

Laboratory Outlier Analysis, Child and Adolescent Acute Placebo Controlled ADHD studies Using BID Dosing

Analyte	Abnormality	Treatment	% Abnormal (n)	p value
CPK	Low	Atomoxetine	10.3% (26)	.005
		Placebo	21.1% (28)	
Calcium	High	Atomoxetine	8.7% (25)	.005
		Placebo	2.2% (4)	
Phosphorus	High	Atomoxetine	2.3% (7)	.048
		Placebo	5.9% (11)	
UA-Protein	Abnormal	Atomoxetine	9.2% (24)	.862
		Placebo	9.9% (15)	

From Sponsor's Tables ISS.4.1.12, ISS.4.1.14, and ISS 4.1.16

Adult Acute Placebo-controlled ADHD Trials

Mean Change Data

The following table summarizes mean change from baseline data for selected labs collected during adult ADHD trials. The differences were generally small and of unknown clinical significance.

Laboratory Mean change from Baseline Results, Adult Acute Placebo Controlled ADHD Studies Using BID Dosing

Analyte/(Units)	Treatment (n)	Change to Endpoint	p value
CPK/(U/L)	Atomoxetine (242)	-7.198	.030
	Placebo (241)	16.718	
Alk Phos/(U/L)	Atomoxetine (244)	2.623	<.001
	Placebo (241)	-2.0	
Chloride/(mmol/L)	Atomoxetine (244)	-0.102	<.001
	Placebo (241)	0.759	
Albumin/(g/L)	Atomoxetine (243)	-0.053	.010
	Placebo (241)	-0.763	
Uric Acid	Atomoxetine (244)	-3.778	.012
	Placebo (241)	5.257	
Platelets	Atomoxetine (243)	7.617	.050
	Placebo (240)	1.329	

From Sponsor's Tables 4.3.11, 4.3.13, and 4.3.15

Outliers

The following table summarized the analytes with statistically significant outlier risk differences by treatment from the adult ADHD studies.

Laboratory Outlier Analysis, Adult Acute Placebo Controlled ADHD studies Using BID Dosing

Analyte	Abnormality	Treatment	% Abnormal (n)	p value
CPK	High	Atomoxetine	0.4% (1)	.003

Phosphorus	High	Placebo	4.7% (11)	.032
		Atomoxetine	4.6% (11)	
		Placebo	1.3% (3)	

From Sponsor's Tables 4.3.12, 4.3.14, and 4.3.16

Poor Metabolizers from Child and Adolescent ADHD Studies

Mean Change

For the lab tests where there appeared to be a significant difference between atomoxetine and placebo in pediatric ADHD subjects, I examined the mean change data from the extensive v. poor metabolizers to look for potential exposure level related differences. In the following table I summarize the results for those tests stratified by metabolic status.

Laboratory Mean change from Baseline Results by Metabolic Status (EM vs. PM)

Analyte/(Units)	Metabolic status (n)	Change to Endpoint	p value
ALT/(U/L)	Extensive (1560)	-0.894	.343
	Poor (115)	-1.443	
CPK/(U/L)	Extensive (1559)	-7.520	.146
	Poor (115)	-14.661	
Alk Phos/(U/L)	Extensive (1557)	-9.979	.058
	Poor (115)	-16.139	
Calcium/(mmol/L)	Extensive (1563)	0.022	.891
	Poor (115)	0.028	
Chloride/(mmol/L)	Extensive (1556)	-0.142	.571
	Poor (115)	0.043	
Total Protein/(g/L)	Extensive (1563)	0.681	.010
	Poor (115)	1.809	
Albumin/(g/L)	Extensive (1561)	0.208	.787
	Poor (115)	0.365	
Uric acid/(μmol/L)	Extensive (1563)	-5.750	.106
	Poor (115)	-13.137	
Creatinine/(μmol/L)	Extensive (1563)	2.194	.959
	Poor (115)	2.229	
Hematocrit	Extensive (1544)	-0.003	.027
	Poor (113)	0.002	
Hemoglobin	Extensive (1557)	0.026	.050
	Poor (114)	0.132	
Platelets	Extensive (1549)	7.312	.008
	Poor (111)	20.721	

From Sponsor's Tables 5.1.11, 5.1.15, and 5.1.19

Although there was no significant difference for platelets in pediatric/adolescent subjects, there was in adults and the poor metabolizers had a greater increase than the extensive metabolizers. The results were similar when the analysis was limited to EM/PM subjects who received a maximum atomoxetine dose of at least ≥ 1.2 mg/kg/day. EM subjects in this analysis had a mean platelet increase of 6.6 GI/L compared to a mean increase of 18.4 GI/L in PM subjects.

Outliers

There did not appear to be any meaningful differences in outlier risk when the sponsor compared the lab results for extensive and poor metabolizers.

Child and Adolescent Acute Placebo Controlled Once Daily ADHD Group

Mean change

As in the BID studies, the children in this study had slight mean decreases in ALT, CPK, UA and slight mean increases in calcium, total protein, albumin, and hemoglobin that were greater than placebo.

Outliers

The lab data outlier analyses from this study revealed no new differences between atomoxetine and placebo subjects.

Child and Adolescent Acute Methylphenidate Controlled ADHD Group

Mean change

There were statistically significantly greater mean decreases in AST, CPK, calcium, uric acid and WBC count among atomoxetine subjects compared to methylphenidate subjects. These changes are of unknown clinical significance.

Outliers

The percentage of low CPK outliers was statistically significantly higher (p=.022) among atomoxetine subjects (47%, 65/138) than methylphenidate subjects (25%, 9/36). No other analyte was statistically significantly different by treatment group.

Depression and Urinary Incontinence Trials

The sponsor provided only a mean change from baseline analysis for the lab data from placebo controlled trials adult depression trials. In the following table, I provide those results with a statistically significant difference between the atomoxetine and placebo groups.

Laboratory Mean Change from Baseline Results, Placebo Controlled Depression Trials

Analyte/(Units)	Treatment (n)	Change to Endpoint	p value
Hematocrit (%)	Atomoxetine (1,059)	-.0004	.004
	Placebo (614)	-.004	
Hemoglobin (mol/L)	Atomoxetine (1,064)	-.007	<.001
	Placebo (615)	-.090	
Erythrocyte count (tril/L)	Atomoxetine (1,064)	-.020	<.001
	Placebo (615)	-.069	
Platelet count (bill/L)	Atomoxetine (1,039)	6.367	.033

	Placebo (598)	1.476	
Alkaline Phos (units/L)	Atomoxetine (903)	-.122	.020
	Placebo (457)	-1.503	
Albumin	Atomoxetine (1,066)	-.332	.006
	Placebo (620)	-.727	
Glucose (mmol/L)	Atomoxetine (1,065)	-5.012	.001
	Placebo (620)	3.653	
Bilirubin/(µmol/L)	Atomoxetine (1,066)	.343	.044
	Placebo (620)	-.084	

From Sponsor's Table 9, Historical Data report, pp.27-9.

Sponsor's Hepatic Lab Test Analysis

In addition to the mean change from baseline and outlier analyses of lab markers of hepatotoxicity (AST, ALT, Total bilirubin) presented above, the sponsor performed additional analyses to look for evidence of atomoxetine related hepatotoxicity. These additional analyses consisted of a more detailed exploration of the distribution of lab results using outlier criteria detailed in a CDER, PhRMA and AASLD workshop. In neither the Child and Adolescent Overall ADHD analysis group nor the Adult Placebo Controlled group, did subjects have ALT elevations of at least 5 times ULN. No subjects in either analysis group experienced both ALT elevations of 3 times ULN AND total bilirubin elevation of at least 1.5 times ULN (Table ISS.6.3.1, p.566, Table ISS.6.3.2, p.567).

The sponsor provided narrative summaries for subjects with either ALT >3 times ULN or subjects with bilirubin >1.5 times ULN (Table ISS.6.3.3, p.569). None of these narratives suggested severe hepatic injury or hepatic failure.

Lab extreme outliers

To supplement the outlier analyses provided by the sponsor, I searched the lab data sets for extreme outliers for selected labs among atomoxetine treated subjects. The goal of this analysis was to identify very abnormal lab values that may provide useful signal information but that are too rare to allow informative quantitative risk comparisons by treatment. I used the Safety Update lab data sets provided by the sponsor, and for the lab data sets not updated, I used the original NDA submission data sets. The submitted lab data sets included the pediatric bid ADHD trials, and the adult ADHD trials. I reviewed the data from the qd pediatric study separately since the sponsor did not include these data with their pooled ISS data sets. This analysis includes lab data from all of the ADHD Phase II/III trials included in the NDA and Safety Update.

In the following table I list the lab tests and the outlier criteria used in this search.

FDA Analysis, Extreme Lab Outlier Cutoffs

Analyte	Outlier value
ALT,AST	≥150U
Total bilirubin	≥2mg/dL
Creatinine	≥1.8mg/dL
CPK	≥1,000U

Hemoglobin	≤10g/dL
WBC	≤2.5 THOU/uL
Platelet count	≤100 THOU/uL
	≥600 THOU/uL

After identifying lab values that met the extreme outlier criteria, I used the available information (data sets, narratives, CRFs, etc.) to create summaries of the cases.

ALT/AST

I identified one atomoxetine subject with a treatment emergent AST and/or ALT ≥150U. That case is summarized below

Subject LYAO3322, a 53-year-old EM male treated with atomoxetine for 78 days, discontinued the trial due to sponsor's decision. This subject had treatment emergent AEs that included gastric reflux, sore throat, increased CPK, lightheadedness, dry mouth, and decreased ability to urinate. LFT abnormalities were not among his recorded AEs. Baseline AST and ALT were normal (31,28 respectively). Day 14 AST and ALT were also normal. On day 49, AST was 181 and ALT was 58. Atomoxetine was held, and on day 56, AST was 36 and ALT was 44 off drug. Atomoxetine was restarted and the subsequent AST and ALT results were normal. This subject's baseline total bilirubin was 1.2mg/dL and was unchanged throughout the study. This subject had a CPK that was 511 at baseline, peaked at 6,712 on day 49, and was 323 at end of study.

Total Bilirubin

I identified four atomoxetine subjects with treatment emergent total bilirubin results ≥2.0mg/dL. Those cases are summarized below.

Subject HFBE 57, a 14-year-old EM male, had a total bilirubin of 0.9mg/dL at baseline. While on atomoxetine, total bilirubin ranged from 1.2 to 2.5mg/dL and at end study was 1.9mg/dL (ULN 1.2mg/dL). The subject had normal AST, ALT, GGT and alkaline phosphatase results throughout the trial. He had no GI AEs during the study.

Subject LYAB 4738, a 12-year-old PM male, had a total bilirubin of 1.6mg/dL at baseline (ULN 1.2mg/dL). His total bilirubin was 1.3mg/dL on day 57 of atomoxetine, and on day 85 it was 2.4mg/dL. This subject had slightly elevated alkaline phosphatase results (highest at baseline 439U/L, ULN 385U/L) and his AST, ALT and GGT were normal throughout the study. He reported the following GI related AEs during the study: decreased appetite and vomiting.

Subject LYAB 5827, a 16-year-old EM male had a total bilirubin of 1.7mg/dL at baseline (ULN 1.2mg/dL). His highest recorded total bilirubin was 2.3mg/dl, following 56 days of atomoxetine. His end study total bilirubin was 1.8mg/dL, following 84 days of atomoxetine. Throughout the study he had normal AST, ALT, GGT, and alkaline phosphatase results. He had no GI AEs during the study.

Subject LYAO 3426, a 21-year-old EM female had a total bilirubin of 1.4mg/dL at baseline (ULN 1.2mg/dL). After 42 days of atomoxetine, her total bilirubin was 2.0mg/dL and her last, off drug total bilirubin was 1.7mg/dL. Throughout the study, her AST,ALT,GGT and alkaline phosphatase results were normal. Her GI AEs were intermittent abdominal pain and constipation.

Creatinine

I identified one atomoxetine subject with a treatment emergent creatinine ≥1.8mg/dL. That case is summarized below.

Subject LYAB 4886, a 10 year old EM male, had a baseline creatinine of 0.6mg/dL. On study day 152 his creatinine was unchanged from baseline but on day 207 it increased to 2.9mg/dL with a

BUN of 25. On study day 213, his creatinine was 0.6mg/dL, while continuing atomoxetine. This subject had no AEs to explain this isolated lab finding and he completed the trial.

CPK

I identified twelve* atomoxetine subjects with treatment emergent CPKs ≥ 1000 U. Many of these subjects also had fractionated CPKs and the CK-MB relative index results did not suggest a cardiac origin. None of the subjects with these CPK results had myalgia adverse events or other adverse events that would explain the CPK elevation. There were also several subjects with CPK abnormalities of similar magnitude at baseline or on other treatments (placebo, active control).

*Atomoxetine subjects with treatment emergent CPK $> 1,000$ U: HFBF 1722, LYAB 4093, LYAB 4364, LYAB 5404, LYAB 4924, LYAC 7304, LYAQ 3295, LYAQ 4123, LYAA 2016, LYAA 2165, LYAA 2544, LYAO 3322

Hemoglobin

I identified 2 atomoxetine subjects with treatment emergent Hemoglobin results ≤ 10 g/dL. Those cases are described below.

Subject **HFBE 281**, an 8-year-old EM male had a normal hemoglobin at baseline and through 98 days of atomoxetine treatment. On day 112, his hemoglobin was 8.8g/dL with a WBC count of 4.78 THOU/uL and a platelet count of 231 THOU/uL. Atomoxetine was held and his next hemoglobin collected five days later was 11.6g/dL with a WBC count of 6.0 THOU/uL and a platelet count of 266 THOU/uL. After restarting atomoxetine his hemoglobin was 12.7g/dL with a WBC count of 5.43 THOU/uL and a platelet count of 312 THOU/uL. This subject was discontinued from the study for taking a banned medication (corticosteroid). There were no AEs of bleeding or any other AEs that would explain the decreased hemoglobin.

Subject **LYAO 3381**, a 42-year-old EM female with a past medical history of anemia, had a baseline hemoglobin of 10.1g/dL that declined to 9.9g/dL during the study.

WBC Count

I identified 3 atomoxetine subjects with treatment emergent WBC results ≤ 2.5 THOU/uL. Those cases are described below.

Subject **HFBE 898**, an 8-year-old EM female had a baseline WBC of 2.23 THOU/uL (1,070 neutrophils). A repeat WBC count was 4.84 THOU/uL and the subject was enrolled and started atomoxetine. On day 15 of atomoxetine, her WBC count was 1.96 THOU/uL (840 neutrophils) and on day 34 it was 1.88 THOU/uL (830 neutrophils). Atomoxetine was stopped and follow up WBC was 6.6 THOU/uL. This subject had no abnormal hemoglobin or platelet results during the study. The subject discontinued for low WBC count but had no other related AEs.

Subject **HFBF 1405**, a 7-year-old EM male had a baseline WBC count of 3.56 THOU/uL. On day 34, his WBC was 2.44 THOU/uL (1,080 neutrophils). His WBC count increased to 3.86 THOU/uL on day 43 and remained above 2.5 THOU/uL for the rest of the study. End study WBC was 4.04 THOU/uL. Hemoglobin and platelet counts were normal throughout the study. He had AEs of rhinitis and cold but no recorded fevers.

Subject **LYAB 5481**, an 8-year-old EM male had a WBC count of 7.41 THOU/uL at baseline. Atomoxetine day 53 WBC was 7.58 THOU/uL, and on day 104 was 2.07 THOU/uL (750 neutrophils). The subject's platelet count on that day, 128 THOU/uL, was also below the LLN (LLN 130 THOU/uL) On atomoxetine day 124, WBC count was 5.02 THOU/uL and it remained above 5.0 THOU/uL for the remainder of the study. The subject had no other abnormal platelet counts and no abnormal hemoglobin results during the study. The subject's recorded AEs were nausea, diarrhea, and myalgia.

Platelets

I identified no atomoxetine subjects with treatment emergent platelet counts ≤ 100 THOU/uL. Four atomoxetine subjects had one or more platelet counts ≥ 600 THOU/uL (HFBF 004 1124, HFBF 018 1688, LYAB 041 4651, LYAB 063 5570). The highest recorded platelet count was 629 THOU/uL (HFBF 004 1124). For two subjects (HFBF 004 1124, HFBF 018 1688) platelet counts decreased with continued atomoxetine treatment, and for 1 subject (LYAB 041 4651) the abnormal platelet count occurred after stopping atomoxetine (reason for d/c: mononucleosis). For the remaining subject (LYAB 063 5570) atomoxetine was stopped at the time of the abnormal platelet count (reason for d/c: lack of efficacy) and the platelet count decreased off drug.

4.6.7 Vital Sign Data

This section reviews pulse, and blood pressure data. The sponsor's analyses of weight and height data are reviewed separately in a later section of this review.

Child and Adolescent overall ADHD studies BID dosing

Mean Change

The sponsor reported a mean increase in systolic blood pressure compared to baseline of 2.62mmHg, a mean increase in diastolic blood pressure of 3.0mmHg and a mean increase in pulse of 6.47bpm. Since these data result from pooling of controlled and open label studies, there are no appropriate comparator data.

Outliers

Twenty one percent of subjects had an outlier value for high systolic BP, 25% for high diastolic BP, and 13% for high pulse during these studies.

Child and Adolescent acute placebo controlled ADHD studies using BID dosing

Mean change from Baseline

The sponsor found increases in mean diastolic and systolic blood pressure and pulse compared to placebo in these pediatric studies. The results are summarized in the following table (from Table ISS.4.1.17, p.121, ISS).

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

Parameter	Treatment (n)	Mean Change	p-value
Diastolic BP	Atomoxetine (335)	2.060	.002
	Placebo (204)	-0.453	
Systolic BP	Atomoxetine (335)	2.791	.148
	Placebo (204)	1.184	
Pulse	Atomoxetine (335)	7.816	<.001
	Placebo (204)	1.532	

Outliers

The sponsor found increases in risk for high systolic and diastolic BP outliers in atomoxetine subjects compared to placebo subjects. The risk for high pulse was increased among atomoxetine subjects and the risk of low pulse was decreased among atomoxetine subjects compared to placebo. Those results are provided below (from table ISS.4.1.18, p.123, ISS).

Diastolic Blood Pressure, Systolic Blood Pressure and Pulse Outlier Risks, Child and Adolescent acute placebo controlled ADHD studies using BID dosing

Parameter	Treatment	Risk (n)	p-value
Diastolic BP, High*	Atomoxetine	19.3% (63/326)	.007
	Placebo	10.5% (21/200)	
Systolic BP, High*	Atomoxetine	17.9% (58/324)	.007
	Placebo	9.1% (18/197)	
Pulse increase of ≥ 25 and to ≥ 110 bpm	Atomoxetine	9.3% (31/335)	<.025
	Placebo	3.9% (8/204)	
Pulse decrease ≥ 20 And to ≤ 65 bpm	Atomoxetine	1.2% (4/335)	.190
	Placebo	2.9% (6/204)	

*Value above 95 percentile of NIH values. These are values for pediatric patients stratified by age, gender, and height percentile. The values appear in the National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents 1996 document. The tables of values are provided as an appendix to this review.

Adult Acute Placebo-controlled ADHD Trials

Mean Change

The sponsor observed mean increases from baseline in diastolic BP, systolic BP, and pulse among adult atomoxetine subjects compared to placebo. Those results are summarized in the following table (from table ISS.4.3.17, p.226, ISS).

Diastolic Blood Pressure, Systolic Blood Pressure and Pulse Mean Change from Baseline to Endpoint, Adult Acute Placebo-controlled ADHD Trials

Parameter	Treatment (n)	Mean Change	p-value
Diastolic BP	Atomoxetine (258)	1.771	.083
	Placebo (258)	0.525	
Systolic BP	Atomoxetine (258)	2.868	.002
	Placebo (258)	-0.002	
Pulse	Atomoxetine (258)	5.262	<.001
	Placebo (258)	-0.328	

Outliers

No adult atomoxetine subjects had increases in systolic BP, diastolic BP, or pulse that met the sponsor's outlier criteria. I examined the sponsor's vital sign data sets for these trials using less extreme outlier criteria* and found similar outlier risks for high diastolic BP, slightly higher risk of high systolic BP among atomoxetine subjects and a 3.5 fold higher risk for high pulse among atomoxetine subjects. Those results are provided in the following table.

FDA analysis: Diastolic BP, Systolic BP and Pulse High Outlier Risks, Adult Acute Placebo-controlled ADHD Trials

Parameter	Treatment	Risk (n)
Diastolic BP, High*	Atomoxetine	2.6% (7/268)
	Placebo	2.3% (6/264)
Systolic BP, High*	Atomoxetine	5.2% (14/268)
	Placebo	3.5% (9/260)
Pulse, High*	Atomoxetine	10.8% (29/268)
	Placebo	3.0% (8/264)

*Subjects not meeting criteria at baseline and with Diastolic BP ≥ 100 on treatment, Systolic BP ≥ 150 on treatment, Pulse ≥ 100 on treatment

Poor Metabolizers from Child and Adolescent ADHD Studies

Mean Change

Poor metabolizers exhibited larger mean increases in blood pressure and pulse in this pooled analysis of children exposed to atomoxetine. The sponsor's results are summarized in the following table (from table ISS.5.1.23, p.305, ISS).

Diastolic Blood Pressure, Systolic Blood Pressure and Pulse Mean Change from Baseline to Endpoint, Child and Adolescent EM vs. PM subjects treated with atomoxetine

Parameter	Metabolic Status (n)	Mean Change	p-value
Diastolic BP	EM (1781)	2.933	.323
	PM (123)	3.772	
Systolic BP	EM(1781)	2.562	.636
	PM (123)	3.020	
Pulse	EM (1781)	6.232	<.001
	PM (123)	10.256	

The results were similar when the analysis was restricted to subjects who received a maximum atomoxetine dose of at least ≥ 1.2 mg/kg/day (data not shown, Table ISS.5.1.24).

Outliers

The percentage of outliers for high diastolic and systolic blood pressure and high pulse were similar between extensive and poor metabolizes exposed to atomoxetine. These results did not change substantially when the analysis was limited to subjects who received a maximum atomoxetine dose of at least ≥ 1.2 mg/kg/day (data not shown, Tables ISS.5.1.25, ISS.5.1.26, ISS pp.308-9).

Child and Adolescent Acute Placebo Controlled Once Daily ADHD Group

Mean change

The sponsor observed mean increases in diastolic BP, systolic blood pressure and pulse in this study, which dosed atomoxetine once daily. Those results are summarized in the table below (from table ISS.5.2.7, p.353, ISS).

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

Parameter	Treatment (n)	Mean Change	p-value
Diastolic BP	Atomoxetine (81)	2.304	.632
	Placebo (83)	1.699	
Systolic BP	Atomoxetine (84)	2.006	.030
	Placebo (83)	-0.711	
Pulse	Atomoxetine (84)	6.804	<.001
	Placebo (83)	-1.223	

Outliers

The sponsor observed a higher risk of high systolic and diastolic blood pressure and high pulse outliers among atomoxetine subjects in this study with p-values $>.05$ for each comparison. Those results are summarized in the following table (from table ISS.5.2.8, p.354, ISS).

Diastolic Blood Pressure, Systolic Blood Pressure and Pulse Outlier Risks, Child and Adolescent acute placebo controlled ADHD study using QD dosing

Parameter	Treatment	Risk (n)	p-value
Diastolic BP, High*	Atomoxetine	9.8% (8)	.565
	Placebo	6.3% (5)	
Systolic BP, High*	Atomoxetine	11.1% (9)	.278
	Placebo	6.1% (5)	
Pulse increase of ≥ 25 and to ≥ 110 bpm	Atomoxetine	7.1% (6)	.117
	Placebo	1.2% (1)	
Pulse decrease ≥ 20 And to ≤ 65 bpm	Atomoxetine	1.2% (1)	.620
	Placebo	2.4% (2)	

*Value above 95 percentile of NIH values. These are values for pediatric patients stratified by age, gender, and height percentile. The values appear in the National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents 1996 document. The tables of values are provided as an appendix to this review.

Child and Adolescent Acute Methylphenidate Controlled ADHD Group

Mean change

The sponsor observed a greater increase in diastolic BP among atomoxetine subjects (2.35mmHg) compared to methylphenidate subjects (1.94mmHg) and a greater increase in systolic BP among methylphenidate subjects (3.17mmHG) compared to atomoxetine subjects (2.34mmHg). Pulse increased in both the atomoxetine (7.42 bpm) and the methylphenidate groups (5.84 bpm). None of the differences had associated p-values $<.05$ (ISS p.391).

Outliers

The sponsor found similar high outlier risks by treatment for diastolic and systolic BPs and pulse when comparing atomoxetine and methylphenidate subjects (ISS, p.393).

Depression and Urinary Incontinence Trials

In this analysis of pooled data from depression and urinary incontinence trials, the sponsor observed an increase in diastolic blood pressure among atomoxetine subjects (1.2mmHg) compared to placebo subjects (-1.0mmHg). There was little difference in mean change from baseline when comparing systolic blood pressure for atomoxetine subjects (-0.2mmHg) to placebo subjects (-1.1mmHg). Pulse was increased from baseline among atomoxetine subjects (5.5 bpm) but not placebo subjects (0 bpm). The sponsor did not perform an outlier analysis of these vital sign data (Table ISS:5.5.10., p.510).

4.6.8 Height and Weight

The sponsor collected controlled comparative data for the 6-12 week trials that allow evaluation of short-term atomoxetine exposure on weight but no long-term placebo data that would allow evaluation of atomoxetine's effect on weight or height (ISS p.547). The sponsor uses population data (weight and height percentiles and z scores) to evaluate long term changes.

In addition to presenting the height and weight data analyses by safety groups, the sponsor included a separate section of the NDA (6.2) that discussed growth effects of atomoxetine.

Child and Adolescent overall ADHD studies BID dosing

The sponsor observed mean increases in weight and height in these analyses but in the absence of comparator data and given the diversity in study designs that were pooled, the results are difficult to interpret. The sponsor reported that 39% (741/1913) atomoxetine subjects lost at least 3.5% of body weight.

Child and Adolescent Acute Placebo Controlled ADHD Studies Using BID Dosing

Mean changes

The sponsor observed a mean decrease in weight among atomoxetine subjects (-0.381kg) compared to an increase in weight among placebo subjects (1.545kg). The sponsor found those atomoxetine subjects reporting anorexia as an AE had a mean decrease in weight of 1.1kg compared to a loss of 0.2kg for those atomoxetine subjects not reporting anorexia.

The sponsor also reported a smaller increase in mean height of 0.89 cm for atomoxetine subjects compared to an increase of 1.14 cm for placebo subjects (p=.072).

Outliers

The risk of a 3.5% decrease in weight was 32.3% (108/334) for atomoxetine subjects compared to 5.9% (12/204) for placebo subjects (p<.001).

Adult Acute Placebo-controlled ADHD Trials

Mean change and outliers

The mean weight change from baseline for adult atomoxetine subjects was -1.21kg compared to a mean increase of 0.36kg for placebo subjects, p<.001 (ISS p.226). The risk of losing at least 7% body weight among atomoxetine subjects was 4.7% (12/258) compared to 0.4% (1/258) for placebo (ISS p.227).

Secondary Safety Databases

The secondary database analyses of the effect of atomoxetine on height and weight generally supported the results from the primary safety databases. When comparing EM and PM subjects, PM subjects had larger decreases in weight and smaller increases in height suggesting an exposure level response. I provide those results in the following table.

Weight and Height Mean change from Baseline for Adolescent and Pediatric Atomoxetine Subjects Receiving $\geq 1.2\text{mg/kg/day}$ by Metabolic Status

Variable	Metabolic Status	N	Mean change	p-value
Weight	EM	1289	0.768	<.001
	PM	67	-1.197	
Height	EM	1069	2.197	.121
	PM	53	1.538	

From Sponsor's table ISS.5.1.24, ISS p.306.

The risk of losing at least 3.5% of body weight for poor metabolizers receiving at least 1.2mg/kg/day atomoxetine was 64% compared to 44.5% for extensive metabolizers receiving at least 1.2mg/kg/day atomoxetine (p=.002).

Additional Analyses of Growth

In the ISS, the sponsor included a separate section that contained additional analyses of weight and height data. These analyses looked at weight and height changes in subjects

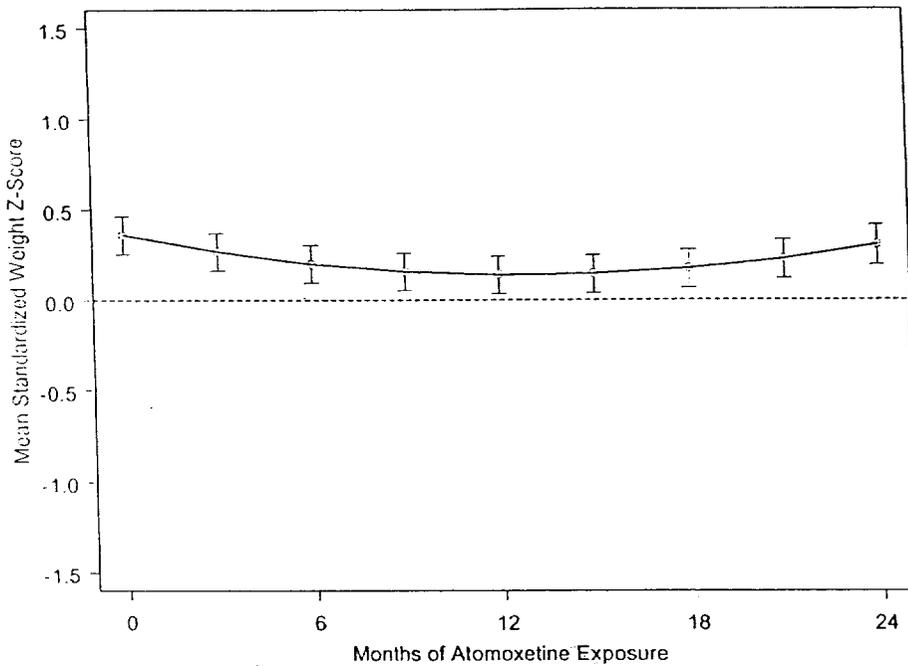
exposed to atomoxetine for at least one year. The sponsor updated these analyses with additional long-term data in their 2-month safety update. I will identify the source of the data in the following sections.

Weight

The sponsor lacked long-term placebo data that would allow an assessment of effects of atomoxetine on weight and height. The sponsor used general population data in the form of weight percentiles and z scores to examine long term effects. A z score is the number of standard deviations away from a mean for a given measurement. The sponsor compared the mean z score at baseline to the mean z score at end point to assess growth in the treated population compared to what would be expected for the general population. Mean decreases in z scores would indicate height or weight gains not reaching expected, based on general population growth data.

In their long-term analyses, the sponsor considered those 423 pediatric and adolescent subjects exposed to atomoxetine for at least 1 year and separately those 74 subjects exposed for at least 1.5 years. They then compared mean z score at baseline for these groups to several points throughout the observation periods. While exposed subjects had a mean increase in weight for one year (4 kg) and 1.5 years (6.5kg) there was a mean decrease in z scores of .25 and a mean decrease in weight percentile of 7.1 at one year. The sponsor also noted a mean decrease in weight z score of .28 and a mean decrease in weight percentile of 7.3 at 1.5 years (Safety update, p.115). This indicates that compared to the general population, the observed weight gain was less than predicted. Since these subjects were on average heavier than the general population at baseline, even after the observed changes, the mean percentile at endpoint was 54. The sponsor provided a plot of z scores over time for this population. It appeared that most of the mean decrease in z scores occurred in the first 3 months of exposure with suggestion of stabilization around 1 year, followed by an increase that does not return to baseline. That graph is provided below.

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Fitted line is a least square line from the statistical model with effects for baseline, days of exposure, and days of exposure squared
 Source data: eagle:/programs_g/rmp/b4zs/is2s/height and weight/z-score repeated by month.sas

Note: Error bars represent 2 standard errors of the mean (SEM)

Model: dependent variable: weight Z-score; independent variables: baseline weight Z-score, days, days squared.

Figure SU.5.3.1. Mean (observed case) standardized weight Z-scores over time, patients with at least 1 Year of atomoxetine exposure, Two-Month Update Growth Analysis Group.

The sponsor stratified the changes based on z scores and percentiles at baseline. The sponsor found that those in the lowest weight percentile at baseline had the smallest mean decrease in z score over the observation period. Those results are provided below.

Mean Weight z scores by Baseline Percentile, Patients with at Least 1 Year Atomoxetine Treatment

Percentile at Baseline	N	z score Mean Change from Baseline
<25 th	66	-0.05
25 th -50 th	93	-0.21
50 th -75 th	101	-0.27
>75 th	163	-0.36

From sponsor's table SU.5.3.3., Safety Update p.116.

Weight /Dose relationship

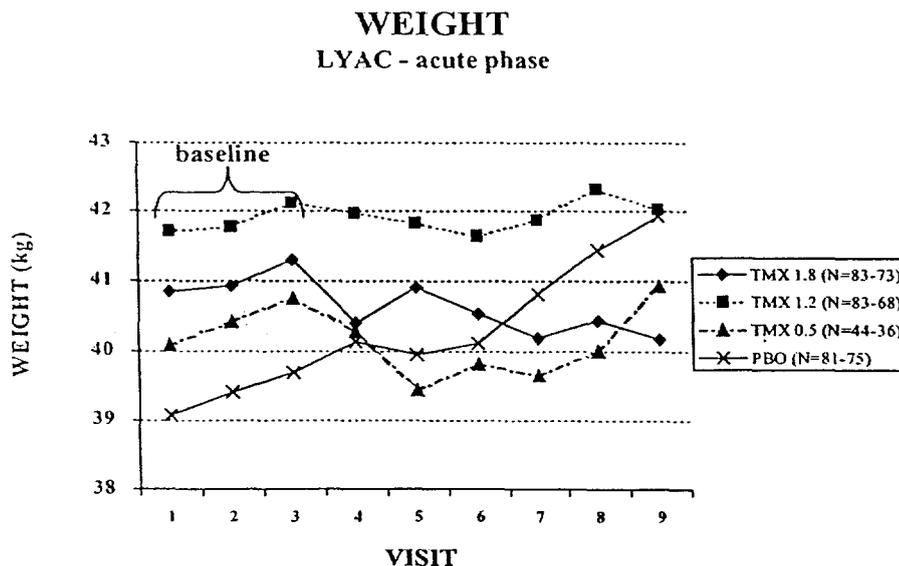
In the ISS, the sponsor noted that data from the pediatric fixed dose study LYAC supported an association between atomoxetine dose and acute weight change. While

placebo subjects gained an average of 1.7kg, subjects randomized to atomoxetine 0.5mg/kg/day gained 0.3kg, subjects randomized to atomoxetine 1.2mg/kg/day lost an average of 0.4kg, and subjects randomized to atomoxetine 1.8mg/kg/day lost an average of 0.5kg (ISS p.554). The outlier data from this study demonstrated that the risk for losing $\geq 3.5\%$ body weight was 1.3% (1/83) for placebo, 7.1% (3/43) for atomoxetine 0.5mg/kg/day, 19.3% (16/84) for atomoxetine 1.2mg/kg/day, and 29.1% (23/81) with a p value $<.001$ for the trend analysis (LYAC study report, p.257).

Using data from pediatric subjects exposed for at least 1 year, the sponsor plotted the mean change in z score by modal daily dose and the resulting fitted line suggested a dose response relationship ($p=.038$). The sponsor noted that the correlation between modal dose and change in weight z score was not significant from 6 months to 1 year (Safety Update, p.119).

Weight by dose and time

The sponsor provided a plot of mean weight by dose and time for study LYAC (LYAC Study report, p.255). The placebo group gained weight over the study. The atomoxetine 0.5mg/kg/day group had a mean weight loss at visits 4 and 5 followed by gain for the rest of the study. The atomoxetine 1.2 and 1.8mg/kg/day groups had mean weight losses beginning around visit 4 followed by rather flat weight curves for the rest of the study. That graph is provided below. Because of the titration design in this study, subjects in the atomoxetine 1.2mg/kg/day group reached their target dose at visit 5 and subjects in the atomoxetine 1.8mg/kg/day reached their target dose at visit 6.



Source data: RMP.B4ZO.LYACCTRM.INTERIM1 (VI1L100P)

Figure LYAC.12.16. Weight means at each visit, B4Z-MC-LYAC.

Height

Using data for subjects exposed to atomoxetine for at least 1 year, the mean increase in height was 6.4cm with a decrease in mean z score of 0.16. Percentile for height decreased from 52 at baseline to 47 at endpoint (Safety update, p.121). Using data for subjects exposed to atomoxetine for at least 1.5 years, the mean increase in height was 9.3cm with a decrease in mean z score of 0.14. Percentile for height decreased from 54 at baseline to 49.5 at endpoint (Safety update, p.121). When height z score change from baseline was stratified by percentiles at baseline the sponsor found that those in the lowest height percentile had an unchanged mean z score while those in higher percentile groupings at baseline had decreased mean z scores over the observation period. Those results are provided below.

Mean Height z scores by Baseline Percentile, Patients with at Least 1 Year Atomoxetine Treatment

Percentile at Baseline	N	z score Mean Change from Baseline
<25 th	60	0.00
25 th -50 th	74	-0.14
50 th -75 th	54	-0.20
>75 th	78	-0.27

From sponsor's table SU.5.4.3., Safety Update p.122.

Since height was not measured at each visit and the intervals differed by study, the sponsor performed a repeated measures ANOVA to analyze the height z score data. The mean height z score declined through 18 months of observation and then increased based on a small number of surviving patients. Those data are included in the following table.

Assessment of Changes in Standardized height z score over time for patients with at least 1 year of atomoxetine treatment

Duration (months)	N	Height z score mean change from baseline	95% CI
0	266		
2	54	-0.02	(-0.10, 0.06)
3	197	-0.03	(-0.08, 0.01)
6	162	-0.10	(-0.15, -0.05)
9	123	-0.08	(-0.16, 0.00)
12	183	-0.16	(-0.23, -0.09)
15	94	-0.12	(-0.21, -0.04)
18	49	-0.18	(-0.31, -0.05)
21	34	-0.10	(-0.29, 0.09)
>21	14	-0.02	(-0.34, 0.30)

From sponsor's table SU.5.4.4, p.123.

Height /Dose relationship

The sponsor reported in the ISS no statistically significant height dose relationship during the 8 week study LYAC. Placebo subjects in this trial gained 1.8cm while atomoxetine 0.5mg/kg/day, 1.2mg/kg/day, and 1.8mg/kg/day subjects gained 1.1cm, 1.0cm, and 1.0cm respectively (LYAC study report, p.252).

Using data from pediatric subjects exposed for at least 1 year, the sponsor plotted the mean change in height z score by modal daily dose and the resulting fitted line had a negative slope that was not significantly different than 0 (P=.432) (Safety Update p.125).

4.7 Special Topics

4.7.1 Atomoxetine QT data

In their NDA submission and 2 month safety update, the sponsor included the following assessments of atomoxetine's effect cardiac repolarization: in vitro ion channel studies, canine Purkinje preparations, whole animal dog studies, human clinical pharmacology studies, and phase III clinical trial data. The following sections summarize these data.

HERG

The sponsor reported that atomoxetine blocked I_{kr} in HERG transfected cells with an IC_{50} of $0.869\mu M$ while its metabolites N-desmethyatomoxetine and 4-hydroxyatomoxetine blocked HERG with an IC_{50} of $5.71\mu M$ and $20.0\mu M$, respectively. Based on these data, the sponsor predicted up to 31% blockade of the cardiac I_{kr} channel in humans at the high end of estimated unbound plasma atomoxetine concentrations (mean $C_{ss, max} + 2$ standard deviations) following a recommended maximum dose of 1.8mg/kg/day . The predicted blockade of HERG by each metabolite at their peak unbound plasma concentrations in humans is approximately 4% for 4-hydroxyatomoxetine and 2% for N-desmethyatomoxetine. The HERG data is summarized in the following graph.

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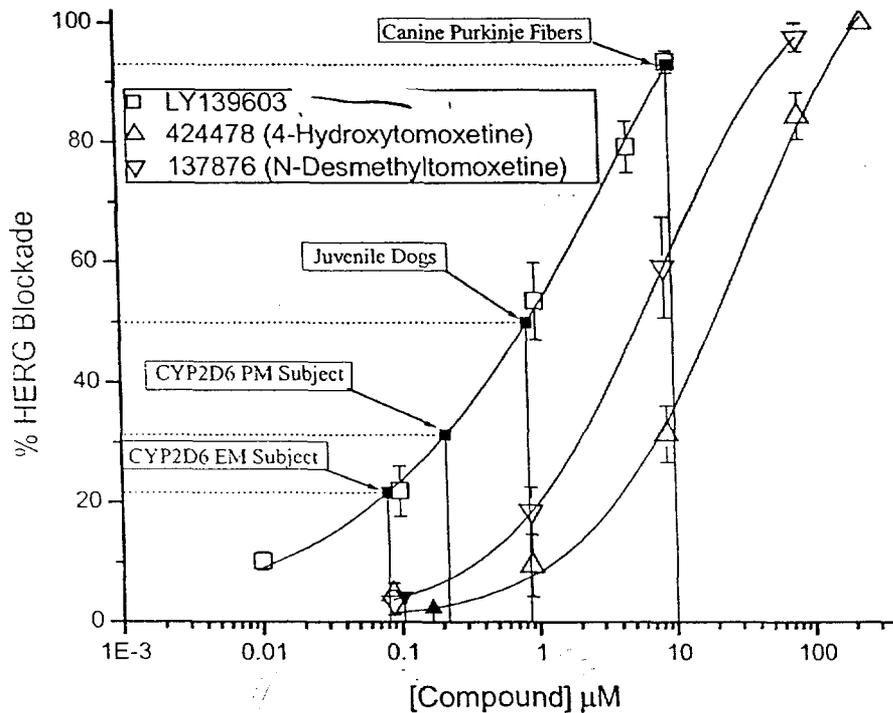


Figure 1: HERG dose-response curves for tomoxetine and its two principal nonconjugated metabolites. Maximum unbound plasma concentrations of parent tomoxetine in poor metabolizers (PM) and extensive metabolizers (EM) are shown superimposed on the tomoxetine curve with the associated predicted HERG blockade. In addition, the maximum unbound concentration from juvenile dogs in a toxicology study in which ECGs were collected and the concentration tested in canine Purkinje fibers are plotted. Maximum unbound concentrations of the two metabolites of tomoxetine are shown on the individual metabolite curves (solid triangles).

Canine Purkinje

The sponsor reported that atomoxetine decreased action potential upstroke velocity (V_{max}) by 54%, amplitude by 12%, and duration (APD_{95}) by 21%. The sponsor states that these findings are consistent with a prolonged PR interval but not consistent with a QT prolongation effect. These effects were observed at a concentration of atomoxetine, which is approximately 45-fold greater than the highest predicted unbound atomoxetine concentration in humans given 1.8mg/kg/day and which, on the basis of the in vitro HERG data, would have been expected to produce a HERG blockade of 93%.

In describing the results of this study, the sponsor's consultant who performed the HERG study noted that "The absence of prolongation of the action potential in Purkinje

fibers is reassuring. However, it should be noted that terfenadine, a compound with well-known properties of QT prolongation and torsade de pointes arrhythmia, also failed to cause action potential prolongation and indeed caused APD shortening in a similar preparation." (General Pharmacology⁵, p.7, Submitted with Atomoxetine ISS)

Our HFD-110 (Cardio-renal division) consultant pharmacologist explained in a 10/31/00 consult that the results of the Purkinje fiber experiments indicate that "atomoxetine affects multiple ion channels". Tomoxetine attenuated V_{max} indicating sodium channel blockade but because the overall action potential duration shortened, atomoxtetine also likely has calcium channel blocking properties.

Instrumented adult dog

Single oral dose

The sponsor reported no compound related changes in adult dogs given single oral doses up to 16mg/kg. The study report cited by the sponsor mentioned no changes in the electrocardiograms, but there was no quantitative assessment of QT intervals.

1 month, multi-dose

The sponsor reported no compound related changes in RR, QT, or corrected QT in young dogs given oral atomoxetine doses up to 16mg/kg/day for 1 month. The conclusion of no compound related changes on QT was based on the finding that there were only 2 dogs with an absolute QTc>260msec during the study, a finding of unknown significance. The investigators did not perform additional quantitative assessments of QT in this study.

IV anesthetized instrumented dogs

The sponsor reported increases in PR and Heart rate and increase in QTc in dogs infused IV dose of 6mg/kg. They state that the prolonged QTc is likely an artifact produced by using Bazett's correction. The investigators reported a 26bpm (+/-5) change in heart rate in this study for dogs exposed to atomoxetine. This study also included an amitriptyline arm. Interestingly, dogs exposed to amitriptyline had an increased heart rate of 100bpm (+/-7), yet while using the same Bazett's correction the investigators reported no significant change in the QTc.

Clinical Pharmacology Studies

I reviewed QT related results from 3 atomoxetine clinical pharmacology trials. Two studies were designed to evaluate QT changes (LYAE, LYAY) and the third study had results that could signal QT prolongation (HFBJ).

LYAE

This study was designed to test the safety, tolerance, and pharmacokinetics of multiple atomoxetine doses. This study exposed healthy EM and PM adults to equally high or higher concentrations of atomoxetine than were intended to be administered to children in the phase III studies (2mg/kg). The study enrolled 16 healthy adults, 10 EM and 6 PM. The 11 male (4 PM), 5 female (2 PM) subjects had an average age of 36 years (range 22-60). The following table displays the dose and schedule employed during this study.

Dose and Schedule of drug administration during study LYAE

Period 1	Placebo	
Period 2	Atomoxetine 30mg bid 5 days	0.7-1.12mg/kg/day
Period 3	Atomoxetine 45 mg bid 5 days	1.05-1.68mg/kg/day

Period 4	Atomoxetine 60mg bid 5 days	1.4-2.24mg/kg/day
Period 5	Atomoxetine 75mg bid 5 days	1.75-2.8mg/kg/day
Period 6	Washout/Observation 5 days	

This was essentially a dose escalation trial where QTc for each subject at each pre-specified time point and dose was compared to that subject's QTc for the corresponding time point on placebo. Subjects were admitted before and for the first 24 hours after the drug or placebo administration on the first day of Study periods 1-5. Subjects were admitted on the evening of Study day 4 of each study period and remained confined until 24 hours after the first dose of the next 5-day study period. They were home on days 2, 3 and 4 (until the evening).

ECG measurements

Twelve lead ECG tracings taken at 25mm/min on _____ machines were performed on study day 5 of periods 1 to 5 at 0,1,2,4, and 12 hours after the morning dose and at the time of final assessment. The sponsor's analyses used Fridericia's correction. ECG intervals were hand measured from at least 2 leads and 5 complexes per lead by cardiologists at _____. The study report did not describe the measuring methodology used or the number of cardiologists employed to measure the intervals.

Results

Fifteen subjects completed per protocol, 1 completed with adjustment of final intended dose to placebo due to adverse events (after all ECGs had been collected).

PK

The sponsor reported that at steady state, the mean atomoxetine $C_{ss,max}$ in EM subjects increased from 320ng/mL to 820ng/mL as the dose increased from 30 to 75mg BID. The mean atomoxetine $C_{ss,max}$ values occurred at a median T_{max} of 1 hour (range 0.5 to 4 hours).

Atomoxetine plasma concentrations were higher in PM subjects than in EM subjects. Mean atomoxetine $C_{ss,max}$ increased from 1,265 to 4,000ng/mL as the dose increased from 30 to 75mg BID. The atomoxetine $C_{ss,max}$ occurred at a median T_{max} of 3 hours (range 1 to 6 hours). The sponsor commented that the higher but later atomoxetine $C_{ss,max}$ appeared to be the product of slower elimination rather than delayed absorption. The PM atomoxetine $C_{ss,min}$ were 50% of the $C_{ss,max}$ and roughly 40-fold higher than the same data in EM subjects.

Plasma concentrations of 4-hydroxytomoxetine were lower than atomoxetine in both EM (3% to 7%) and PM (0.1% to 0.2%) subjects with the $C_{ss,min}$ being approximately 50% of $C_{ss,max}$ values. The 4-hydroxytomoxetine plasma concentrations peaked about 1 to 2 hours after the atomoxetine peak. Plasma concentrations of *N*-desmethylatomoxetine were approximately 3% to 6% of atomoxetine in EM subjects and 40% to 50% of atomoxetine concentrations in PM subjects.

Adverse Events

There was one ECG related adverse event in this study. A subject had an apparent increase in QTc based on Bazett's correction but the sponsor reported that the QTc ranged from 395-414msec with Fridericia's correction on the day of the event. The other

reported cardiovascular related AEs were postural hypotension (n=2), and vasodilatation (n=2). There were no reports of tachycardia, palpitations or syncope in this study.

QTc

EM Mean Change from Placebo

After 5 days at a given dose, the pooled mean QTc for that day showed no statistically significant difference from pooled baseline placebo data. Those data are provided in the following table.

Sponsor's analysis, QTc change from placebo for EM subjects

Dose	Time of Measurement Postdose (hr)	Least Square Mean (msec)	Difference from Placebo	p	95% (CI)
0	0,1,2,4,12	379.4			
30	0,1,2,4,12	382.0	2.6	.25	-1.9, 7.2
45	0,1,2,4,12	382.1	2.7	.23	-1.8, 7.2
60	0,1,2,4,12	379.3	-0.1	.97	-4.6, 4.4
75	0,1,2,4,12	380.1	0.7	.75	-3.8, 5.2

I calculated the QTc change from placebo by time for EM subjects and did not find strong evidence of drug related changes in QTc. I performed this analysis using the sponsor's data sets to look for trends suggestive of drug related QTc prolongation for the individual measurement time points. Those results are provided in the following table.

FDA analysis, QTc change from placebo for EM subjects by time

Time	30mg bid	45mg bid	60mg bid	75mg bid
0	2.4	2.8	6.0	-2.8
1	-0.3	6.2	-3.7	2.3
2	9.2	3.5	1.5	5.6
4	0.3	0.9	-2.4	0.5
12	2.0	0.6	-1.4	0

PM Mean Change from Placebo

When comparing the pre-dose measurement among PM subjects after 5 days on 60mg, and 75 mg, to placebo pre-dose, there was a statistically significant increase in QTc. This finding was not present post dose in the 60mg group, but there was a suggestion of prolongation at 75mg post dose.

Sponsor's analysis, QTc change from placebo (baseline) for PM subjects

Dose	Time of Measurement Post dose (hr)	Least Square Mean (msec)	Difference from Placebo	p	95% (CI)
0	0	400.3			
30	0	402.7	2.5	.65	-8.3, 13.2
45	0	400.6	0.4	.95	-10.4, 11.1
60	0	417.2	16.9	.0022	6.1, 27.6
75	0	414.9	14.6	.0078	3.9, 25.4
0	1,2,4,12	395.5			
30	1,2,4,12	390.3	-5.2	.1	-11.5, 1.1
45	1,2,4,12	396.9	1.4	.65	-4.8, 7.7

60	1,2,4,12	397.1	1.6	.62	-4.7, 7.8
75	1,2,4,12	401.7	6.2	.053	-0.1, 12.4

My analysis of the PM Mean QTc change from placebo by time found QTc prolongation at the 75mg BID dose at most of the measurement time points. I performed this analysis using the sponsor's data sets to look for trends suggestive of drug related QTc prolongation for the individual measurement time points. The results are provided in the following table.

FDA analysis, QTc change from placebo (baseline) for PM subjects by time

Time	30	45	60	75
0	2.4	0.3	16.8	14.6
1	-7.5	5.1	0.5	4.5
2	-5.1	-13.3	8	0.7
4	-7.8	10.4	1	10.4
12	-1.3	3.4	-3.3	8.9

I repeated the mean change analyses using a data based rate correction for QT (not shown) and the results were similar to the results displayed above using Fridericia's correction.

QTc Outliers

Absolute QTc

No subjects met the criteria for prolonged absolute QTc in this study (QTc>450msec in males and QTc>470msec in females). Two subjects had borderline QTc values (430-450msec for males, 450-470msec for females). Subject 9 a PM male, had a single borderline QTc of 431.8msec on 75mg bid. Subject 10, a PM male, had one QTc result on 30mg bid of 438.3msec, on 45mg bid had one QTc result of 438msec, and on 60mg bid had one QTc of 434.5msec. Subject 10's longest QTc on 75mg bid was 412.8msec (normal). These outlier results were the same when the analysis was repeated using a data based rate correction for QT.

QTc change from baseline

No subjects in this study had an increase QTc from baseline of at least 60 msec. In the table below, I identify subjects with increases in QTc of at least 30msec. I calculated a baseline QTc for each subject by averaging each individual's QTc on the day they received placebo. I then subtracted each subject's on drug QTc measurement from their baseline and looked for increases in QTc >30msec and increases >60msec.

Subjects in study LYAE with increases in QTc of at least 30msec

Subject	Metabolic status	Dose	Time	QTc change from baseline (absolute QTc)
02	PM	45	12	31.5 (427.9)
		60	0,1,2	34.4 (430.9)
		75	0	43.8 (440.2)
		75	1	34.4 (430.9)
09	PM	75	0	33.7 (431.8)
15	EM	45	1	32.5 (392.7)
		60	2	33.3 (393.6)

QTc Plasma atomoxetine concentration relationship

EM Subjects

A plot of change in QTc v. atomoxetine plasma concentration did not suggest a relationship for EM subjects (data not shown).

PM Subjects

The atomoxetine plasma concentration vs. QTc change from baseline graphs suggest a positive relationship at several time points. The largest effect was at the pre dose observation with an estimated mean change of 32msec for the highest pre dose concentration and a 10msec change for the median pre dose concentration. The sponsor's analyses are provided below.

Table LYAE.12.7. Model Estimates of QTc(F) Change from Placebo at Different Tomoxetine Concentrations

Genotype	Concentration (ng/mL)	Predicted Mean (msec)	95% Confidence Interval	p-Value
EM	1221.23 (Highest for EM Subjects)	-6.21	(-39.9, 27.5)	0.72
PM at each Time				
Pre-dose	3821.41 (Highest)	32.4	(17.3, 47.5)	0.0001
	1166.295 (Median)	9.89	(5.29, 14.5)	0.0001
1 hour	4793.46 (Highest)	7.49	(-5.51, 20.5)	0.26
	1823.29 (Median)	2.85	(-2.09, 7.79)	0.26
2 hour	5596.93 (Highest)	7.33	(-6.30, 21.0)	0.29
	2227.08 (Median)	2.92	(-2.51, 8.34)	0.29
4 hour	4541.89 (Highest)	15.0	(3.50, 26.5)	0.011
	2195.67 (Median)	7.25	(1.69, 12.8)	0.011
12 hour	4064.52 (Highest)	19.4	(3.84, 35.0)	0.015
	1431.05 (Median)	6.84	(1.35, 12.3)	0.015

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Using data provided by the sponsor, I plotted QTc change from baseline by concentration for atomoxetine and its metabolites (N-desmethyatomoxetine, 4-hydroxyatomoxetine) and found similar results to those illustrated above. There did not appear to be a relationship among EM subjects, and the relationship among PM subjects was positive at some time points (data not shown).

LYAY

The sponsor explored the effect of relatively high plasma concentrations of atomoxetine on cardiac repolarization in this study. The sponsor attempted to create phenotypic poor metabolizers by giving atomoxetine concomitantly with fluoxetine, an inhibitor of CYP2D6. All subjects were given fluoxetine 60mg qd for 7 days followed by fluoxetine 20mg qd for 14 days. Subjects were then given atomoxetine 10mg bid and fluoxetine 20mg qd for 5 days. Subjects then got atomoxetine 45mg bid and fluoxetine 20mg qd for five days. Lastly, subjects got atomoxetine 75mg bid for nine doses followed by a dose of placebo and fluoxetine 20mg qd.

Twelve-lead ECGs were recorded at baseline (study days -2 and -1) at the times that approximated the times of ECGs on dosing days. In addition, ECGs were recorded on fluoxetine and on fluoxetine+ atomoxetine at pre-dose (time 0) and 1,2,4,8, and 12 hours post dose. The sponsor did not discuss the methods used to measure the QT interval.

The investigators compared the difference between no drug treatment and fluoxetine with placebo to assess the effect of fluoxetine on the particular electrocardiographic variable. The investigators then compared the difference between the fluoxetine with placebo treatment and the fluoxetine with atomoxetine (different doses at different times) to assess the effect that the addition of atomoxetine would have on the particular variable.

The investigators examined the change in QTc for atomoxetine+fluoxetine compared to fluoxetine+placebo by concentration and the change in QTc for atomoxetine+fluoxetine compared to pre-fluoxetine (no drug, baseline). For the change from fluoxetine+placebo analysis, the mean QTc change was estimated for the median concentration of the 75mg atomoxetine dose and the maximum concentration of the 75mg atomoxetine dose at each time of an ECG measurement. For the change from the pre-fluoxetine analysis, the mean QTc change was estimated for a placebo observation (concentration equal to zero), the median concentration of the 75mg atomoxetine dose, and the maximum concentration of the 75mg atomoxetine dose at each time of an ECG measurement.

Investigators enrolled 20 subjects (15 men), and all but subject 1015 were EM. Fifteen subjects completed the study according to protocol

Results

PK

The sponsor commented that "EM subjects pre-treated with fluoxetine to approximate steady state levels of fluoxetine had atomoxetine plasma concentration which approximated PM subject concentrations." (LYAY study report p.52). In the table below, I provide PK parameters from study LYAE (EM and PM) and the results from this study. These results suggest that the plasma atomoxetine levels achieved following treatment with fluoxetine and atomoxetine 75mg bid in this study fell closer to the 60mg PM subjects in study LYAE.

PK Parameters from Study LYAE

Parameter	EM (n=10)		PM (n=6)	
	Atom 60mg BID	Atom 75mg BID	Atom 60mg BID	Atom 75mg BID
C _{ss,avc} (ng/mL)	222.14	308.55	2225.79	3118.65
C _{ss,max} (ng/mL)	645.46	820.97	2918.79	3998.76
AUC (µg•hr/mL)	2.67	3.70	26.7	37.4
T _{max} (hr, median)	1 (.5-2)	1.5 (1-4)	3 (1-4)	3 (2-4)
CL _{ss} /F (L/hr/kg)	.355	.322	.0331	.0299

From table LYAE.11.1, LYAE Study Report, p.54

PK Parameters from Study LYAY

PK Parameter	Flu+Atom 10mg BID	Flu+Atom 45mg BID	Flu+Atom 75mg BID
C _{ss,avc} (ng/mL)	252.83	1201.38	1936.09
C _{ss,max} (ng/mL)	339.31	1686.22	2784.10
AUC (ug•hr/mL)	3.03	14.4	23.2
T _{max} (hr, median)	2 (1-2)	2 (1-8)	2 (1-4)
CL _{ss} /F (L/hr/kg)	.0522	.0489	.0506

From table LYAY 11.1, LYAY Study Report, p.51

Cardiovascular Adverse Events

Two subjects experienced syncope and those events are summarized below. No subjects had adverse events of palpitations or tachycardia while treated with atomoxetine and fluoxetine.

Subject 1009, a 43-year-old male had a syncopal episode that led to withdrawal while receiving atomoxetine 45mg bid and fluoxetine. The event was described as precipitated by rising from a squatting position. The subject awoke after sliding down the wall to a sitting position. There was no evidence of head injury or confusion and an ECG performed 10 minutes after the event showed NSR rate 62 bpm. There was no mention of QT interval prolongation. The subject did not have a QTcF > 430msec during the study.

Subject 1020, a 26-year-old male had a syncopal episode that led to discontinuation while receiving atomoxetine 10mg bid and fluoxetine. The event occurred just after voiding urine on the first day of atomoxetine + fluoxetine. The subject had lightheadedness several hours before the event. The subject had adverse events of nausea and diarrhea prior to the syncopal event and vital signs taken the day before his first dose of atomoxetine included a standing HR=108, and a supine HR=66. The subject did not have a QTcF>430msec during the study.

QTc Results

Mean change

The sponsor provided a comparison of QTcF on fluoxetine to no drug and at time points 0, 1,2, and 8, there was a 4-5.6msec increase in QTcF with the largest increase observed at the pre-dose time point. At the 4 and 12 hour time points there was essentially no change in QTcF (LYAY study report, p.69).

When atomoxetine plus fluoxetine was compared to fluoxetine alone, there was no evidence of QTc prolongation. Those results are included in the following table.

Sponsor's analysis, QTc change from placebo (baseline) for subjects in study LYAY

Time	Atomoxetine Dose*	Least Squares Mean	Difference from Placebo	95% CI for difference	P
0	Placebo	392.7			
	10mg bid	390.4	-2.3	(-5.9, 1.3)	0.2159
	45mg bid	390.4	-2.3	(-5.9, 1.4)	0.2264
	75mg bid	388.8	-3.9	(-7.6, -0.1)	0.0425
1	Placebo	392.5			
	10mg bid	389.9	-2.6	(-6.2, 0.9)	0.1474
	45mg bid	391.8	-0.7	(-4.4, 2.9)	0.6932
	75mg bid	390.6	-1.9	(-5.6, 1.8)	0.3131
2	Placebo	387.6			
	10mg bid	388.9	1.3	(-2.4, 4.9)	0.4943
	45mg bid	389.2	1.6	(-2.1, 5.3)	0.3980
	75mg bid	387.0	-0.6	(-4.4, 3.1)	0.7364
4	Placebo	386.3			
	10mg bid	384.4	-1.9	(-5.5, 1.7)	0.3004
	45mg bid	387.5	1.2	(-2.5, 4.9)	0.5155
	75mg bid	387.5	1.2	(-2.6, 4.9)	0.5375
8	Placebo	388.4			
	10mg bid	380.6	-7.8	(-11.4, -4.1)	.0001
	45mg bid	385.4	-3.0	(-6.7, 0.7)	0.1103
	75mg bid	385.7	-2.7	(-6.5, 1.0)	0.1540
12	Placebo	386.2			
	10mg bid	384.2	-2.0	(-5.6, 1.6)	0.2705
	45mg bid	386.3	0.1	(-3.6, 3.8)	0.9553
	75mg bid	383.7	-2.4	(-6.2, 1.3)	0.1972

* All Subjects are also taking fluoxetine

QTc Outliers

Absolute QTc

No subjects had a QTcF >430msec during this study.

Change from baseline

On p.74 of the LYAY study report, the sponsor reported that no subjects had an increase in the QTc interval of >30msec when comparing atomoxetine plus fluoxetine to fluoxetine baseline. Two subjects had increases of >30msec when compared to pre-fluoxetine baseline. Subject 1003 had an increase of 35msec at 0 hour, prior to atomoxetine dosing. Subject 1004 had an increase of 34 msec at 2 hours after the first 10mg atomoxetine dose.

QTc Plasma atomoxetine concentration relationship

The sponsor plotted the plasma concentration v. change in QTc at the different time points examined during the dosing interval. They fit a line and then predicted the change in QTc for the median plasma concentration and maximum plasma concentration associated with 75mg bid dose at each time point. For comparison, the sponsor used the pre fluoxetine QTc baseline in the first analysis (Table LYAY.12.6, p.72 LYAY study

report) and the fluoxetine QTc baseline in the second analysis (Table LYAY.12.7, p.73 LYAY study report).

For the pre-fluoxetine comparison, the largest predicted mean QTc change from baseline (3.4msec, 95% CI -2.7, 9.4) occurred at hour 4, at the maximum atomoxetine concentration. The rest of the predicted QTc changes were small or negative. For the fluoxetine comparison, the largest predicted mean QTc change from baseline (5.5msec, 95% CI -1.0, 11.9) occurred at hour 4, at the maximum atomoxetine concentration. The rest of the QTc changes were small or negative.

The plasma atomoxetine concentration versus change in QTc graphs are provided below. There did not appear to be a consistent relationship between plasma atomoxetine concentration and QTc from these graphs.

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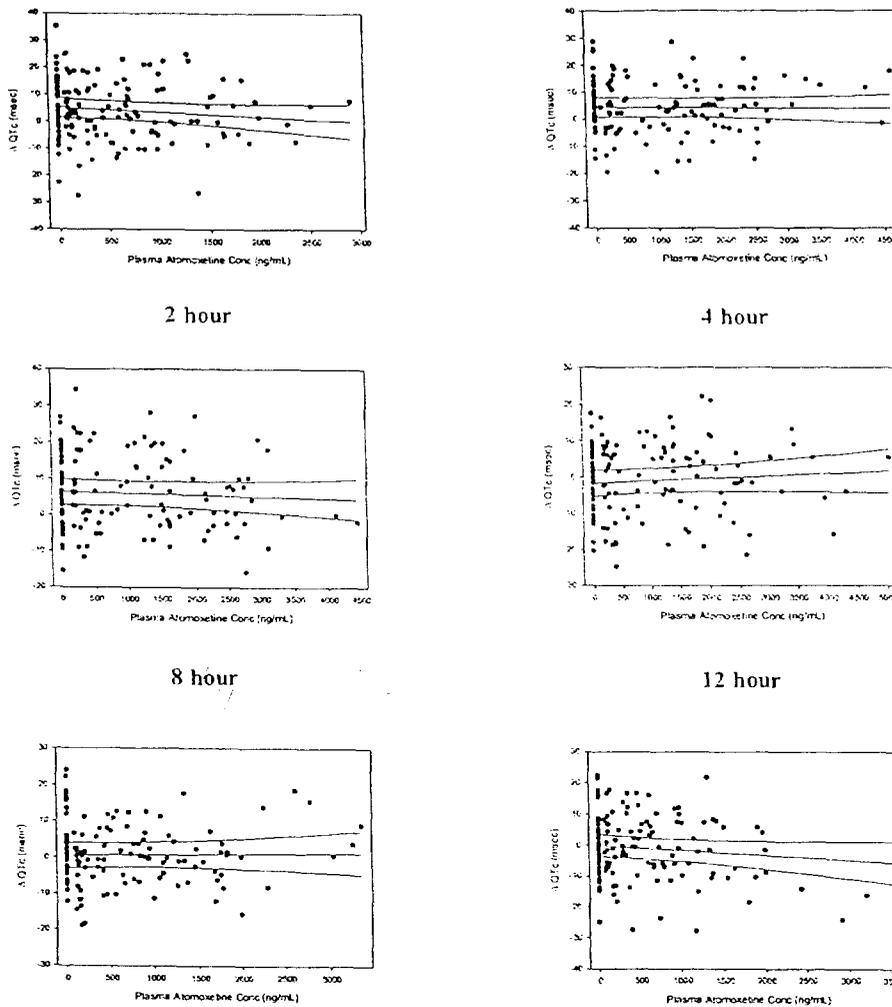


Figure LYAY.12.2. Individual and mean \pm 95% confidence interval ΔQTc versus plasma atomoxetine concentration by time for PM subjects.

HFBJ

In this study, 27 subjects (16 EM, 11PM) were first put through a dose escalation which included single doses of atomoxetine at 10, 30, 60, 90, and 120mg. EM subjects had a 4 day washout between doses while PM subjects had a 14 day washout between doses. The EM subjects who completed the first phase were then randomized to receive either atomoxetine 40mg bid or placebo for 7 days. The completing PM subjects were all given atomoxetine in the multi-dose phase.

The sponsor compared the ECGs collected 2 hours and 24 hours after dosing to individual baseline mean QTc interval data collected during the initial and subsequent

placebo treatment during the single dose escalation. Neither the study report nor the protocol indicated who read the ECGs or the methodology used for reading. The sponsor used Fridericia's correction in their analyses.

Results

Cardiovascular adverse events

The study reported noted two EM subjects and two PM subjects with palpitations. There were no reports of arrhythmia or syncope (HFBJ Study report, pp.101-107).

One subject (0111) discontinued for palpitations and chest pain following the 9th of 14 planned doses during the multi-dose phase. The sponsor reported that the subject's ECG was normal and without changes from the pre-study ECG (HFBJ Study report, p.70).

QTc

Mean change

Single dose phase

The sponsor documented small (range -5.2 to 5.8), non-statistically significant changes in QTc compared to placebo for the EM subjects during the single dose, escalation phase of the study. In the PM group, the observed QTc changes compared to placebo were increased with p values <.05 at 2 hours following the 30 and 90mg doses and at 24 hours following the 60 and 90mg doses. Those results are provided below.

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Table HFBJ.12.6. Effect of Atomoxetine Single Doses on QT_{c(F)} Intervals in EM Subjects

Dose (mg)	Time of Measurement Postdose (hr)	Least Square Mean (msec)	Difference from Placebo	P-Value	95% Confidence Interval
0	2	376.6			
10	2	375.4	-1.2	0.7014	(-7.5, 5.1)
30	2	382.4	5.8	0.0721	(-0.5, 12.0)
60	2	377.8	1.2	0.7223	(-5.3, 7.6)
90	2	380.0	3.4	0.2989	(-3.0, 9.8)
120	2	378.2	1.5	0.6363	(-4.9, 8.0)
0	24	378.0			
10	24	372.9	-5.2	0.1057	(-11, 1.1)
30	24	373.7	-4.3	0.1754	(-11, 2.0)
60	24	373.8	-4.3	0.1920	(-11, 2.2)
90	24	374.2	-3.9	0.2340	(-10, 2.5)
120	24	374.1	-4.0	0.2264	(-10, 2.5)

Table HFBJ.12.7. Effect of Atomoxetine Single Doses on QT_{c(F)} Intervals in PM Subjects

Dose (mg)	Time of Measurement Postdose (hr)	Least Square Mean (msec)	Difference from Placebo	P-Value	95% Confidence Interval
0	2	382.8			
10	2	383.3	0.5	0.8731	(-5.7, 6.6)
30	2	389.4	6.5	0.0381	(0.4, 12.7)
60	2	387.8	5.0	0.1131	(-1.2, 11.2)
90	2	390.7	7.9	0.0127	(1.7, 14.1)
120	2	388.8	6.0	0.0638	(-0.4, 12.3)
0	24	383.9			
10	24	382.2	-1.8	0.5717	(-7.9, 4.4)
30	24	385.6	1.6	0.5995	(-4.5, 7.8)
60	24	390.9	7.0	0.0272	(0.8, 13.2)
90	24	390.7	6.8	0.0326	(0.6, 12.9)
120	24	384.9	1.0	0.7543	(-5.3, 7.4)

Multi dose phase

The mean QTc increases compared to placebo were similar for the EM and PM groups in the multi dose phase of this trial. Both results had wide confidence intervals that included 0. Those results are summarized below.

Table HFBJ.12.8. Effect of Multiple Dose Atomoxetine on QTc(F) Intervals in EM and PM Subjects

CYP2D6 Status	Dose	Days	Least Square Mean (msec)	Difference from Placebo	p-Value	95% Confidence Interval
EM	Placebo	1-7	369.0			
EM	40 mg BID	1-7	374.5	5.5	0.43	(-8.9, 19.9)
PM	40 mg BID	1-7	376.9	7.9	0.28	(-6.9, 22.8)

Abbreviations: EM = extensive metabolizer; PM = poor metabolizer.

Outliers

The sponsor reported that no subjects had an absolute QTc above the upper limit of normal (450msec in males, 470msec in females). Ten of the 27 subjects (5/16 EM, 5/11 PM) had an increase in QTc of at least 30msec. No subjects had an increase in QTc at least 60msec. Subjects with increases in QTc of greater than 30 are identified below.

Table HFBJ.12.10. Individual QTc(F) Interval Changes >30 msec at Different Atomoxetine Doses Single Dose

Subject	QTc(F) interval (msec)	Baseline QTc(F) interval (msec)	Change in QTc(F) interval (msec)	Dose of atomoxetine	Time Post Dose (hr)
		366.3			
		374.2			
		370.0			
		369.5			
		370.1			
		380.0			
		380.0			
		379.3			
		378.6			
		382.9			
		326.6			
		326.6			
		377.7			
		373.9			
		373.9			
		369.2			

Abbreviations: EM = extensive metabolizer; PM = poor metabolizer; n = 27.

When outlier risk was analyzed as a percentage of the number of observations at each treatment/dose, there appeared to be a suggestion of dose response although the highest atomoxetine dose had the lowest risk. I provide those results in the following table.

Risk of QTc increase from baseline outlier as a percentage of the total number of observations, HFBJ

Treatment	# outliers	# observations	% outliers
Placebo	4	102	3.9%
10mg	2	54	3.7%
30mg	2	54	3.7%
60mg	3	52	5.8%
90mg	4	52	7.7%
120mg	1	50	2%

Data from HFBJ study report, p.112

Using plasma concentration data, the sponsor modeled the concentration QTc change relationship and portrayed the estimated QTc difference for the median plasma concentration observed following the 120mg dose for EM and PM groups separately. The largest predicted difference (4.2msec increase) was for the PM group at 2 hours post dose and had a p value of 0.15 (HFBJ study report, Table HFBJ.12.9. p.112).

Pooled Clinical Pharmacology Studies ECG Data

The sponsor presented pooled analyses of clinical pharmacology study ECG data with separate presentations of single and multi-dose study data. The sponsor's presentations included mean change analyses and outlier analyses. The sponsor used only data from subjects that were given atomoxetine alone and removed ECGs performed during co-administration of other drugs with atomoxetine (ISS p.427).

Mean change analyses

Single dose studies

The sponsor presented a table that provided the mean QTc change for atomoxetine subjects exposed to single 120mg doses compared to placebo. There was prolongation of QTc of 5.6msec at 1 hour ($p=.0694$) among EM subjects with the remaining time points showing smaller positive or negative changes. Among the PM subjects, the mean changes ranged from 4.8msec to 7.8msec over the examined time points. Those data are presented below.

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Table ISS.5.4.47. Comparison of 120-mg Atomoxetine and Placebo Fridericia-Corrected QT Interval (msec) In EM and PM Subjects

CYP2D6	Time	Treatment	Least-Square Mean	Difference Means	90% Confidence Interval	P-value
EM	1 HOUR	0	388.8	5.6	(-0.4, 11.6)	0.0694
		120	394.4			
	2 HOURS	0	380.2	2.4	(-2.7, 7.5)	
		120	382.6			
4 HOURS	0	388.6	-1.5	(-8.1, 5.1)		
	120	387.1				
24 HOURS	0	378.2	-2.3	(-7.5, 2.9)		
	120	375.9				
PM	1 HOUR	0	393.4	6.5	(-6.7, 19.8)	0.3328
		120	400.0			
	2 HOURS	0	385.2	7.2	(0.9, 13.4)	
		120	392.3			
4 HOURS	0	391.9	7.8	(-5.4, 21.0)		
	120	399.7				
24 HOURS	0	385.9	4.8	(-1.4, 11.1)		
	120	390.7				

Source Data: Data on file at Lilly Clinic.

Multi-dose studies

The sponsor presented a table that provided the mean QTc change for subjects exposed to different atomoxetine doses compared to placebo. Among EM subjects, there did not appear to be consistent evidence of QTc prolongation among atomoxetine subjects or evidence of dose response. Data for some of the PM subjects in this analysis, particularly those receiving 60mg bid and 75mg bid, come from trial LYAE (see above) and therefore reflect the findings of that study, providing little new information.

Outlier Analyses

When examining QTc increase >30msec, the sponsor did not find evidence of dose response from single dose EM or PM data or for the EM multi-dose data, based on a small number of events. The PM multi-dose data suggested dose response. That analysis is provided below. As mentioned above, these data include study LYAE and therefore provide little new information.

Analysis of Change in QTcF from baseline>30msec, Multiple dose PM data

Amount of Atomoxetine	Number of Events	Total number of time intervals
0mg	0	30
20mg	0	9
30mg	0	29
40mg	1	42
45mg	1	30
60mg	4	46

75mg	5	30
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Data from table ISS.5.4.50

The sponsor identified a single subject from clinical pharmacology studies with a QTc prolongation of at least 60msec when atomoxetine was administered alone. This female PM subject had a baseline QTc of 316.9msec and following a 40mg atomoxetine dose had a QTc of 400msec (+83.1msec increase) and a QTc of 403.4msec (+86.5msec). The sponsor commented that change is the result of the low baseline value and that the subject had "other" baseline QTc results that were higher (range 398.4 to 413.2msec).

Phase II/III study data

The sponsor's Phase II/III QT data analyses were included in separate sections of the ISS by safety subgroup. The sponsor also included QT information in a separate section, 6.1 where they provided an overview of cardiac effects along with additional analyses.

ADHD Child and adolescent overall analysis group

Mean change

The sponsor showed that the mean QTc change from baseline during these trials was -3.17 using Fridericia's correction and was -0.88 using a data based correction. There are no comparator data.

In ISS table A8.3, the sponsor identified subjects in this group that had QTcF results that met categorical outlier criteria. Five atomoxetine subjects had QTcF>500 (HFBE-5 QTc=626, LYAB-4054 QTc=523, LYAB-4806 QTc=509, LYBB-6564 QTc=510*, and LYBB-8105 QTc=501).

*No baseline QTc for this subject

An additional seventeen subjects met outlier criteria for absolute QTc (>450 males, >470 females) but did not exceed 500msec. The sponsor identified 14 subjects with a change from baseline of ≥60msec.

The sponsor provided the following table summarizing QTc outliers.

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Table ISS.4.2.19. Number of Patients Meeting CPMP Categorical QTc Interval Criteria Part I (Numerical Increases) Child and Adolescent Overall Integrated ADHD Database

		Atomoxetine			95% CI	
		N	n	%	Lower	Upper
Corrected QT Interval	Criteria*					
QTcD	Increases of at least 30	1880	206	11.0%	9.5%	12.4%
	Increases of at least 60	1880	21	1.1%	0.6%	1.6%
	Increases to Values of > 500	1880	4	0.2%	0.0%	0.4%
QTcF	Increases of at least 30	1880	151	8.0%	6.8%	9.3%
	Increases of at least 60	1880	14	0.7%	0.4%	1.1%
	Increases to Values of > 500	1880	4	0.2%	0.0%	0.4%

Population: All patients with a baseline and a post-baseline measurement, except patients reported as not taking any study drug.

*Computation based on the maximum treatment period value.

Source data: eagle:/programs_g/rmp/b4zs/iss/sect2_2/rpt/sect2.2.37.sas.

The sponsor identified one subject who discontinued from these trials for QT prolongation, based on Bazett's correction (longest QTc=482). The sponsor demonstrated that the QTc was less prolonged when corrected using Fridericia's correction (QTc=465). The sponsor showed that during the study, this subject's QTc increased on drug, decreased while continuing drug, continued to decrease after stopping drug, and then increased again off drug.

ADHD Child and adolescent acute placebo controlled analysis group

ECGs were performed at baseline (visits 1 or 2) and at visits 5,9,12,13 and at discontinuation during trials HFBD and HFBK. ECGs were performed at baseline and at visits 2,3,5,7 and at discontinuation during trial LYAC. The protocols for these trials did not specify timing of ECG measurement in relation to last dose or time of day:

Mean change

The sponsor reported that the Mean QTc (data corrected) change from baseline to endpoint among those randomized to atomoxetine was -3.083msec compared to -4.424msec for placebo. Using Fridericia's correction, the mean QTc change from baseline to endpoint among those randomized to atomoxetine was -5.345msec compared to -4.362msec for placebo.

Outliers

The risk for QTc outlier was greater among placebo subjects than atomoxetine subjects in these trials. The sponsor identified subjects with an increase QTc from baseline of at least 30msec and to a value of at least 440msec for their data corrected rate adjustment and an increase of at least 30msec to a value of at least 435msec using Fridericia's correction. The risk among placebo subjects was 3.5% (data corrected) and 2.5%

(Fridericia) compared to 0.9% (data corrected) and 0.3% (Fridericia) among atomoxetine subjects.

No subjects in these trials had an increased QTc of at least 60msec and no subjects had a QTc>500msec.

The sponsor also included a shift table summarizing QTc changes from baseline to endpoint from these trials. The table suggests a higher risk of a borderline or prolonged QTc among placebo subjects who were normal at baseline compared to atomoxetine subjects who were normal at baseline. Those data are provided below.

Table ISS.4.1.22. Number of Patients Meeting CPMP Categorical QTc Interval Criteria Part 2 (Interpretation at Baseline and Maximum)
Child and Adolescent Acute Placebo-Controlled ADHD Analysis Group

		Atomoxetine			Placebo		
		At Maximum*			At Maximum*		
		Normal	Borderline	Prolonged	Normal	Borderline	Prolonged
Corrected QT Interval	At Baseline						
	QTcD						
	Normal	292	17	0	169	18	2
	Borderline	8	5	2	9	2	0
	Prolonged	0	1	0	0	1	1
	QTcF						
	Normal	307	9	0	184	12	2
	Borderline	4	3	1	1	2	1
	Prolonged	0	1	0	0	0	0

*Criteria: For Males: Normal is <430, Borderline is ≥430 and <450, Prolonged is ≥450
For Females: Normal is <450, Borderline is ≥450 and <470, Prolonged is ≥470

The results were similar regardless of whether the final QTc or the maximum QTc was used in the analysis.

Adult Acute Placebo Controlled ADHD Studies

ECGs were performed at visits 1,3,4,6,7,8 and at discontinuation during trials LYAA and LYAO. The protocols for these trials did not specify timing of ECG measurement in relation to last dose or time of day.

Mean Change data

The QTcF mean change from baseline to endpoint among the atomoxetine subjects was -2.653 compared to 0.857 among placebo subjects. Using a data based correction, the mean change from baseline among the atomoxetine subjects was 0.627 compared to 0.768 among the placebo subjects.

Outliers

A slightly higher percentage of placebo subjects had increases in QTc of 30 and, 60msec compared to atomoxetine regardless of whether corrected using Fridericia's method or a data based correction (Table ISS.4.3.20, p.231 ISS). No atomoxetine subjects and 1 placebo subject had an absolute QTc>500 in the adult placebo controlled trials. Risks for absolute QTc>450 in males and >470 in females were similar for the atomoxetine and placebo groups (Tables ISS.4.3.21 and ISS.4.3.22)

Poor Metabolizers from Child and Adolescent ADHD Studies

These analyses utilize data from adolescent and pediatric atomoxetine subjects from both controlled and open label studies to compare extensive metabolizers to poor metabolizers. These data were updated in the sponsor's 2 month safety update and reflect the most current submission. One exception was for an outlier analysis identified below that appeared in the ISS and was not updated in the safety update.

Mean change

There appeared to be little difference between poor metabolizers and extensive metabolizers when comparing mean QTc change from baseline to endpoint. Using Fridericia's correction, the QTc mean change was -2.903 for EMs compared to -3.510 for PMs, p=.51. A data based correction yielded a mean QTc change of -0.647 for EMs and -0.042 for PMs, p=.141 (2 Month Safety Update, Table SU.4.6.21, p.90).

When considering only those subjects who received a maximum dose of atomoxetine ≥1.2mg/kg/day and using Fridericia's correction, the mean change among EMs was -3.597 and among PMs was -2.586. Among subjects receiving a maximum dose of atomoxetine ≥1.2mg/kg/day and using a data based correction, the mean QTc change was -1.132 for EMs and 1.226 for PMs (2 Month Safety Update, Table SU.4.6.22, p.91).

Outliers

A higher percentage of PMs (4.5%, 8/176) met increased outlier criteria for QTc* than EMs (2.1%, 40/1918) (2 Month Safety Update, Table SU.4.6.23, p.92). Considering only those subjects who received a maximum dose of atomoxetine ≥1.2mg/kg/day, 4.5% (5/112) of PMs met increased QTc outlier criteria* compared to 2.4% (35/1434) of EMs, p=.206 (2 Month Safety Update, Table SU.4.6.24, p.91).

*Using Fridericia's correction includes those with an increase of at least 30 and to at least 435.

An ISS analysis using different outlier criteria (subjects with increases ≥30, ≥60, and subjects with QTc>500) suggested little difference in risk between PMs and EMs (Tables ISS.5.1.30, ISS.5.1.32) for most of the comparisons. One comparison resulted in a difference with a p value <.05. Using a data based correction, the risk for QTc increase of at least 60 was 3.4% (4/119) for PMs and 1% (17/1750) for EMs (p=0.04).

The sponsor provided shift tables that suggest an increased risk of a borderline or prolonged QTc among those PMs who were normal at baseline. I've summarized those data in the table below.

Percentage of adolescent and pediatric subjects with a normal QTc at baseline who had a normal, borderline, or prolonged QTc, stratified by metabolic status

	Extensive			Poor		
	At Maximum			At Maximum		
	Normal	Borderline	Prolonged	Normal	Borderline	Prolonged
Overall	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)
QTc D	89% (1621)	10% (185)	1.3% (23)	82% (137)	15% (25)	3.6% (6)
QTcF	94% (1759)	5.1% (96)	0.7% (14)	91% (156)	6.4% (11)	2.3% (4)
≥1.2mg/kg/day*						
QTcD	87%	12% (158)	1.4% (19)	83% (91)	13% (14)	3.7% (4)

	(1196)					
QTcF	94% (1314)	5.5% (77)	1% (13)	94% (104)	3.6% (4)	2.7% (3)

Criteria for males: Normal <430, Borderline >=430 and <450, Prolonged >=450
 Criteria for females: Normal <450, Borderline >=450 and <470, Prolonged >=470

* Maximum dose recorded during a study

Data from Safety Update, Tables SU.4.6.27 and SU.4.6.28, pp.97-98

Other ISS database QTc presentations

The sponsor summarized QTc data collected during once daily dosing pediatric studies, methylphenidate controlled studies, and the adult depression and urinary incontinence studies. These analyses provided little additional useful information about the relationship between atomoxetine and QTc.

Additional NDA QTc Analyses

In addition to providing a summary of QTc findings from the atomoxetine development program, the sponsor provided additional analyses in this section of the NDA.

In their first presentation the sponsor provided a graph illustrating the mean QTc change from baseline for subjects observed at least 1 year from the pediatric ADHD database. For those subjects who could tolerate treatment for 1 year there did not appear to be progressive increase in QTc. There appeared to be a 4msec increase in the first month of treatment. (ISS p.537)

The sponsor also provided a graph of the changes from baseline to final QTc versus daily dose in patients with at least 1 year of atomoxetine treatment in the child and adolescent ADHD group. There did not appear to be strong evidence of a dose response relationship from this graph.

The sponsor identified two subjects with QTc outliers and provided additional information for these subjects. The sponsor noted that Subject LYBB-44-7029 had QTcB of 480, 458, and 465msec on atomoxetine and after the trial was diagnosed with congenital long QT syndrome. The sponsor identified subject LYAB-62-5541 with increases in QTc during the study but noted that these findings occurred during a period that the study medication was stopped.

Safety Update presentations

The sponsor included two new analyses of QTc data in the safety update. The first was a plasma concentration QTc relationship analysis and the second looked at the effect of fluoxetine in study LYAQ.

Plasma concentration versus QTc change from baseline

The sponsor provided plots of the atomoxetine plasma concentration vs. QTc change from baseline using data from 357 adolescent and pediatric subjects in open label ADHD trials LYBB and LYAQ (Safety update, Section 7, p.134-139). The data did not support a relationship between QTc change from baseline and plasma atomoxetine concentration at trough, peak or combined timing, although each subject's baseline appears to have been a single ECG and the highest atomoxetine plasma concentration plotted was <2000ng/mL.

Study LYAQ

The investigators administered fluoxetine, an inhibitor of CYP2D6, to convert genotypic extensive metabolizers into phenotypic poor metabolizers. The sponsor stated that criteria for phenotypic poor metabolizers were agreed upon a priori using the mean atomoxetine plasma concentrations for each dose expected in genotypic poor metabolizers. Subjects within 2 standard deviations of expected mean concentrations for a given dose were defined as poor metabolizers. Forty-six of the 141 subjects treated with fluoxetine and atomoxetine met criteria for poor metabolizers. The sponsors used a data based correction in their analyses.

Subjects exposed to atomoxetine and placebo had a mean QTc change from baseline of -3.36 while those exposed to atomoxetine plus fluoxetine had a mean QTc change from baseline of 4.64. There was no fluoxetine-alone treatment arm in this study. Considering fluoxetine plus atomoxetine subjects by their phenotypic metabolic status, phenotypic extensive metabolizers had a mean QTc change from baseline of 4.9 while phenotypic poor metabolizers had a mean QTc change from baseline of 3.76.

The sponsor pooled data from all studies to create a table looking at mean QTc change from baseline for combinations of metabolic status and presence or absence of concomitant fluoxetine. This likely includes a variety of doses and data from studies of different designs therefore the interpretation of these results is not straightforward.

QTc changes from baseline, stratified by metabolic status and concomitant fluoxetine

		Fluoxetine		p-value
		Yes	No	
CYP2D6	EM	4.90	-0.91	<.001
	PM	3.76	-1.26	<.001
	p-value	.64	.81	

The sponsor interprets these findings as supporting an association between fluoxetine and increase in QTc although the sponsor acknowledges that it is not possible to rule out an atomoxetine-fluoxetine interaction.

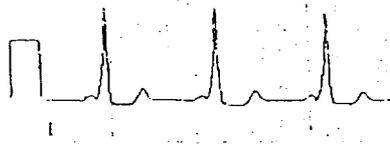
The sponsor reported that no patients in either the atomoxetine + fluoxetine group or the atomoxetine + placebo group with >60msec increase in QTc.

4.8 Wolf Parkinson White Syndrome

During the NDA review, the sponsor submitted reports of two atomoxetine subjects from ongoing studies with ECG findings consistent with Wolf Parkinson White syndrome (WPW). While both reports mentioned ECG findings of WPW, neither report noted arrhythmias. In the first case, the subject had 11 normal ECGs over a one-year period while taking atomoxetine prior to the ECG with the abnormality. In that case, the subject discontinued atomoxetine and subsequent ECGs were normal. In the second case, the subject had a short PR interval noted on a pre atomoxetine/screen ECG (108msec) and had a family history of WPW. This subject discontinued atomoxetine and had persistent ECG findings of WPW. Neither subject had a documented rechallenge.

WPW is a syndrome of recurrent tachyarrhythmias in individuals with electrocardiographic evidence of pre-excitation. WPW may be identified on an ECG tracing by the presence of a shortened PR interval (<120msec), a widened QRS

complex (>120msec) and a delta wave (slurred slow rising onset of the QRS complex). An example of such an ECG is provided below.



WPW results from cardiac impulse conduction over an accessory pathway, which allows activation of all or part of the ventricular muscle earlier, in relation to atrial events, than would be expected by way of the normal atrioventricular conduction system. In Western countries, the prevalence of WPW is 1.5-3/1,000 persons. The pre-excitation can be intermittent and may have led to an underestimation of the true prevalence of WPW.*
 *Al-Khatib S, Pritchett E. Clinical Features of Wolf-Parkinson-White syndrome. American Heart Journal 1999;138:403-13.

To further investigate WPW in atomoxetine subjects we asked the sponsor to identify any other cases in their atomoxetine database. The sponsor identified 11 subjects with possible WPW after examining the conduction field in the ECG database for abnormalities. I summarize the data for these subjects in the following table.

Subjects identified with ECG results consistent with WPW, ADHD safety database

Subject	Treatment	Comments
LYAB-037-4482, 12-yr-old male	ATX	Short PR at baseline (91msec), WPW identified on visit 4 ECG
LYAB-042-4691, 15-yr-old male	ATX	Short PR at baseline (112msec), WPW not identified
LYAB-051-5105, 7-yr-old male	ATX	Short PR at baseline (92msec), WPW not identified
LYAB-056-5303, 9-yr-old male	ATX	Short PR at baseline (100msec), APD* visit 12, WPW visit 13, Short PR remaining visits
LYAB-085-4163, 11-yr-old male	ATX	Short PR at baseline (100msec), Visit 6 WPW, Visits 20-29 WPW
LYAB-096-6165, 10-yr-old male	ATX	R axis deviation at baseline, APD* visit 6-10, 13, 14, WPW at visit 15 (PR 120msec, QRS 80msec)
LYAC-017-7264, 12-yr-old male	ATX	WPW identified at baseline and throughout study
LYAC-055-7526, 11-yr-old male	ATX	WPW identified at baseline and throughout study
LYAA-075-2356, 43-yr-old male	PBO	Short PR at baseline, and intermittently during study
LYAO-021-3554 69-yr-old female	ATX	Normal at baseline and through visit 6, short PR visits 7 (96msec) and 8 (100msec) remaining ECGs normal
LYAO-083-3456, 48-yr-old male	ATX	Short PR at baseline only (108msec), intermittent incomplete RBBB,

*Atrial Premature Depolarization

Nine of these eleven subjects had either short PR or WPW identified on their baseline ECGs. One subject had a treatment emergent ECG with shortened PR. The remaining subject had a single ECG with a machine reading of WPW but the PR interval (120msec by my reading) and QRS (80msec) are not consistent with the machine diagnosis.

4.9 Drug Demographic Interactions

The sponsor explored the adverse event profile and lab data by gender, origin (race) and age. The sponsor presented risks for the overall ADHD group but since there is no comparator in this database, one cannot examine relative risks by demographic strata. Therefore one cannot determine if the observed risk differences are due to a demographic/drug interaction or merely reflect background differences in risk for the particular stratum.

The sponsor also presented the results from the pediatric placebo controlled ADHD trials and the adult placebo controlled ADHD trials, which do allow for comparisons of relative risks. These results will be summarized below.

4.9.1 Adverse Events by Gender

Child and Adolescent Placebo Controlled BID ADHD Studies

In general, the relative risks for adverse events were similar when stratified by gender. In the following table, I summarize AEs from Child and Adolescent Placebo Controlled BID ADHD Database where the relative risk compared to placebo was >2 in at least one of the gender groups and there was at least a two fold difference when comparing the relative risks between gender groups.

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

Event	Risk in Females		RR _F	Risk in Males		RR _M
	ATX (n=92)	PBO (n=45)		ATX (n=248)	PBO (n=162)	
Headache	29.3% (27)	11.1% (5)	2.6	25.4% (63)	30.2% (49)	0.8
Anorexia	14.1% (13)	13.3% (6)	1.1	15.3% (38)	4.3% (7)	3.6
Vomiting	15.2% (14)	2.2% (1)	6.9	9.3% (23)	11.7 (19)	0.8
Cough increase	19.6% (18)	4.4% (2)	4.5	7.3% (18)	9.9% (16)	0.7
Nervousness	5.4% (5)	11.1% (5)	0.5	10.1% (25)	4.3% (7)	2.3
Emotional lability	2.2% (2)	8.9% (4)	0.2	6.5% (16)	0.6% (1)	10.8
Infection	7.6% (7)	2.2% (1)	3.5	2% (5)	3.7% (6)	0.5
Abnl dreams	4.3% (4)	2.2% (1)	2.0	0.4% (1)	2.5% (4)	0.2
Sleep disorder	2.2% (2)	2.2% (1)	1.0	1.6% (4)	0.6% (1)	0.4

From Sponsor's Table ISS.A10.2, pp.2222-2229.

Adult ADHD Placebo Controlled Studies

Like the pediatric studies there were few adverse events in the adult studies with differing risks by gender. In the following table, I list the treatment emergent AEs where the relative risk compared to placebo was >2 in at least one of the gender groups and there was at least a two fold difference when comparing the relative risks between gender groups.

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

Event	Risk in Females		RR _F	Risk in Males		RR _M
	ATX (n=95)	PBO (n=91)		ATX (n=174)	PBO (n=172)	
Abdominal pain	3.2% (3)	1.1% (1)	2.9	4.6% (8)	6.4% (11)	0.7

Nervousness	4.2% (4)	3.3% (3)	1.3%	2.9% (5)	0.6% (1)	4.8%
Rash	3.2% (3)	4.4% (4)	0.7%	2.9% (5)	0.6% (1)	4.8%
Asthenia	10.5% (10)	2.2% (2)	4.8%	3.4% (6)	3.5% (3)	1.0%
Dizziness	4.2% (4)	3.3% (3)	1.3%	7.5% (13)	1.2% (2)	6.3%
Sinusitis	7.4% (7)	7.7% (7)	1.0%	6.3% (11)	1.7% (3)	3.7%
Parathesia	3.2% (3)	3.3% (3)	1.0%	4.6% (8)	1.7% (3)	2.7%
Chills	1.1% (1)	2.2% (2)	0.5%	4.0% (7)	0.6% (1)	6.7%

From Sponsor's Table ISS.A10.5, pp.2242-2250.

When comparing the results of pediatric and adult AE analyses stratified by gender, Nervousness was the only AE that demonstrated a similar result in both data sets. The relative risk for nervousness compared to placebo was higher among males compared to females in both analyses.

4.9.2 Lab Outliers by Gender

The sponsor found no statistically significant differences for lab outliers from Child and Adolescent Placebo Controlled BID ADHD studies or Adult placebo controlled studies when stratified by gender (ISS p.578, 584).

4.9.3 Vital Signs, Weight, and QTc by Gender

Child and Adolescent Placebo Controlled BID ADHD studies

With the exception of systolic blood pressure, the vital sign mean changes from baseline compared to placebo were similar for females and males. For systolic blood pressure, the mean change in females compared to placebo was -1.09mmHg while the mean change compared to placebo in males was 0.8mmHg (ISS, p.580).

The sponsor demonstrated that the data corrected QTc mean change from baseline compared to placebo was similar for female (3.7) and male (0.9) atomoxetine pediatric subjects (ISS, p.583).

Adult ADHD Placebo Controlled Studies

The vital sign mean changes from baseline compared to placebo were similar for adult females and adult males. In contrast to the pediatric results, systolic BP was increased compared to placebo for both adult females (3.43mmHg) and adult males (2.54mmHg) (ISS,p.585).

The data corrected QTc mean change from baseline compared to placebo for atomoxetine adult females was -1.08 and atomoxetine adult males was 0.37 (ISS, p.587).

4.9.4 Adverse Events by Origin (Race)

Child and Adolescent Placebo Controlled BID ADHD Studies

The sponsor compared AE profiles for Caucasians and non-Caucasians. There were infrequent differences in the RR for AEs in this stratified analysis. Using the criteria from above, the AEs with RRs that differed by origin are listed below.