, pulse and blood pressure were measured seated, twice at each visit, with measurements separated by three minutes. BP analyses used the average of the two measurements. Orthostatic blood pressure measurements were not performed in phase II/III trials. Weight was measured at each visit and height was measured at baseline and end of study. A central lab analyzed serum chemistry, hematology, and urinalysis tests. analyzed ECGs from studies HFBD, HFBK, HFBE, HFBC, and HFBF. analyzed ECGs from studies LYAC, LYAB, LYBB, LYAO, and LYAA (ISS, p.135, 190). The sponsor did not describe the methodology for ECG interval measurement in the ISS.

4.4 Audit Findings and Evaluation of the AE Coding

I reviewed the investigator actual/verbatim terms listed in the CRFs of selected atomoxetine subjects with serious AEs or who discontinued for AEs and the terms were accurately summarized in the narrative summaries, and the electronic data sets. I repeated these comparisons for lab and vital sign data across the available data sources. I found agreement between sources, even when the data point was clearly a mistake (example, subject LYAZ 1028 was listed with a heart rate of 18bpm and subject LYAE 1001 had a systolic BP of 116mmHg and the associated diastolic BP was 169mmHg). These obvious mistakes did not appear to occur commonly in the NDA.

Using the electronic data sets, I reviewed the results of the coding process that the sponsor used to group the investigator terms for adverse event analyses. I compared investigator verbatim terms for adverse events to the coded terms (COSTART and MEDRA). I did not find evidence of splitting of similar events. A few of the COSTART terms were of limited usefulness because they subsumed a wide range of verbatim terms. For example, the coded term PERSONALITY DISORDER subsumed verbatim terms ranging from shyness to oppositional disorder. The coded terms PAIN and INFECTION also subsumed a wide range of potentially unrelated events. I rarely encountered occurrences where verbatim terms were coded to an incorrect term (ex. dry heaves coded to pulmonary hypertension, encopresis coded to constipation and scarlet fever coded to fever).

4.5 Clinical Pharmacology Studies Safety

4.5.1 Clinical Pharmacology Exposure

On p. 399 of the ISS, the sponsor reported that 322 subjects enrolled in 17 atomoxetine clinical pharmacology (CP) studies. CP study BZ4-EW-E002 (12 subjects) was conducted during the 1980s and the sponsor did not include data from this study in pooled analyses, but reported results separately. Sixteen subjects were enrolled in the abuse potential study LYAD. Except for 6 chronic renal insufficiency patients and 11 patients with liver disease, the enrollees in CP studies were healthy volunteers. The age range of enrollees was 18 to 63 years and 61% of participants were males. The clinical pharmacology studies included 39 PM subjects. In CP studies, the sponsor used single atomoxetine doses from 5 to 120mg and multiple atomoxetine doses from 20mg to 75mg twice a day with a maximum of 2.8mg/kg/day. The atomoxetine CP studies used a variety of designs including single blind, double blind, placebo controlled, open label and combinations.

4.5.2 Clinical Pharmacology Mortality

No deaths occurred in subjects exposed to atomoxetine in CP trials or trial LYAD. There was one death in a liver disease patient (spontaneous bacterial peritonitis) that occurred following exposure to sorbitol and debrisoquine (ISS, p.412).

4.5.3 Clinical Pharmacology Serious Averse Events

The sponsor reported no serious adverse events in CP studies or trial LYAD (ISS, p.412, LYAD Study Report).

4.5.4 Clinical Pharmacology Discontinuations for Adverse Events

Ten subjects (2.9%, 10/350) discontinued from CP studies for AEs. Four subjects discontinued for syncope, and one each for palpitation, dyspnea, nervousness, dizziness, nausea, and chest pain (ISS, p.413). Below I summarize 2 of the syncope AEs leading to discontinuation. The other two syncope events are discussed as part of the study LYAY review section of the QT review.

Subject **HFBG-2476** a 40-year-old female EM, completed the three 40mg treatment but did not continue into the two 5mg treatments. She was withdrawn from the study because of a syncopal episode which occurred about 24 hours after her third atomoxetine single dose. She was standing for her morning vital signs at the time of the event and felt faint and then slid onto the bed. Her vital signs at the time were BP 98/46 with a pulse of 56 and the ECG reportedly showed sinus bradycardia. Her pre study blood pressure was 99/60 with a pulse of 79 (HFBG study report). The CRF noted that the subject was discharged due to an orthostatic hypotensive event followed by fainting.

Subject **LYAZ-1037** a 20-year-old female EM receiving 60mg doses, was withdrawn after Treatment A (fasted), the second of 3 planned treatments, due to an adverse event of syncope. Ninety-one minutes following a 60mg dose of atomoxetine while fasting she sat up during a blood draw and then slumped. No vital signs were recorded during the episode but 30 minutes later her supine BP was 120/70 with a pulse of 76 and her standing BP was 110/76 with a pulse of 76.

The sponsor identified an additional subject with a non-serious event that did not lead to discontinuation. That event is summarized below.

Subject **LYAE-1009** a 28-year-old PM male developed dizziness, ataxia, myoclonic jerking of his legs at night and 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 over the next 48 hours.

4.5.6 Clinical Pharmacology Treatment Emergent AEs

Since the sponsor limited their discussions to adverse events attributed to atomoxetine, I read the study reports to examine all AEs from these studies. I read through the study report AE listings and found no events coded to liver failure, renal failure, rhabdomyolysis, aplastic anemia, toxic epidermal necrolysis or Stevens-Johnson syndrome. The treatment emergent AEs reported during study LYAD were similar to the treatment emergent AEs reported in the clinical pharmacology trials.

The sponsor's clinical pharmacology trial AE analyses include only those AEs that were considered in the investigator's opinion related to drug treatment. The sponsor classified the AEs into those occurring within 12 hours of exposure and those occurring within 24 hours of exposure. The four most common AEs occurring within 12 hours of atomoxetine exposure were nausea, dizziness, somnolence, and headache.

The sponsor compared CP treatment related AEs for EM subjects and PM subjects within 12 hours. This analysis focused on studies LYAE, and HFBJ since these studies covered a broad dose range and had similar numbers of EM and PM subjects. In these two studies 71% (12/17) of PM subjects and 54% (14/26) of EM subjects had at least 1 AE. The sponsor included a larger number of studies when comparing AEs at 24 hours. They found that 65% of EM subjects (n=158) had AEs compared to 96% (n=28) of PM subjects. In general, there were too few specific events to allow reliable risk comparisons (ISS pp. 419, 427).

Cardiovascular AEs

The sponsor noted the occurrence of syncope and orthostatic hypotension AEs during these studies and attempted to further explore these findings. Their intention was to use logistic regression to examine the dose relationship for hypotension related AEs. They created a case definition for symptomatic orthostatic hypotension (SOH) that included the following VS changes: fall in SBP>=25mmHg or fall in DBP>=10mmHg with a standing DBP<70mmHg and a standing HR>100bpm. When these VS were reported within 24 hours of recording an AE of syncope, orthostatic hypotension, hypotension, or dizziness, a case of SOH occurred.

There were too few subjects with SOH events (n=8) or the other AEs to allow reliable analyses using logistic regression. However, because there were sufficient numbers of dizziness AEs, the sponsor created the following three logistic regression models based on time since last dose: 0-12 hours and 12 to 48 hours following single doses and 12 to 96 hours following multiple atomoxetine doses. They examined relationship to dose for EM and PM subjects. The sponsor reported a dose response for dizziness and they perceived a plateau of risk at 90mg for EM and 60mg for PM (shown below). The sponsor reported that there did not appear to be a dose response for the 12-48 hour analysis. For the 12 to 96 hour model there appeared to be a dose response for the EM but not PM subjects, while risk was higher among PM compared to EM subjects. The sponsor noted that these results might be suspect based on the small number of events observed (ISS p.434). The sponsor's analyses suggest dose response for dizziness but it is not clear that all or even most of the dizziness reported AEs are related to hemodynamic changes, limiting conclusions for events such as syncope or orthostatic hypotension.

APPEARS THIS WAY
ON ORIGINAL

Table ISS.5.4.16. Analysis of Dizziness 0 to 12 hours after Administration of a Single Atomoxetine Dose

Amount of Atomoxetine (mg)[a]	Number of Events	Total Number of Time Intervals	Percent of Events	Model Predicted Percent of Events	p-value Difference from Placebo	p-value for Quandratic Effect	p-value for EM/PM Difference
EM							
0.0	0	65	0.00	0.58		0.0308	0.3040
5.0	0	40	0.00	0.82	0.0000		
7.9	0	2	0.00	1.00	0.0000		
10.0	0	16	0.00	1.16	0.0000		0.5140
20.0	1	41	2.44	2.18	0.0000		0.9040
30.0	2	32	6.25	3.86	0.0000		0.5673
31.7	1	20	5.00	4.23	0.0000		
40.0	13	156	8.33	6.40	0.0000		0.1964
60.0	18	153	11.76	14.30	0.0000		0.0532
90.0	5	15	33.33	29.36	0.0000		0.6364
120.0	6	15	40.00	38.32	0.0000		0.1501
PM							
0.0	0	28	0.00	0.15		0.0002	
5.0							
7.9							
10.0	0	11	0.00	0.61	0.0000		
20.0	0	13	0.00	2.00	0.0000		
30.0	3	17	17.65	5.34	0.0000		
31.7							
40.0	0	22	0.00	11.51	0.0000		
60.0	6	19	31.58	28.45	0.0000		
90.0	4	11	36.36	34.81	0.0000		
120.0	1	10	10.00	12.02	0.0006		

a The intravenous dose administered in LYAK and LYAM was converted to the equivalent oral dose based on the bioavailability data in EM subjects (7.9 and 31.7 for EM and PM subjects).
Source Data: Data on file at Lilly Clinic.

Eight 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). Six of the subjects with SOH events were female (3 PM, 3 EM). None of the SOH events occurred within 24 hours of first atomoxetine dose. Four subjects had events 48-60 hours since first dose. Seven of the subjects had an SOH event at the 40-60mg dose range.

4.5.7 Clinical Pharmacology Lab data

The sponsor analyzed lab data outliers from all clinical pharmacology studies and commented that the observed abnormalities were not clinically important (ISS p.436). There were no appropriate comparator data to allow interpretation of the observed outlier risks.

Renal lab data

The sponsor observed small fluctuations in serum creatinine and the highest observed value (excluding renal insufficiency studies) was 1.6mg/dL.

Hepatic lab data
The sponsor noted 3 subjects with at least 2 fold elevations above ULN in ALT (n=2) or AST (n=1) in clinical pharmacology studies (not including hepatic impairment studies). The sponsor reported that the elevations resolved during further observation. One subject had an elevation of total bilirubin ≥1.5 times ULN (max value 1.9mg/dL) which was not associated with abnormal AST, ALT, or alkaline phosphatase results.

4.5.8 Clinical Pharmacology Vital signs
Multidose studies
Heart rate
In their pooled analyses for multiple dose studies, the sponsor combined HR data from contiguous days (2-5, 6-7) rather than displaying HR for each day of dosing. Results were stratified by CYP2D6 metabolic status. They presented the pre-dose mean HR and the 1-hour post dose mean HR for each dose group. They compared the mean heart rate for each atomoxetine dose group to the mean heart rate for placebo data. This analysis did not consider the baseline heart rate in the different groups. In a separate table, they compared each of the mean heart rates for the day groupings and doses to the other doses on that day, within the same metabolic category.

The sponsor found statistically significant higher mean HRs compared to placebo at most of the atomoxetine doses. The sponsor reported a maximum mean standing heart rate difference of +36.1bpm compared to placebo for pre-dose PM subjects taking 20mg on days 2-5. The greatest mean standing difference in heart rate among EM subjects compared to placebo was +16.5bpm on day 2-5, pre-dose in the 45 and 75mg groups. This analysis found higher mean heart rates compared to placebo among PM subjects compared to EM subjects although there did not appear to be strong evidence of dose response within the different metabolic groups. The pulse increases on day 6-7 were not materially different than those observed on days 2-5, although the dose ranges studied were smaller (Table ISS.5.4.23, p.441).

An analysis of mean supine heart rates found lower mean values compared to standing heart rates but provided little additional information about drug related effects.

Orthostatic BP changes
The sponsor found evidence of orthostatic blood pressure changes in clinical pharmacology 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 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 at time 0). The orthostatic diastolic 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).

Supine BP
The sponsor compared supine blood pressures for EM subjects to PM subjects at different atomoxetine doses for pre dose and 1 hour post dose. The PM subjects generally had higher supine systolic blood pressures than the EM subjects with the greatest difference, 19mmHg at 75mg and at the pre-dose measurement (Table

ISS.5.4.30, p.448). Similarly, the PM subjects generally had higher supine diastolic blood pressures than the EM subjects with the greatest difference, 10.9mmHg at 75mg and at the pre-dose measurement (Table ISS.5.4.32, p.450).

Single Dose studies
Heart Rate
The sponsor provided a table of mean standing heart rates at 0.5, 1, 2, 2.5, 3 and 4 hours following single doses of atomoxetine (5mg to 120mg), stratified by metabolic status. The mean heart rates increased in both groups with increasing dose and the highest heart rate was at the last measurement in most cases making it impossible to determine how long the increased heart rate lasted. There was no notable difference in the magnitude of HR increase between the two metabolic groups in this analysis. The highest observed mean heart rate was 116bpm among PM subjects 4 hours after a 60mg dose of atomoxetine (Table ISS.5.4.33, p.452).

The sponsor provided a table of mean orthostatic heart rate changes at 0.5, 1, 2, 2.5, 3 and 4 hours following single doses of atomoxetine (5mg to 120mg), stratified by metabolic status. As with the standing heart rate analysis, there was no remarkable difference between the two metabolic groups in this analysis. The mean orthostatic heart rate changes increased in both groups with increasing dose and the highest orthostatic heart rate change was at the last measurement in most cases making it impossible to determine how long the change lasted. The highest observed mean orthostatic heart rate change was 55bpm among PM subjects 4 hours after a 60mg dose of atomoxetine (Table ISS.5.4.34, p.455).

Blood Pressure
Orthostatic Changes
The sponsor examined orthostatic blood pressure changes in clinical pharmacology single dose studies. At most of the doses and time points there was little difference between EM and PM subjects. The largest mean orthostatic systolic blood pressure change was -13.3mmHg, 2.5 hours following a 120mg dose (Table 33, p.2156). The sponsor observed increases in diastolic orthostatic BP following single doses. The largest mean orthostatic diastolic blood pressure change was 7.5mmHg, 3 hours following a 120mg dose among EM subjects (Table 36, p.2167). These results appeared only in an appendix table and the sponsor did not discuss these findings which appear inconsistent with the other BP findings.

4.5.9 Abuse potential study LYAD
The sponsor conducted study LYAD to examine abuse potential of atomoxetine. The safety data from this study do not appear in any of the pooled analyses and so are reviewed separately here.

Sixteen recreational drug-using EM subjects (11 female) were enrolled in this randomized double blind placebo and comparator controlled 5-week trial. Subjects underwent pre treatment evaluation followed by single doses of atomoxetine (3 different doses), methylphenidate (2 different doses), or placebo, according to a randomized treatment sequence. The study included a washout period between doses (2-10 days). The study included atomoxetine single doses of 20,45, and 90mg. Methylphenidate was dosed at 20mg and 40mg. Subjects were evaluated with several abuse potential scales following study drug dosing. AEs, labs and vital signs were collected during the study.

AEs

The sponsor reported no deaths, SAEs, or discontinuations due to AEs. The sponsor listed the treatment emergent AEs. The treatment emergent AEs were consistent with AEs seen in the sponsor's pooled analyses. Nausea, somnolence, chills, dizziness, and sweating were the only AEs reported by at least 2 subjects taking any one of the three atomoxetine doses (LYAD Study report, p.119).

Lab data

The sponsor provided a summary of the lab data that included mean change from baseline to endpoint and an analysis of outliers. Since only baseline and end study data were collected, it is not possible to provide an analysis by treatment and therefore these analyses provide little useful information.

Vital Signs

Blood pressure and heart rate were taken pre-dose, and 30, 60, 90, 120, 150, 180, and 240 minutes post dose (LYAD Study report, p.127). The sponsor provided a mean change and maximum change from baseline and an outlier analysis by treatment.

Blood Pressure

Maximum Change from Baseline

The sponsor reported a SBP maximum change from baseline of 15mmHg for atomoxetine 90mg compared to 3.7mmHg for placebo. Increases were also seen for methylphenidate 20mg (6.2mmHg), methylphenidate 40mg (8mmHg) atomoxetine 20mg (6.3mmHg) and atomoxetine 45mg (12.9mmHg) (LYAD Study Report, p.129). There were no statistically significant differences when comparing the methylphenidate or atomoxetine treatment periods to placebo for the maximum DBP change from baseline (LYAD Study Report, p.133).

Mean Change from Baseline

The sponsor found statistically significant increases in SBP for most treatment periods compared to placebo, and for methylphenidate 40mg and atomoxetine 90mg compared to placebo for DBP. Those results are displayed in the following table.

Systolic BP Mean Change from baseline by treatment, Study LYAD

Treatment (n)	Mean Change to endpoint	p-value
Systolic Blood Pressure		
Placebo (15)	-9.3mmHg	
MPH 20mg (16)	14.5mmHg	.006
MPH 40mg (14)	11.2mmHg	<.001
TMX 20mg	9.5mmHg	.498
TMX 45mg	10.1mmHg	<.001
TMX 90mg	7.8mmHg	<.001
Diastiolic Blood Pressure		
Placebo (15)	-4.1mmHg	
MPH 20mg (16)	-1.7mmHG	.907
MPH 40mg (14)	2.9mmHg	.032
TMX 20mg (14)	-0.3mmHg	.904
TMX 45mg (15)	-2.7mmHg	.136
TMX 90mg (15)	3.0mmHg	.005

From Sponsor's Tables LYAD.12.3, LYAD.12.5, LYAD Study Report, p.129, 133.

The sponsor also presented a graph of mean systolic blood pressure by time after each dose (Figure LYAD.12.2, LYAD Study Report p.130). This graph suggested that the SBP increase occurred 30-60 minutes following most doses and appeared to persist through the 240-minute measurement (last available measurement).

Heart Rate
The sponsor observed a mean decrease in heart rate for placebo compared to baseline and decreases for most treatment regimens that were not as negative compared to the placebo group. While the HR maximum change from baseline was negative for the placebo treatment period, it was positive for the active treatment regimens. Those results are displayed in the following table.

Treatment (n)	Mean Change	p-value	Maximum Change	p-value
PLA (15)	-11.5		-3.3	
MPH 20mg (16)	-4.4	<.001	3.8	.011
MPH 40mg (14)	0.2	<.001	8.4	<.001
TMX 20mg (14)	-8.3	.004	0.4	.142
TMX 45mg (15)	-5.3	<.001	3.5	.007
TMX 90mg (15)	-1.3	<.001	11.8	<.001

From Sponsor's Table LYAD 12.7, Study Report LYAD, p.137.

ECGs
ECGs were performed at baseline and end study. No subjects with a normal ECG at baseline had an abnormal ECG at endpoint (LYAD Study Report, p.142).

4.6 Phase II/III Studies, Safety

4.6.1 Mortality

No deaths were reported in the NDA or Safety Update from ADHD clinical trials (ISS p. 237). The sponsor reported four deaths from their historical database (depression trials). Two deaths occurred in placebo subjects and two in atomoxetine subjects. I summarize the deaths below.

Subject **HFAG-01209127** a 61-year-old male was killed in an automobile accident during the placebo lead in phase of a depression trial.
Subject **HFAX-004-5730** a 39-year-old male committed suicide while on placebo in a depression trial.
Subject **HFAG-011-1849** a 32-year-old male developed rectal hemorrhage and infection and discontinued atomoxetine 30 days after randomization. He was subsequently diagnosed with AIDS and died due to complications of this disease.
Subject **HFAH-003-2212** a 55-year-old male discontinued atomoxetine for depression following 1 year of treatment. Routine CXR at the time of discontinuation revealed a blastic bone lesion and he was subsequently found to have a poorly differentiated carcinoma with brain metastases. He died from complications of the carcinoma.

4.6.2 Serious Adverse Events

The sponsor provided a listing of the SAEs that occurred during ADHD clinical trials through 7/31/2001 starting on page 238 of the ISS (2.1%, 48/2,337 atomoxetine ADHD subjects). The sponsor included the SAEs occurring through 8/2001 in the Application Summary section of the NDA (one additional atomoxetine subject). Page 218 of the Safety Update listed SAEs occurring from 9/1/2001-11/15/2001 (13 atomoxetine subjects). These listings, when combined, include 62 atomoxetine-exposed subjects with

SAEs in the ADHD development program. Below, I identify the SAEs that were reported for more than one atomoxetine subject.

Appendicitis	HFBF-001-1100, HFBF-015-1597, LYAC-025-7469, LYAF-541-1405 LYAF-590-3063, LYAI-007-4283, LYAI-067-5005, LYAI-071-7925, LYAI-521-5561
Depression	HFBF-015-1586, HFBF-017-1659, LYAB-051-5098, LYAI-089-8602, LYBB-056-7442
Accidental Injury	HFBF-001-1086, HFBF-012-1454, LYAO-61-3406, LYBB-206-8588 LYAR-072-5115
Burns	LYAC-001-7012, LYAI-001-4046, LYAF-541-1404
Hostility	HFBE-023-0887, LYAB-045-4873
Urinary Tract Inf.	LYAC-068-7753, LYAR-081-5967
Convulsions	LYAB-057-5333, LYAI-088-8570
Overdose	HFBF-004-1125, LYAB-053-5167

There was one atomoxetine ADHD subject with an SAE of abnormal liver function tests, one subject with angioedema, and one with syncope. One SAE was coded to rash (Subject LYAB-001-7012) but the actual event was a second-degree burn from spilled hot soup. No subjects were identified with acute hepatic failure, acute renal failure, rhabdomyolysis, aplastic anemia, Stevens Johnson syndrome, or toxic epidermal necrolysis. Below I summarize information for select ADHD SAEs.

Angioedema

Subject **LYAB-096-6164**, a 14-year-old EM male with a past history of angioedema (x2) began atomoxetine on 10/24/2000. On 5/17/01, he awoke with a pruritic rash. He went to an emergency department and was initially treated with antihistamines and steroids. His symptoms progressed and he developed lip swelling that was treated with SQ epinephrine. He was admitted and improved by the next day.

Abnormal LFTs, Confusion

Subject **LYAF-652-9053**, a 9-year-old PM female started atomoxetine on 8/20/01. The drug was briefly stopped for nausea and vomiting and was then restarted. On 9/5/01, the subject developed fever, headache and vomiting and atomoxetine was held. Within 24 hours the subject developed hives and facial puffiness along with intermittent confusion. She was treated with promethazine. The subject also developed diarrhea and vomiting. LFTs were noted to be elevated (GGT 71, ALT 169, AST 136, bilirubin not reported). The sponsor commented that the LFTs were improving off atomoxetine and that hepatitis serology was negative. The sponsor reported that they made numerous attempts to obtain additional follow up but that the parents refused additional lab studies.

Convulsions

Subject **LYAB-057-5333**, a 9-year-old EM male experienced grand mal seizures. Nine months after beginning study medication, while playing baseball, he experienced a brief seizure (5/19/2001). He was taken to the hospital and had a normal head CT and chemistry panel. He was sent home with neurology follow-up. The next day the parents reported that he was acting

strangely and they were instructed to go to the hospital. En route he seized and had 2 additional seizures at the hospital. Work up included LP (preliminarily normal), EEG, and MRI (results not provided). Study drug was stopped 6/11/2001. On 6/13/2001 he experienced another grand mal seizure and had a Dilantin level of 5 at the time. The sponsor noted that the patient was born at 36 weeks gestation and spent 12 days in the NICU for immature lungs and had 2 respiratory arrests.

Subject **LYAI-088-8570**, a 6-year-old EM male first received atomoxetine on 1/3/01. On 11/5/01 he went to his dentist for a tooth extraction, which included local lidocaine and "a small amount of gas". He returned home following the procedure, ate some soup, and then fell on the floor and lost consciousness for a few minutes. He was limp and urinated on himself. Following the event, he was "spacey" for an hour. He was seen by his pediatrician and was alert and had a normal neurological exam and normal electrolytes (not provided). The pediatrician called the event a suspected seizure and results of a sleep deprived EEG were pending. This subject also had an episode of "fainting" while enrolled in a prior atomoxetine study (LYBB). The sponsor reported that the subject continued atomoxetine for another month without additional seizure-like episodes but the subject discontinued at that time for lack of efficacy.

Syncope

Subject **LYAB-063-5565**, a 7-year-old EM male first received atomoxetine on 7/28/2000. On 7/31/2001, after an amusement park ride, the subject noted intermittent dizziness and headaches. On August 2, 2001, he "passed out" with no details about the event provided. He sustained a bruise on his face. Work up included labs (hematology, chemistry and urine) and an ECG. An EEG was performed and reported as normal. Atomoxetine was held and the subject was admitted for observation and had 2 additional syncopal episodes. The sponsor reported that labs, drug screen, ECG, and CT results were negative. This subject took atomoxetine for 5 additional months without experiencing another syncopal episode.

Appendicitis

The sponsor provided table 4.4.2 with narratives for the subjects who developed appendicitis and abdominal pain SAEs and narratives for appendicitis SAEs in the NDA and safety update. In the following table, I present information abstracted from the sponsor's table and narratives to summarize selected data for the appendicitis cases.

Summary of Appendicitis cases in ADHD atomoxetine subjects through the Safety Update (through 11/15/01)

Pt ID	Study Design	Age	Sex	Dose (mg/kg/day)	Duration (days)	Outcome
HFBF-001-1100	Open label ext.	11	M	1.68	208	Surgery
HFBF-015-1597	Open label ext.	10	M	0.31	122	Surgery, ruptured
LYAC-025-7469	DB ext.	12	M	1.80	60	Surgery
LYAF-541-1405	Relapse prev	10	M	1.21	49	Surgery
LYAI-007-4283	Open label ext	13	M	1.52	270	Surgery, ruptured
LYAI-067-5005	Open label ext	9	M	1.77	126	Surgery
LYAI-071-7925	Open label ext	12	F	1.64	150	Recovered next day
LYAF-590-3063	Relapse prev	11	M	1.63	27	Surgery, inflamed
LYAI-521-5561	Open label ext	7	M	1.16	11	Surgery

The sponsor calculated an appendicitis incidence rate (5.01/1,000PY) using the number of appendicitis cases in the numerator (n=9) and the person time exposure in pediatric subjects in the denominator (1,795PY). Since one of the cases recovered without treatment by the next day, making the diagnosis of appendicitis unlikely, a more appropriate incidence rate would use 8 cases in the numerator and yield an appendicitis

rate of 4.5/1,000PY. The sponsor compared the observe risk of appendicitis in atomoxetine subjects to a background rate of appendicitis of 4/1,000PY from Nelson's Pediatric Medicine textbook. This textbook did not cite the source of the appendicitis incidence data.

An Office of Drug Safety (ODS) consultant epidemiologist provided an estimate of the background incidence of appendicitis using Hospital Discharge Survey Data. The data provided by ODS summarized the incidences (per 100,000/year) by age (6yrs-18 yrs) and year (1995-1999). Since the NDA data had cases and exposure for ages 6-18, I pooled the background data to arrive at a rate of appendicitis among 6-18 year olds of 1.8/1,000/yr.

The risk for appendicitis observed in pediatric patients in the atomoxetine ADHD development program was 2.5 times higher than the background rate estimated from Hospital Discharge Survey data (p=0.11).

The observed increased appendicitis risk compared to background did not appear to be due to the age distribution in the study group. Since there was variation in the background appendicitis rates by age, and the distribution of person time in the study population varied by age, I calculated a standardized morbidity ratio (SMR) to adjust for the age distribution. I multiplied the background appendicitis rates for each age (6-18, from the ODS consult) by the person time for that age group in the study population (provided by the sponsor in a 4/25/02 e-mail) to determine the number of expected appendicitis cases. I then divided the observed number of cases by the expected. The SMR for appendicitis was 2.4, which was similar to the rate ratio calculated above.

4.6.3 SAEs by Safety Analysis Groups

Child and Adolescent overall ADHD studies BID dosing

The SAE risk among subjects assigned to atomoxetine during the BID ADHD studies through 3/1/01 was 1.0% (19/1,982). These events were considered above in the overall section.

Child and Adolescent acute placebo controlled ADHD studies using BID dosing

The sponsor reported seven SAEs in these trials with four occurring on atomoxetine (1.2%, 4/340) and three on placebo (1.4%, 3/207). Furthermore, the sponsor reported that two atomoxetine events that investigators reported as serious (overdose, outpatient ear surgery) did not subsequently meet the regulatory definition for SAEs. The two remaining SAEs on atomoxetine in these trials were burns (LYAC-001-7012) and urinary tract infection/nephritis (LYAC-068-7753).

Adult Acute Placebo-controlled ADHD Trials

The sponsor reported 5 SAEs in these trials, with a distribution of 0.7% (2/270) of atomoxetine subjects and 1.3% (3/266) of placebo subjects. One of the atomoxetine SAEs was a basal cell carcinoma (LYAA-072-2186) and the other an automobile accident, with no comment in the narrative about whether the subject was a driver or passenger (LYAO-061-3406).

Poor Metabolizers from Child and Adolescent ADHD Studies

In the NDA, the SAE risk for PM subjects (2.4%, 3/125) was similar to the SAE risk in EM subjects (2.3%, 42/1,804) (ISS, p.258). In the two-month safety update, the sponsor provided a list of PM subjects with SAEs but did not calculate updated risks or make

comparisons. The SAEs identified among the PM subjects in the Safety update were hostility (HFBE-023-0887), fracture while sliding down an icy slope (LYBB-035-6545), accidental injury from a firecracker (LYBB-206-8588), gastrointestinal infection (LYAF-601-7009) and confusion and abnormal LFTs (LYAF-652-9053).

Child and Adolescent Acute Placebo Controlled Once Daily ADHD Group
There were no SAEs in the 85 pediatric subjects assigned to atomoxetine in the once daily dosing study LYAT.

Child and Adolescent Acute Methylphenidate Controlled ADHD Group
In studies HFBD and HFBK, there were no atomoxetine SAEs. In study HFBE, there were 2 atomoxetine SAEs a heart murmur, and hostility.

Serious Adverse Events from Depression and Urinary Incontinence Trials
The sponsor reported 89 serious adverse events for 1,275 atomoxetine subjects in the pooled depression and urinary incontinence trials (Historical data, p.1). They provided a listing of the serious adverse events in table 5 of their historical data report. Table 5 is included as an appendix to this review. In the following table, I have included the serious adverse events with at least 3 reports in atomoxetine subjects.

Serious Adverse Events with at least 3 reports in Depression and Urinary Incontinence Trials

Event	n	% (N=1,275)
Surgical Procedure*	7	.50%
Intentional Overdose	5	.39%
Liver function tests abnormal	5	.39%
Depression	5	.39%
CPK increased	4	.31%
Extrasystole	3	.24%
Hypertension	3	.24%
Tachycardia	3	.24%

*Cervical fusion n=2, mastectomy n=2;choleycystectomy, penile implant, orchiectomy n=1 each, From Sponsor's Table 1.1, 3/28/02 submission

There were no reports of hepatic failure, renal failure, seizures, aplastic anemia, rhabdomyolysis, Stevens Johnson syndrome or toxic epidermal necrolysis. There were two reports of syncope and one report of each of the following: kidney calculus, leukemia, urticaria, and paralysis.

I read through all of the patient summaries for SAEs in depression and urinary incontinence trials and below I summarize selected events of potential interest. The summaries provided by the sponsor contained few details about the events.

HFAB-004-1069 51-year-old female experienced syncope secondary to orthostatic hypotension resulting in laceration on her forehead on a daily atomoxetine dose of 50mg/day. This subject had a history of hypotension. Admission sitting BP was 110/80mmHg and standing was 90/60mmHg. After one week on study drug, sitting BP was 96/76mmHg, and standing BP was 86/64mmHg.
HFAH-011-2477 32-year-old female experienced 2 syncopal episodes while taking atomoxetine 40mg BID. This occurred 25 days after the start of therapy.
HFAG-014-1958 39-year-old male developed urticaria within a month of starting the study and discontinued with resolution of urticaria within a week.

HFAH-003-2212 55-year-old male lung cancer patient who died had bronchial nerve impingement coded as paralysis and listed as a separate SAE.

4.6.4 Discontinuations for Adverse Events

While the sponsor's ISS analyses presented death and serious adverse events through 7/31/01, they presented discontinuations for adverse events through the database cutoffs. Discontinuations due to adverse events were updated in the Safety Update through 9/2001 for the overall group (Table SU.6.2). The events listed in the updated table were similar to the AEs leading to discontinuation from the ISS analyses. The sponsor also identified the AEs leading to discontinuation by metabolic status in the safety update and those are considered in the EM vs. PM section that follows.

Child and Adolescent overall ADHD studies BID dosing

The sponsor reported that 4.5% (82/1,933) of subjects discontinued from all Child and Adolescent ADHD studies for adverse events (ISS p.144). In the following table, I list the adverse events leading to discontinuation of at least 3 subjects from these studies.

Adverse Events Leading to Discontinuation of at least 3 Subjects, Child and Adolescent overall ADHD studies

Event	Number of Discontinuations	% N=1,933
Nervousness	8	0.4
Somnolence	6	0.3
Emotional lability	5	0.3
Depression	4	0.2
Twitching	4	0.2
Agitation	3	0.2
Anxiety	3	0.2
Headache	3	0.2
Nausea	3	0.2
Palpitation	3	0.2
Tachycardia	3	0.2

From Sponsor's Table ISS.4.2.5, p.144

In addition to the events listed above, two subjects discontinued for rash, one for urticaria, one for allergic reaction, and one subject discontinued for abnormal LFTs. There were no discontinuations for liver failure, renal failure, aplastic anemia, rhabdomyolysis, Stevens Johnson syndrome or toxic epidermal necrolysis.
Below I summarize information from narratives, CRFs and data sets for selected AEs leading to discontinuation.

Twitching

HFBE-006-212 This 7-year-old EM male developed motor and auditory tics after 84 days of atomoxetine treatment. When seen for a follow up visit about 3 weeks after drug discontinuation, the tics were described as having subsided to their baseline level, although they were not listed as a historical condition and the visit 1 AE questionnaire recorded that tics were not occurring at visit 1.

HFBE-007-250 This 7-year-old EM male was reported to have tic (head and neck area), truncal arching, facial grimacing, right arm swinging, vocal humming and finger pointing after 33 days of treatment with atomoxetine. The narrative reported that vocal humming persisted but it was unclear whether or not the other symptoms resolved. The adverse event data set listed the truncal arching, right arm swinging and finger pointing as resolved seven days after atomoxetine discontinuation.

LYAB-042-4688 This 7-year-old EM male developed a motor tick 10 days after starting atomoxetine. At visit 9 the subject reportedly had a normal neuro exam but at visit 10, atomoxetine dose was decreased due to increased severity of the tics. Five days after stopping atomoxetine, some symptoms of motor tics remained. In the CRF, tics were absent at visit 1. Tics were first recorded at Visit 8.
LYAB-057-5326 This 8-year-old female had tics noted during visit 4 which led to discontinuation at visit 15. The onset of the tic disorder preceded drug therapy according to study records. Tic worsened during the study despite treatment with Tenex and study drug dose reduction. The investigator reported that the tics were not resolved at the last visit.

Palpitations
HFBE-002-11 This 8-year-old Hispanic EM male was reported to have palpitations that started after 15 days of treatment with atomoxetine. The maximum-recorded pulse was 95bpm and the baseline pulse was 78bpm. The narrative stated that the subject also experienced abdominal pain, diarrhea, and chest pain but did not mention lightheadedness, or syncope. The CRF documented no dizziness or lightheadedness and stated that the subject was discontinued due to ECG and palpitation x3. The ECG reports (tracings not included) were all interpreted as normal and unchanged. There were no data from an event recorder or Holter monitor. The adverse event data set listed the event as resolved. The ECG data set classified the study ECGs as normal with the highest HR=100 (5/11/99) after discontinuation and resolution of palpitations. On 5/5 the ECG HR=80.
HFBF-19-1743 (HFBK-019-3739) This 8-year-old EM male developed palpitations after 131 days on study drug. ECGs were reportedly within normal limits and the subject reportedly had a Holter monitor that was reported normal. The CRF comment section noted a pounding and a racing heart sensation associated with dizziness. The AE checklist noted heart racing/pounding at visits 3 and 8 but not at visits 5,6,7 or 9 (visit 1,2 not recorded).
LYBB-055-7392 This 9-year-old EM female developed palpitations 3 days after beginning atomoxetine. The palpitations lasted until discontinuation 3 days later. The subject's baseline pulse was 85 and the highest recorded on drug pulse was 82bpm.

Tachycardia
HFBE-003-0042 This 9-year-old EM male developed tachycardia 63 days after starting treatment with atomoxetine. The maximum recorded pulse was 90bpm and his baseline pulse was 72bpm. The narrative stated that the subject also experienced abdominal pain, nervousness, headache, and flu syndrome, but did not mention lightheadedness, or syncope. There were no data from an event recorder or Holter monitor. The adverse event data set listed the tachycardia as resolved. The CRF captured the AE in their questionnaire as heart racing, pounding. The CRF comments section described the event as occurring 1-4 times a day lasting 1-4 minutes, accompanied by nausea but no chest pain. ECG, pulse and blood pressure noted as WNL.
LYAB-015-4721 This 6-year-old PM male developed intermittent tachycardia 33 days after starting atomoxetine. Heart racing/pounding was first noted at visit 8 on the AE questionnaire. Vital signs from visit 8 noted a pulse of 122bpm, the highest recorded pulse during the study (visit 1 pulse 104bpm). The subject's ECG HR was 116bpm at visit 13. The rhythm on that ECG was reported as sinus tachycardia. The tachycardia episodes were described as lasting one day, and were associated with chest pain. There was no event recorder or Holter monitor data. The narrative did not describe associated lightheadedness or syncope.
LYAB-062-5525 This 9-year-old EM male developed tachycardia after 54 days of treatment with atomoxetine. An elevated pulse was recorded at visit 8 (HR=126bpm) with a HR of 114 on the ECG (rhythm reported as sinus tachycardia). Heart racing/pounding was recorded as an AE at visit 9 (pulse=104bpm, ECG HR=95bpm). Baseline pulse was 86bpm.

Rash
HFBE-015-0556 This 9-year-old EM male developed a "body skin rash" after 15 days of atomoxetine treatment. Neither the narrative nor the CRF described the rash or provided an outcome for this event. The adverse event data set listed the event as resolved after 2 days.

LYAB-090-6023 This 14-year-old PM male developed a rash on the left side, upper trunk after 40 days of treatment with atomoxetine. The rash was not further described, and the narrative did not mention if the rash improved following discontinuation but the CRF included a stop date suggesting resolution.

Allergic Reaction

LYAC-019-7806 This 15-year-old EM male developed an allergic reaction 2 days after starting atomoxetine. He developed swelling, pruritis, and rash. He was treated with prednisone for 4 days. The pruritis, swelling and rash reportedly resolved 1 week later.

Hypertension

LYAB-052-5125 This 8-year-old EM male developed "mild" hypertension 13 days after starting atomoxetine. The subject's baseline BP was 117/81 and at visit 5 the subject had a BP of 122/82 in the vital sign section of the CRF while the comments section noted a BP of 120/94. The hypertension resolved 10 days after stopping atomoxetine.

Liver Function Tests Abnormal

LYAB-084-4924 This 8-year-old EM female developed increased LFT first noted after 109 days of treatment with atomoxetine. At visit 1, the subject had an AST=59 and an ALT=49. At visit 2, her AST =63 and ALT=50. At visit 8 (5 weeks of therapy) AST=71 and ALT=87. At visit 11 AST=76 and ALT=68. CPK at baseline was 973. The subject did not have a total bilirubin at baseline but the highest recorded total bilirubin was 0.3mg/dL at visit 2. CPK went to 1,808 during the study.

Tremor

LYAB-055-5253 This 16-year-old EM male developed shaking hands 157 days after starting atomoxetine. The data set stated that the tremors improved 28 days after discontinuing atomoxetine.

Urticaria

LYAB-041-4642 This 16-year-old EM male developed itching and urticaria after 45 days of atomoxetine. The CRF also noted aching, swollen joints and generalized itching. He was seen at an urgent care center and treat with loratidine, and a Medrol dose pack and was advised to stop the study drug. Two days later the subject went to an emergency department with continuing symptoms. The discharge diagnosis at that time was erythema multiforme. The data set described the event as not resolved at the last visit.

Child and Adolescent acute placebo controlled ADHD studies using BID dosing

The sponsor reported that 3.8% (13/340) atomoxetine subjects discontinued for adverse events compared to 1.4% (3/207) placebo subjects. Nervousness was the only AE leading to discontinuation of more than one atomoxetine subject (n=2).

Adult Acute Placebo-controlled ADHD Trials

The sponsor reported that 8.5% (23/270) atomoxetine subjects discontinued for adverse events compared to 3.4% (9/266) placebo subjects. No single AE was responsible for this observed difference in discontinuation due to AE risk. Insomnia (n=3), chest pain (n=2), palpitation (n=2), and urinary retention (n=2) were the only AEs leading to discontinuation of more than 1 atomoxetine subject in these studies. One atomoxetine adult discontinued for urticaria, and one for hypertension.

Palpitations

LYAO-21-3585 This 42 year old EM female developed palpitations 14 days after starting atomoxetine treatment. The ECG from the onset date had a HR of 72bpm. At discontinuation the

event had not resolved and the ECG HR was 77bpm. Baseline pulse was 60bpm with the highest recorded on drug pulse of 80bpm.
LYAA-69-2015 This 28 year old EM Hispanic male developed palpitations on the day of randomization to study drug. The event was described as racing heart and was associated with parasthesias. He continued on study drug for 33 days. The events were reported as resolved. The subject's baseline pulse was 80bpm and the highest recorded on drug pulse was 86bpm.

Hypertension
LYAO-79-3108 This 43 year old EM male discontinued for high blood pressure after approximately 40 days on study drug. The visit 1 BP was 153/94. Visit 5, the subject had a blood pressure of 141/99. The subject had a past medical history significant for hypertension. The CRF did not suggest associated symptoms.

Hypotension
LYAA-77-2524 This 57 year old EM male developed an AE of hypotension along with sweats, hot flashes, and nausea. Baseline BP was 129/81. On the day of discontinuation, BP was 120/80.

Urticaria
LYAA-106-1114 This 35 year old EM male discontinued for hives. He had a past medical history significant for hives that occurred with stress and the severity of this AE waxed and waned during the study.

Among the Safety Update discontinuations for adverse events were two cases of hypertension in adults enrolled in ongoing extension trials. Those cases are summarized below.

Hypertension
LYAR-55-5920 This 59 year old male with a history of hypertension, controlled with atenolol, developed increased blood pressure and discontinued from the trial. This subject had a baseline BP of 140/88mmHg. While receiving placebo in the preceding controlled trial, his highest recorded BP was 160/100mmHg. Approximately one month after starting atomoxetine, this subject had a blood pressure of 150/100mmHg. Atenolol was switched to telmisartan and the subject discontinued from the trial.
LYAR-55-5924 This 28 year old male received atomoxetine in a prior controlled trial, had a high blood pressure reading after a total of 121 total days of treatment and discontinued. During the controlled trial, on treatment BP ranged from 110/70-150/90mmHg. During the extension trial, he had an on treatment BP of 190/110mmHg and atomoxetine was stopped. The blood pressure elevation was reportedly resolved 2 days after stopping atomoxetine.

Poor Metabolizers from Child and Adolescent ADHD Studies
In the NDA, the sponsor reported that 4.8% (6/124) of PM subjects discontinued for AEs compared to 4.2% (76/1,798) of EM subjects (ISS, p.258). In the Safety Update, the sponsor reported that 3.3% (6/181) of PM subjects discontinued for AEs compared to 4.2% (82/1,974) EM subjects (Safety Update, p.31). No AE led to discontinuation of more than 1 PM subject. The AEs leading to discontinuation among PMs were somnolence, anxiety, headache, tachycardia, constipation, and rash (table SU.4.6.1, p.31 Safety Update).

When considering only those atomoxetine subjects who received a maximum daily dose ≥1.2mg/kg/day, the discontinuation due to AE risk among PMs in the NDA was 3% (2/67) and among EMs was 3% (39/1,290) (ISS, p.258). In the safety update, the discontinuation due to AE risk among PM subjects who received a maximum daily dose ≥1.2mg/kg/day was 1.8% (2/112) compared to 3% (43/1449) among EM subjects (Safety

Update, p.32). Since PM subjects had shorter mean exposure time than EM subjects in this analysis (Safety Update, p.26), I calculated discontinuation for AEs rates using person time in the denominator of the risk calculation. The rate of discontinuation for AEs among EM subjects was 6.3/100PY (43/679PY) compared to 7.1/100PY (2/28PY) among PM subjects.

Child and Adolescent Acute Placebo Controlled Once Daily ADHD Group
The discontinuation due to AE risk was 2.4% (2/85) for the atomoxetine QD group and 1.2% (1/86) for the placebo group. The AEs leading to discontinuation for the atomoxetine QD subjects were somnolence and vomiting (ISS, p.333).

Child and Adolescent Acute Methylphenidate Controlled ADHD Group
The sponsor reported that 5.1% (16/313) of atomoxetine subjects discontinued for adverse events from these trials compared to 8.5% (7/82) of the methylphenidate treated subjects (Table ISS. 5.3.3, p. 364). The sponsor did not provide a comparison of the frequency of specific adverse events leading to discontinuation by treatment.

Depression and Urinary Incontinence Trials
The sponsor summarized the events leading to discontinuation from their adult placebo controlled depression trials by treatment in table ISS.5.5.8. Almost 13% (145/1,153) of atomoxetine subjects discontinued for adverse events compared to 4.6% (30/654) of placebo subjects (p<.001). In the following table, I provide the risks by treatment for events leading to discontinuation of at least 3 atomoxetine subjects and at least twice as frequently compared to placebo.

Events leading to discontinuation of at least 3 atomoxetine subjects and at least twice as frequently as placebo in historical adult depression trials

Event	Atomoxetine N=1,153 % (n)	Placebo N=654 % (n)	p value
Discontinued for AE	12.6% (145)	4.6% (30)	<.001
Insomnia	1.8% (21)	0.2% (1)	.001
Somnolence	0.9% (10)	0.2% (1)	.066
Vasodilatation	0.8% (9)	0	.031
Sweating	0.7% (8)	0	.057
Thinking Abnormal	0.7% (8)	0	.057
Urinary Retention	0.5% (6)	0	.093
Urination Impaired	0.5% (6)	0	.166
Tachycardia	0.3% (4)	0	.303
Constipation	0.3% (3)	0	.558
Dizziness	0.3% (3)	0	.558
Tremor	0.3% (3)	0	.558
Urinary Frequency	0.3% (3)	0	.558

From Sponsor's Table ISS.5.5.8, p.503-4.

Using a table of discontinuations from all depression trials I looked for events of special interest (Table 2.1, p.130, 3/28/02 submission). There were no discontinuations for liver failure, renal failure, aplastic anemia, rhabdomyolysis, Stevens Johnson syndrome or toxic epidermal necrolysis. There were two discontinuations for abnormal liver function tests, one for twitching, one for angioedema, and one for urticaria.

4.6.5 Treatment Emergent Adverse Events
Child and Adolescent overall ADHD studies BID dosing

The sponsor provided a listing of all treatment emergent adverse events from the child and adolescent ADHD trials as Table ISS.4.2.6. From that list, I selected the events occurring in at least 5% of the atomoxetine subjects.

Treatment Emergent Adverse Events Occurring in at Least 5% of Atomoxetine Subjects, Child and Adolescent overall ADHD studies BID dosing

Event	Atomoxetine N=1,933 % (n)
Headache	31.9% (617)
Rhinitis	26.8% (518)
Abdominal Pain	21.3% (411)
Pharyngitis	15.1% (292)
Anorexia	14.6% (282)
Vomiting	14.1% (272)
Cough Increased	12.1% (234)
Nausea	11.0% (212)
Fever	10.8% (209)
Insomnia	10.6% (205)
Somnolence	10.6% (204)
Nervousness	10.0% (193)
Accidental Injury	9.4% (181)
Asthenia	9.2% (177)
Flu Syndrome	8.5% (164)
Pain	6.9% (134)
Infection	6.6% (127)
Diarrhea	6.4% (123)
Rash	6.3% (121)
Dizziness	6.1% (117)
Emotional Lability	6.1% (117)
Dyspepsia	5.7% (111)
Sinusitis	5.3% (103)
Constipation	5.0% (96)

From Sponsor's Table ISS.4.2.6, pp.145-9.

I also examined the list for less common AEs of interest. I found the following events and risks: Allergic reaction 4.9%, (n=94); Tachycardia 2.5%, (n=49); Postural Hypotension 1.2% (n=23); Photosensitivity Reaction 0.8%, (n=15); Hypertension 0.7% (n=13); Urticaria 0.5% (n=10); Syncope 0.4% (n=7); Convulsions 0.2% (n=4); Anaphylactoid reaction 0.1%, (n=1); Pulmonary Hypertension 0.1% (n=1); Withdrawal syndrome 0.1% (n=1). There were no AEs coded as liver failure, renal failure, rhabdomyolysis, aplastic anemia, Stevens Johnson syndrome, or toxic epidermal necrolysis.

I examined the AE data set to further characterize these less common events. I compared the ACTTERM variable (verbatim term) to the Event variable (COSTART term). For the allergic reaction events, many of these AEs referred to environmental and food allergies. The photosensitivity event subsumed a sunburn verbatim term. I found that the COSTART term Pulmonary Hypertension was associated with a verbatim term of Dry Heaves, an apparent mistake. Several of the verbatim terms for the syncope events mentioned vasovagal reactions. In the following table I summarize some of the details for the syncope AEs.

Details for Syncope AEs from Pediatric and Adolescent ADHD Trials

Subject/ Metabolic	Demographics	ATX Dose /Days to onset	Verbatim
HFBE 165/EM	9yrs, Male	40mg/33 days	Fainted
HFBE 321/EM	13yrs, Male	20mg/5 days	Fainting spell
HFBF 1172/EM	10yrs, Male	50mg/152 days	Vasovagal reaction
HFBF 1244/EM	11yrs, Female	60mg/62 days	Blackout
LYAB 4330/EM	13yrs, Male	?/15 days	Syncope
LYAB 6441/PM	11yrs, Male	50mg/40 days	Vasovagal reaction
LYAB 5747/PM	11yrs, Male	40mg/55 days	Vagal shock

Data from AE electronic data sets, 10/01, 12/01 submissions

I identified 4 subjects with treatment emergent events coded as convulsions. Since these events were not classified as serious, or listed as the reason for discontinuation, there were no narratives. I used the submitted data sets to construct the following summaries for these cases.

HFBF 017-1649, A 10-year-old male EM received placebo in prior controlled trial, entered extension. Sixteen days after starting atomoxetine, he had a "psychomotor seizure" that lasted 15 seconds and was associated with a fall. The subject had been taking atomoxetine 10mg/day at the time. Atomoxetine was temporarily held and the patient had an EEG that was normal. Atomoxetine was restarted and the subject continued in the trial for over 300 days, reaching a maximal atomoxetine dose of 50mg/day, without additional episodes. The subject had normal blood pressure measurements throughout the study, and aside from a low MCV that was present prior to starting atomoxetine, lab results were unremarkable. The subject had a baseline QTc (Fridericia) of 405, and his longest on drug QTc was 412. The subject's only recorded concomitant medication was aspirin.

LYAB-056-5309, An 8-year-old male EM entered this open label trial and after 6 days of treatment experienced "possible seizure". He was taking atomoxetine 15mg/day at the time of the event. The subject also had AEs of fever, headache, and vomiting at that time. The parents described the events as two ten-minute episodes of staring into space, no response to calling his name, inappropriate giggling, and drooling. He continued in the trial for a total of 95 days of treatment, reaching a maximal atomoxetine dose of 60mg/day, without additional episodes. He withdrew for lack of efficacy. On treatment BP ranged from 90-110/64-80mmHg. Lab results during the study were unremarkable. This subject had a baseline QTc (Fridericia) of 415 and his highest recorded QTc on atomoxetine was 420. Ibuprofen was the only concomitant medication around the time of the event.

LYAB-059-5416, A 7-year-old female EM with no history of seizures enrolled in this open label trial and twenty one days after starting atomoxetine, on a dose of 20mg/day, experienced a convulsion AE. The comment field of the CRF contained no notation or description for this event. No other AEs were reported at that time. The subject was listed as discontinuing on study day 22 due to physician decision. Lab results during the study were unremarkable. On treatment BP measurements ranged from 93-103/47-76mmHg. This subject had a baseline QTc (Fridericia) of 397 and her longest on treatment QTc was 396. Concomitant medications were topical fluticasone propionate, and lidocaine/prilocaine (Emla patch).

LYBB-019-8942, A 10-year-old male EM with no history of seizures enrolled in this open label trial and after 41 days of treatment, on a dose of 35mg/day, experienced a "convulsive syncope" AE. Other AEs reported around that time were abdominal pain, asthenia, pharyngitis, and rhinitis. The comment field of the CRF contained no notation or description for this event. The patient was classified as completing the study period. Lab results during the study were unremarkable. On treatment BP measurements ranged from 92-121/61-84mmHg. Pre treatment QTc (Fridericia) results were 390 and 404. The highest on treatment QTc for this subject was 417. Concomitant

medications around the time of the event were acetaminophen, penicillin, phenylephrine/pheylpropanolamine/brompheniamine, and ibuprofen.

Child and Adolescent Acute Placebo Controlled ADHD Studies Using BID Dosing
The sponsor provided table ISS.4.1.8 that includes the adverse event risks by treatment for these trials. In the following table, I present the events occurring in at least 3 atomoxetine subjects and at least twice as frequently compared to placebo.

Adverse Events Occurring in at least 3 Atomoxetine Subjects and at least Twice as Frequently Compared to Placebo in Child and Adolescent Acute Placebo Controlled ADHD Studies Using BID Dosing

Event	Atomoxetine N=340 % (n)	Placebo N=207 % (n)	p value
Anorexia	15% (51)	6.3% (13)	.002
Emotional Lability	5.3% (18)	2.4% (5)	.126
Dyspepsia	3.5% (12)	1.4% (3)	.184
Constipation	2.9% (10)	1.4% (3)	.388
Weight Loss	2.4% (8)	0	.027
Hostility	2.1% (7)	0.5% (1)	.269
Postural Hypotension	1.8% (6)	0.5% (1)	.262
Pruritis	1.8% (6)	0	.088
Gastroenteritis	1.5% (5)	0.5% (1)	.416
Tachycardia	1.5% (5)	0.5% (1)	.416
Chest pain	1.2% (4)	0	.303
Mydriasis	1.2% (4)	0	.303
Albuminuria	0.9% (3)	0	.293
ECG abnormal	0.9% (3)	0	.293

Other events of potential interest: Hypertension: atomoxetine 0.6% (2/340), placebo 0; Urticaria: atomoxetine 0.6% (2/340), placebo 0.5% (1/207); Twitching: atomoxetine 0.6% (2/340), placebo 0.5% (1/207); Palpitation: atomoxetine 0.6% (2/340), placebo 0.5% (1/207).
From Sponsor's Table 4.1.8, pp.95-99.

In addition to the AEs collected by open-ended questions, the sponsor analyzed AEs identified from a questionnaire (BBAEQ-M). In the following table, I identify BBAEQ-M AEs occurring or worsening in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo.

BBAEQ-M Adverse Events Occurring or Worsening in at least 1% of Atomoxetine subjects and at least twice as frequently compared to Placebo, Child and Adolescent Acute Placebo Controlled ADHD Studies Using BID Dosing

Event	Atomoxetine N=335 % (n)	Placebo N=204 % (n)	p value
Nightmares	8.5% (28)	4.1% (8)	.073
Decreased Appetite	33.4% (109)	13.3% (26)	<.001
Heart Racing	5.4% (18)	2.5% (5)	.126
Dizzy	10.8% (36)	5.4% (11)	.040

From sponsor's table ISS.4.1.10, p.107.

Adult Acute Placebo-controlled ADHD Trials
The sponsor provided table ISS.4.3.8 that includes the adverse event risks by treatment for these trials. In the following table, I present the events occurring in at least 3 atomoxetine subjects and at least twice as frequently compared to placebo.

Adverse Events Occurring in at least 3 Atomoxetine Subjects and at least Twice as Frequently Compared to Placebo in Adult Acute Placebo Controlled ADHD Studies

Event	Atomoxetine N=269 % (n)	Placebo N=263 % (n)	p value
Dry Mouth	21.2% (57)	6.8% (18)	<.001
Insomnia	20.8% (56)	8.7% (23)	<.001
Nausea	12.3% (33)	4.9% (13)	.003
Anorexia	11.5% (31)	3.4% (9)	<.001
Constipation	10.8% (29)	3.8% (10)	.002
Libido decreased	7.1% (19)	1.9% (5)	.006
Dizziness	6.3% (17)	1.9% (5)	.015
Impotence	9.8% (17)	1.2% (2)	<.001
Myalgia	5.6% (15)	2.7% (7)	.126
Sweating	5.2% (14)	0.8% (2)	.004
Dysuria	4.8% (13)	0.4% (1)	.002
Abnormal Ejaculation	6.3% (11)	2.3% (4)	.111
Palpitation	4.1% (11)	1.1% (3)	.054
Vasodilitation	4.1% (11)	1.9% (5)	.204
Nervousness	3.3% (9)	1.5% (4)	.261
Chest Pain	3% (8)	1.5% (4)	.383
Chills	3% (8)	1.1% (3)	.222
Surgical Procedure	3% (8)	1.5% (4)	.383
Tachycardia	3% (8)	0.8% (2)	.106
Dysmenorrhea	7.4% (7)	3.3% (3)	.331
Menstrual disorder	7.4% (7)	3.3% (3)	.331
Urinary retention	2.6% (7)	0	.015
Urination impaired	2.6% (7)	0	.015
Prostatic disorder	3.4% (6)	0	.030
Unexpected benefit	2.2% (6)	0	.030
Weight loss	2.2% (6)	0.8% (2)	.286
Flatulence	1.9% (5)	0.8% (2)	.450
Euphoria	1.5% (4)	0	.124
Pruritis	1.5% (4)	0	.124
Tremor	1.5% (4)	0.4% (1)	.373
CNS stimulation	1.1% (3)	0	.249
Hair disorder	1.1% (3)	0	.249
Herpes simplex	1.1% (3)	0.4% (1)	.624
Laryngitis	1.1% (3)	0.4% (1)	.624
Neurosis	1.1% (3)	0	.249
Oliguria	1.1% (3)	0	.249
Rectal disorder	1.1% (3)	0	.249

Other adverse events of interest: Hypertension: atomoxetine 0.7% (n=2), placebo 1.9% (n=5); Rash: atomoxetine 3% (n=8), placebo 1.9% (n=5); Urticaria: atomoxetine 0.7% (n=2), placebo 0; Postural Hypotension: atomoxetine 0.4% (n=1), placebo 0.
From Sponsor's Table ISS.4.3.8, pp. 201-5.

In addition to the AEs collected by open-ended questions, the sponsor analyzed AEs identified from a questionnaire (AMDP-5). In the following table, I identify AMDP-5 AEs occurring or worsening in at least 1% of atomoxetine subjects and at least twice as frequently compared to placebo.

AMDP-5 Adverse Events Occurring or worsening in at least 1% of Atomoxetine subjects and at least twice as frequently compared to Placebo, Adult Acute Placebo Controlled ADHD Studies

Event	Atomoxetine N=256 % (n)	Placebo N=259 % (n)	p value
Interrupted Sleep	43.4% (105)	22% (53)	<.001
Decreased Appetite	39.5% (101)	18.9% (49)	<.001
Excessive Thirsty	31.8% (81)	15.4% (39)	<.001
Dry Mouth	46.5% (118)	19% (49)	<.001
Nausea	23.9% (61)	11.6% (30)	<.001
Constipation	25.9% (66)	11.3% (29)	<.001
Increased Perspiration	19% (48)	7.4% (19)	<.001
Micturition difficulties	20.9% (53)	8.5% (22)	<.001
Hot flashes	18.6% (47)	5.4% (14)	<.001
Chills	18.4% (47)	8.1% (21)	<.001
Delayed Ejaculation	12.7% (21)	4.1% (7)	.005
Dependent Edema	1.2% (3)	0.4% (1)	.371

Other events of interest: Dizziness ATX 18.8% (48), PBO 9.7% (25); Palpitations ATX 12.1% (31), PBO 6.2% (16); Decreased libido ATX 21.7% (53), PBO 12% (30) Parasthesia ATX 11.9% (30), PBO 6.6% (17)
From Sponsor's table ISS.4.3.10., p.214.

Poor Metabolizers from Child and Adolescent ADHD Studies
Using the AE table for Pediatric ADHD trials BID dosing above, I identified AEs that occurred more frequently among atomoxetine subjects than placebo subjects. For those events occurring more commonly among atomoxetine subjects, I identified the AEs with an increased risk among PM subjects compared to EM subjects. Those events are included in the table below.

Comparison of the Risk for Selected AEs among EM and PM Subjects from Pediatric ADHD Studies, NDA Submission

Event	EM, N=1,798 % (n)	PM, N=124 % (n)	p value
Emotional Lability	6% (108)	7.3% (9)	.559
Constipation	4.9% (89)	5.6% (7)	.670
Weight Loss	3.1% (55)	5.6% (7)	.115
Hostility	2.8% (51)	4% (5)	.115
Tachycardia	2.5% (45)	3.2% (4)	.553
Chest Pain	2.2% (39)	4% (5)	.251
Mydriasis	0.6% (10)	1.6% (2)	.179
Albuminuria	0.2% (4)	0.8% (1)	.284

Other events of interest: Urinary incontinence: PM 2.4% (n=3), EM 1% (n=18) p=.149; Syncope: PM 1.6% (n=2), EM 0.3% (n=5) p=.07; urticaria: PM 0.8% (n=1), EM 0.5% (n=9) p=.488.
From Sponsor's Table ISS.5.1.9, pp. 263-278.

The results did not appear to change meaningfully when only those exposed to>=1.2mg/kg/day were considered in the analysis, based 67 PM subjects exposed to this dose (Table ISS.5.1.10).

I was not able to repeat the above analysis using data from the Safety Update since the sponsor used COSTART to code AE terms in the NDA and MedDRA in the Safety Update. In the table below, I identify AEs that occurring in at least 1% of PM subjects and at least twice as frequently compared to EM subjects in the Safety Update. The

sponsor reported that in this analysis the mean exposure among EM subjects (141 days) was similar to the mean exposure among PM subjects (123 days). Because of this similarity, relative risks for AEs based on person time in the denominator would be similar to risks calculated using persons. For convenience, I present the risks calculated by the sponsor.

AE Risks Occurring in at least 1% of PM subjects and at least Twice as Frequently Compared to EM Subjects from Pediatric ADHD Studies, Safety Update

Event	EM, N=1,974 % (n)	PM, N=181 % (n)	p value
Mood Swings	1.9% (38)	3.9% (7)	.096
Sedation	1.7% (34)	4.4% (8)	.021
Tachycardia NOS	1.1% (21)	2.2% (4)	.152
Enuresis	0.9% (18)	2.2% (4)	.107
Hypersomnia	0.8% (15)	1.7% (3)	.188
Depressed Mood	0.7% (13)	1.7% (3)	.145
Animal bite	0.6% (11)	1.7% (3)	.107
Mydriasis	0.6% (11)	2.2% (4)	.031
Hand Fracture	0.5% (10)	1.1% (2)	.267
Tremor NEC	0.5% (10)	2.2% (4)	.025
Feeling Jittery	0.4% (8)	2.2% (4)	.014
Vision Blurred	0.4% (8)	1.1% (2)	.203
Weakness	0.3% (5)	1.1% (2)	.111
Syncope	0.2% (3)	1.1% (2)	.059
Vasovagal attack	0.1% (1)	1.1% (2)	.020
Laryngitis	0	1.1% (2)	.007

Other events of interest: urticaria: PM 1.1% (n=2), EM 0.6% (n=12), hypertension: PM 0.6% (n=1), EM 0.2% (n=4).
From Sponsor's Table SU.4.6.3, pp.34-44.

When considering only the atomoxetine subjects who received a maximum dose of ≥1.2mg/kg/day, the list of AEs occurring in at least 1% of PM subjects and at least 2 times greater than EM subjects changed. Animal bite, mydriasis, depressed mood, tremor, feeling jittery, syncope, and laryngitis remained on the list. The following events also met the listing criteria: lethargy, early morning awakening, increased activity, and dysmenorrhea (Table SU.4.6.4, pp.45-55).

The sponsor reported that for the analysis of subjects who received a maximum dose of ≥1.2mg/kg/day, the mean exposure among EM subjects (171 days) was almost double the mean exposure among PM subjects (90 days) (Safety Update, p.26). I calculated rates for AEs using the number of persons with a particular AE in the numerator and person years in the denominator ({mean exposure in days x number exposed}/365) to explore the impact of this differential duration of exposure. The following table summarizes AEs occurring in at least 2 PM subjects and at least twice as frequently compared to EM subjects.

FDA analysis: Rates for AEs Occurring in at least 2 PM subjects and at least twice as Frequently Compared to EM Subjects from Pediatric ADHD Studies, Subjects who received a Maximum Atomoxetine dose of ≥1.2mg/kg/day

Event	EM, 679 PY rate/100PY (n)	PM, 28 PY rate/100PY (n)	RR
Gastroenteritis viral NOS	9.0 (61)	25.0 (7)	2.8

Chest pain NEC	5.0 (34)	10.7 (3)	2.1
Mood swings	5.0 (34)	10.7 (3)	2.1
Sedation	4.4 (30)	14.3 (4)	3.3
Limb injury NOS	4.1 (28)	10.7 (3)	2.6
Lethargy	3.8 (26)	14.3 (4)	3.8
Middle Insomnia	3.8 (26)	10.7 (3)	2.8
Aggression	3.4 (23)	10.7 (3)	3.1
Palpitations	2.7 (18)	7.1 (2)	2.6
Early Morning Awakening	2.4 (16)	10.7 (3)	4.5
Pruritis NOS	2.2 (15)	7.1 (2)	3.2
Increased Activity	1.9 (13)	7.1 (2)	3.7
Animal Bite	1.5 (10)	7.1 (2)	4.7
Mydriasis	1.3 (9)	10.7 (2)	8.2
Depressed Mood	1.2 (8)	7.1 (2)	5.9
Tremor NEC	1.2 (8)	10.7 (3)	8.9
Feeling Jittery	0.6 (4)	7.1 (2)	11.8
Syncope	0.1 (1)	7.1 (2)	71.0
Laryngitis	0	7.1 (2)	

Other events of interest: Vomiting EM 33/100PY (228), PM 53/100PY (15) RR=1.6; Dermatitis NOS EM 8.4/100PY (57), PM 14.3/100PY (4) RR=1.7; Initial Insomnia EM 6/100PY (41), PM 11/100PY (3) RR=1.8; Urticaria NOS EM 1.2/100PY (8), PM 3.6/100PY (1) RR=3

Child and Adolescent Acute Placebo Controlled Once Daily ADHD Group
The sponsor listed the adverse events from the once daily pediatric study in table ISS.5.2.3. In the following table, I summarize those events occurring in at least 3 atomoxetine once daily patients and that occurred at least twice as frequently compared to placebo.

Adverse events occurring in at least 3 atomoxetine subjects and at least twice as frequently compared to placebo in child and adolescent acute placebo controlled ADHD study using QD dosing

Event	Atomoxetine N=85 % (n)	Placebo N=85 % (n)	p value
Anorexia	20% (17)	5.9% (5)	.011
Abdominal Pain	16.5% (14)	8.2% (7)	.161
Vomiting	15.3% (13)	1.2% (1)	.001
Nausea	11.8% (10)	2.4% (2)	.032
Asthenia	10.6% (9)	1.2% (1)	.018
Dyspepsia	9.4% (8)	0	.007
Fever	7.1% (6)	3.5% (3)	.496
Dizziness	5.9% (5)	0	.059
Diarrhea	3.5% (3)	1.2% (1)	.621
Dry Mouth	3.5% (3)	1.2% (1)	.621

Other events of interest: Tachycardia: atomoxetine 0, placebo 2.4% (n=2); Palpitation: atomoxetine 2.4% (n=2), placebo 0; Urticaria, hypertension, and syncope were not reported as treatment emergent AEs in this study.
From Sponsor's Table ISS.5.2.3, pp.335-6.

Child and Adolescent Acute Methylphenidate Controlled ADHD Group
The sponsor listed the adverse events from the methylphenidate-controlled studies in table ISS.5.3.5. In the following table, I summarize those events occurring in at least 3 atomoxetine patients and that occurred at least twice as frequently compared to methylphenidate.

Adverse Events occurring in at least 3 Atomoxetine Subjects and at least Twice as Frequently Compared to Methylphenidate in Methylphenidate Controlled ADHD studies

Event	Atomoxetine N=313 % (n)	Methylphenidate N=77 % (n)	p value
Vomiting	13.1% (41)	6.5% (5)	.118
Asthenia	7.0% (22)	1.3% (1)	.060
Allergic Reaction	3.5% (11)	1.3% (1)	.474
Sinusitis	3.5% (11)	1.3% (1)	.474
Constipation	3.2% (10)	0	.221
Hostility	3.2% (10)	1.3% (1)	.700
Unexpected benefit	2.9% (9)	0	.215
Abnormal dreams	2.6% (8)	0	.365
Chest pain	2.6% (8)	1.3% (1)	1.00
Personality disorder	2.6% (8)	1.3% (1)	1.00
Gastrointestinal disorder	1.9% (6)	0	.603
Sleep disorder	1.9% (6)	0	.603
Nausea and vomiting	1.6% (5)	0	.588
Gastroenteritis	1.3% (4)	0	1.00
Tooth disorder	1.3% (4)	0	1.00
Conjunctivitis	1.0% (3)	0	1.00
Ear disorder	1.0% (3)	0	1.00
Leukopenia	1.0% (3)	0	1.00
Mydriasis	1.0% (3)	0	1.00
Otitis Externa	1.0% (3)	0	1.00
Surgical Procedure	1.0% (3)	0	1.00

From Sponsor's Table ISS.5.3.5, p.367-371.

Depression and Urinary Incontinence Trials

In their summary of data from depression and urinary incontinence trials, the sponsor provided table 6, which listed the treatment emergent adverse events from placebo controlled depression trials. Table 6 included only the AEs that occurred in at least 5% of atomoxetine subjects. In the following table, I list the events from table 6 that occurred at least twice as frequently among atomoxetine subjects compared to placebo.

Treatment Emergent AEs from Depression and Urinary Incontinence Trials that Occurred in at least 5% of Atomoxetine Subjects and Twice as Commonly when compared to Placebo

Event	Atomoxetine n=1,153 % (n)	Placebo n=654 % (n)	p value
Insomnia	35.6% (397)	16.8% (110)	<.001
Dry Mouth	33.7% (389)	16.1% (105)	<.001
Nausea	23.6% (272)	10.9% (71)	<.001
Constipation	17.2% (198)	6.4% (42)	<.001
Anorexia	9.3% (107)	2.3% (15)	<.001
Sweating	8.8% (21)	3.2% (21)	<.001

Other events of interest Dizziness: atomoxetine 16.6% (n=191), placebo 9.2% (n=60) p <.001; Palpitations atomoxetine 6.8% (n=78), placebo 3.8% (n=25) p=.011.

4.6.6 Laboratory Data

The sponsor's analyses of lab data focused on discontinuations for abnormal lab results, mean change from baseline to endpoint, and outliers. The sponsor provided the lab data reference ranges (pediatric, adult) used in their analyses as Appendix ISS.6. I reviewed

these reference ranges and they appeared appropriate. The sponsor used these limits to identify outliers. In addition to the analyses provided by the sponsor, I used the submitted lab data sets to examine extreme outliers for selected lab tests.

Child and Adolescent overall ADHD studies BID dosing

Discontinuations

The sponsor identified two atomoxetine subjects from these trials that discontinued for a lab abnormality. Those discontinuations are summarized below

Subject **LYAB-084-4924**, an 8-year-old EM female, discontinued for abnormal transaminases (see above). This subject had abnormally high transaminases at baseline that increased slightly on atomoxetine and were not associated with increased total bilirubin. The highest recorded AST was 76 and ALT was 87.

Subject **LYAB-064-5616**, a 9-year-old EM male, discontinued from the study for mononucleosis which was mapped to the preferred term lymphocytosis.

Mean change data

The sponsor provided table ISS.4.2.9 (Chemistry), table ISS.4.3.11 (Hematology), and table ISS.4.3.13 (Urinalysis) that summarized the mean change laboratory data for these studies. In the following table, I list selected analytes with statistically significant changes from baseline from these studies.

Laboratory Mean change from Baseline Results, Child and Adolescent Overall ADHD Studies Using BID Dosing

Analyte/(Units)	N	Change to Endpoint	p value
ALT/(U/L)	1,683	-0.93	<.001
CPK/(U/L)	1,682	-8.09	<.001
Alk Phos/(U/L)	1,680	-10.5	<.001
Calcium/(mmol/L)	1,686	0.02	<.001
Albumin/(g/L)	1,684	0.22	.003
Uric acid/(µmol/L)	1,686	-6.22	<.001
Creatinine/(µmol/L)	1,686	2.2 (0.03mg/dL)	<.001
Total bilirubin/(µmol/L)	1,387	-0.37	<.001
Hemoglobin	1,679	0.03	.002
Leukocyte count	1,679	0.15	.006
Platelets	1,668	8.25	<.001

From Sponsor's Tables ISS.4.2.9, ISS.4.2.11, and ISS 4.2.13

There are no comparator data for this safety group population.

Outliers

The sponsor provided outliers for these studies in table ISS.4.2.10 (Chemistry), table ISS.4.2.12 (Hematology) and Table ISS.4.2.14 (Urinalysis). Without a comparison group, these risks are difficult to interpret. In the following table I identify the lab tests where at least 10% of atomoxetine subjects had an abnormal treatment emergent result.

Laboratory Outlier Analysis, Child and Adolescent Overall ADHD studies Using BID Dosing

Analyte	Abnormality	N	%
Calcium	High	248/1,543	16.1%
Albumin	High	229/1,583	14.5%
Hematocrit	Low	223/1,473	15.1%

Leukocyte count	Low	171/1,580	10.8%
MCV	Low	202/1,523	13.3%
Platelets	High	158/1,523	10%
UA protein	Abnormal	139/1,300	10.7%

From Sponsor's Tables ISS.4.2.10, ISS.4.2.12, and ISS 4.2.14

Child and Adolescent acute placebo controlled ADHD studies using BID dosing
Mean change data
In the following table, I list selected lab tests with a significant difference for mean change from baseline when comparing atomoxetine to placebo.

Laboratory Mean change from Baseline Results, Child and Adolescent Acute Placebo Controlled ADHD studies Using BID Dosing

Analyte/(Units)	Treatment (n)	Change to Endpoint	p value
ALT/(U/L)	Atomoxetine (319)	-2.031	.011
	Placebo (199)	-1.015	
CPK/(U/L)	Atomoxetine (319)	-21.223	<.001
	Placebo (199)	-0.427	
Alk Phos/(U/L)	Atomoxetine (319)	-7.245	<.001
	Placebo (199)	9.201	
Calcium/(mmol/L)	Atomoxetine (320)	0.016	.008
	Placebo (199)	-0.012	
Chloride/(mmol/L)	Atomoxetine (318)	-0.321	.009
	Placebo (197)	0.406	
Total Protein	Atomoxetine (320)	1.219	<.001
	Placebo (199)	-0.352	
Albumin/(g/L)	Atomoxetine (320)	.0647	<.001
	Placebo (199)	-0.357	
Uric acid/(µmol/L)	Atomoxetine (320)	-17.082	<.001
	Placebo (199)	4.454	
Creatinine/(µmol/L)	Atomoxetine (320)	1.575	.047
	Placebo (199)	0	
Hematocrit	Atomoxetine (317)	0	.020
	Placebo (198)	-0.006	
Hemoglobin	Atomoxetine (318)	0.106	<.001
	Placebo (198)	-0.071	

From Sponsor's Tables ISS.4.1.11, ISS.4.1.13, and ISS 4.1.15

Outliers
The following table provides selected outlier risk results by treatment from the sponsor's analysis of lab outliers.