

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Atomoxetine has been shown to be effective in the treatment of ADHD in the pediatric and adult population. The sponsor also provided evidence to support effectiveness of atomoxetine for both once and twice daily dosing.

From a clinical efficacy perspective, it is recommended that atomoxetine be approved for the treatment of ADHD in the pediatric and adult population.

B. Recommendation on Phase 4 Studies and Risk Management Steps

The sponsor has collected a very limited profile of patients who are genotypically CYP2D6 poor metabolizers (PMs); the number of PMs is too low to determine an accurate efficacy or safety profile. Also, the sponsor has not identified a lowest effective dose, and has only identified the high end dosage range (the 1.2 mg/kg/day and 1.8 mg/kg/day showed similar results). It is recommended that the sponsor consider these issues as they enter Phase IV of drug development.

The one relapse prevention study submitted demonstrated negative findings. It is recommended that the sponsor continue to assess efficacy for long term use, as well as generate safety data extending beyond one year.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The sponsor states that they have conducted a total of 14 studies in patients diagnosed with ADHD of which 3 of these studies are ongoing, and the data was not included in the original submission. Of the eleven studies submitted in patients with ADHD, there were seven placebo controlled studies and four open label studies.

B. Efficacy

Atomoxetine is a norepinephrine reuptake inhibitor that has been adequately studied to support a claim for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in both the pediatric and adult populations. There were seven placebo-controlled efficacy studies submitted, of which five were conducted in the pediatric population, and two studies included only adults. The **five pediatric studies** included **three** short term placebo-controlled studies with twice daily dosing (HFBD, HFBK, LYAC), **one** short term placebo controlled study with once daily dosing (LYAT), and **one** relapse prevention study with twice daily dosing (HFBE). The **two adult studies** were both short term placebo-controlled with twice daily dosing (LYAA, LYAO). Study HFBE, a year long, placebo controlled relapse prevention study, had negative results and was not reviewed, because the study did not support any of the claims which the sponsor has requested in this current submission.

This review is primarily concerned with the efficacy of atomoxetine. Please refer to the review by Dr. Gerald Boehm (HFD-120) for the safety review for atomoxetine.

C. Dosing

As stated in the proposed labeling, dosing in the pediatric population, in individuals ≤ 70 kg body weight, is to be initiated at approximately 0.5 mg/kg, titrated to 1.2 mg/kg after 3-7 days, and, if needed, further titration up to 1.2 mg/kg over a period of 2-4 weeks. Dosing for pediatric patients weighing > 70 kg and for adults begins with an initial daily dose of 40 mg, titrated to 80 mg after 3-7 days, and then titrated up to a maximum of 120 mg over a 2-4 week period depending of efficacy response. For pediatric patients ≤ 70 kg, the maximum recommended dose is 1.8 mg/kg or 120 mg, which ever is less. For patients > 70 kg, the maximum recommended dose is 120 mg daily.

E. Special Populations

In patients diagnosed with moderate to severe hepatic insufficiency (with CYP2D6 extensive metabolizer genotype), a reduced clearance, increased exposure, and increased half life of atomoxetine was observed after administration of a single dose of 20 mg atomoxetine. Clearances observed were 20.0 L/hr for moderate hepatic insufficiency, 10.8 L/hr for severe hepatic insufficiency compared to 41.5 L/hr for individuals with normal hepatic functioning. It is recommended that, when administered, dosages of atomoxetine be adjusted according to the severity of hepatotoxicity.

Patients diagnosed with end stage renal disease (with CYP2D6 extensive metabolizer genotype) were observed to have a higher systemic exposure of atomoxetine and its metabolites after administration of a single dose of 20 mg atomoxetine. Dose adjustment of atomoxetine would be needed according to the severity of renal insufficiency.

For both of these conditions, it would be prudent to consider the need for further dose adjustment if the patient also is a CYP2D6 poor metabolizer.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

Atomoxetine HCl is an inhibitor of the pre-synaptic norepinephrine transporter, and is considered the R(-) isomer by x-ray diffraction. Originally, the sponsor had requested the trade name to be ~~Strattera~~ but a revised request has proposed the trade name to be Strattera. The proposed indication is for the treatment of attention deficit and hyperactivity disorder (ADHD) in both the pediatric and adult populations, and can be administered as a single dose in the morning or evenly divided doses in the morning and late afternoon/early evening. As stated in the proposed labeling, dosing in the pediatric population, in individuals ≤ 70 kg body weight, is to be initiated at approximately 0.5 mg/kg, titrated to 1.2 mg/kg after 3-7 days, and, if needed, further titration up to 1.2 mg/kg over a period of 2-4 weeks. Dosing for pediatric patients weighing > 70 kg and for adults is an initial daily dose of 40 mg, titrated to 80 mg after 3-7 days, and then titrated up to a maximum of 120 mg over a 2-4 week period depending of efficacy response. For pediatric patients ≤ 70 kg, the maximum recommended dose is 1.8 mg/kg or 120 mg, which ever is less. For patients > 70 kg, the maximum recommended dose is 120 mg daily.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

The chemical structure for atomoxetine HCl is the following:



The chemical name is benzenepropanamine, N-methyl-gamma(2-methylphenoxy) hydrochloride, (-). Atomoxetine has been determined to be the R(-) isomer by x-ray diffraction. The proposed capsule formulations would include atomoxetine 5 mg, 10 mg, 18 mg, 25 mg, 40 mg, or 60 mg.

The most recent proposed (1/31/02) trade name for atomoxetine is "Strattera."

B. Animal Pharmacology and Toxicology

Atomoxetine HCl is identified as a potent inhibitor of the pre-synaptic norepinephrine transporter (NET). Two primary metabolites identified were 4-hydroxyatomoxetine (demonstrating a similar in vitro potency to NET as atomoxetine) and N-desmethylatomoxetine (demonstrating less NET in vitro potency than atomoxetine).

In a single dose oral toxicity study, the estimated median lethal oral doses in cats was 25 mg/kg, in dogs 37 mg/kg, in rats 190 mg/kg, and in mice 274 mg/kg. At sublethal doses, clinical signs observed were mydriasis, reduced pupillary light reflex, mucoid stools, salivation, emesis, lethargy, weak legs, tremors, myoclonic jerking, and convulsions.

In repeat dose rodent toxicology studies, decreased body weight gain and hepatic toxicity (increased liver weights, hepatocellular vacuolation, and increased ALT values) were observed, with a high incidence of mortality in male mice in the 3 month toxicokinetic study.

In studies in young rats, delays in onset of puberty were observed in addition to decreases in epididymal sperm count of rats. This did not appear to have effects on the rodents' ability to reproduce.

In rat reproduction studies, there was a decrease in the weight of the fetus and decreased survival was observed at average doses of 23 mg/kg/day.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

For complete details, please refer to the Clinical Pharmacology and Biopharmaceutics review by Hong Zhao, Ph.D.

Atomoxetine HCl is metabolized primary through the CYP2D6 enzymatic pathway. Atomoxetine has been shown to be rapidly absorbed, reaching a maximum concentration approximately 1-2 hours after dosing.

In humans, variations of the CYP2D6 genotype has been characterized as being phenotypically poor metabolizers (PM) or extensive metabolizers (EM). In adult CYP2D6 extensive metabolizers, the mean elimination half-life is approximately 5.2 hour with a mean apparent plasma clearance of 0.35 L/hr/kg, while in CYP2D6 poor metabolizers, the mean elimination half-life is 12.6 hours with a mean apparent plasma clearance of 0.034L/hr/kg. The AUC of atomoxetine is 10 time greater in CYP2D6 poor metabolizers (PMs) than in extensive metabolizers (EMs); while the C_{max} is 5 times greater in PMs than observed in EMs.

The major metabolite identified in PMs and EMs is 4-hydroxyatomoxetine (equipotent to atomoxetine, but with less circulation), and is metabolized as 6% of atomoxetine concentration in EMs, and at a slower rate in PMs as 0.1% of atomoxetine concentration. Another metabolite identified is N-desmethylatomoxetine (less potency than atomoxetine) which circulates as 5% of atomoxetine concentration in EMs and as 45% of atomoxetine concentration in PMs. Elimination is primary through the urine (>80 % of dose), and some through feces (< 17% of the dose). Excretion of atomoxetine is primary in the metabolized form as 4-hydroxyatomoxetine-*O*-glucuronide with less than 3% of unchanged atomoxetine being excreted.

In adults, there was some decrease in C_{max} (↓38%) and delayed t_{max} (by 3 hours) observed with a high fat diet, whereas in a population analysis in the pediatric studies, there was only a 9% decrease in C_{max}. Food effects were not considered to be clinically significant.

B. Pharmacodynamics

For complete details, please refer to the Clinical Pharmacology and Biopharmaceutics review by Hong Zhao, PhD.

Effects reported by Dr. Zhao in the pharmacological studies included postural hypotension with compensatory heart rate increases observed following a single dose, and in some cases after multiple doses. Also observed were clinically significant decreases in orthostatic systolic blood pressure, which appeared to be more pronounced in CYP2D6 poor metabolizers (PMs) than in extensive metabolizers (EMs).

Dose-related mean heart rate increases were confirmed by ECG analysis and found to be statistically significant; PMs were found to have maximum heart rates at 10 bpm greater than those observed in EMs. PMs were also noted to have the largest QTc prolongation (30 msec after 75 mg bid) at trough.

IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data in this review are the clinical trials submitted by the sponsor.

B. Tables Listing the Clinical Trials Reviewed for Efficacy

Table 1 (below) summarizes the placebo controlled efficacy studies included in this submission for atomoxetine. All studies included in this table were reviewed with the exception of Study HFBE, the pediatric relapse prevention study. Study HFBE was not reviewed because the results were negative and did not support any of the claims which the sponsor had based this current submission.

Table 1: Table of all Placebo-Controlled Efficacy Studies in NDA 21-411

STUDY	DESIGN	POPULATION	DOSE
PEDIATRIC STUDIES—SHORT TERM PLACEBO CONTROLLED—BID DOSING			
HFBF	Double-blind, placebo and MPH controlled, multicenter, 9 week study Stratified according to prior exposure to MPH. Extensive Metabolizers only.	<u>Stimulant-Naïve:</u> Atomoxetine: n=30 (M:20; F:10) MPH: n=20 (M:19; F:1) Pbo: n=27 (M:23; F:4) <u>Stimulant-Prior Use:</u> Atomoxetine: n=35 (M:27; F:8) Pbo: n=35 (M:30; F:5) Ages: 7-12	Atomox: 5-90 mg/day (bid) (max dose: 2 mg/kg/day or 90 mg/day) MPH: 5-60 mg/day (bid) (max dose: 1.5 mg/kg/day or 60 mg/day)
HFBK	Double-blind, placebo and MPH controlled, multicenter, 9 week study Stratified according to prior exposure to MPH Extensive Metabolizers only.	<u>Stimulant-Naïve:</u> Atomoxetine: n=26 (M:20; F:6) MPH: n=18 (M:16; F:2) Pbo: n=26 (M:17; F:9) <u>Stimulant-Prior Use:</u> Atomoxetine: n=38 (M:31; F:7) Pbo: n=36 (M:33; F:3) Ages: 7-12	Atomox: 5-90 mg/day (bid) (max dose: 2 mg/kg/day or 90 mg/day) MPH: 5-60 mg/day (bid) or 60 mg/day
LYAC	Double-blind, placebo-controlled, 8 week study Stratified by CYP2D6 status and prior exposure to MPH	Atomoxetine: n=213 (M:152; F:61) Pbo: n=84 (M:60; F:24) PM: atomox: n= 10 pbo: n=6 Ages: 8-18	Atomox: 1.2 or 1.8 mg/kg/day (bid) (0.5 mg/kg/day was not statistically analyzed)
PEDIATRIC STUDIES—SHORT TERM PLACEBO CONTROLLED—ONCE DAILY DOSING			
LYAT	Double-blind, placebo-controlled, 6 week study	Atomoxetine: n=85 (M:59; F:26) Pbo: n=86 (M:60; F:26) (PM: atomox: n=1 pbo: n=4) all others were EM Ages: 6-16	Atomox: 0.5-1.5 mg/kg/day (ONCE DAILY DOSING)
PEDIATRIC STUDIES—RELAPSE PREVENTION—BID DOSING			
HFBE	Relapse Prevention Study: <i>Period II:</i> multiple center, open label (10 weeks): Atomox. or MPH <i>Period III:</i> double-blind, placebo-controlled discontinuation study (48 weeks): Atomox. or placebo	Atomoxetine: n=184 (M:167;F:17) MPH: n=44 (M:44; F: 0) Ages: 7-15	Atomox: 5-90 mg/day (bid) 0.4-2 mg/kg/day MPH: 5-60 mg/day (qd to tid)
ADULT STUDIES—SHORT TERM PLACEBO CONTROLLED—BID DOSING			
LYAA	Double-blind, placebo-controlled, 10 week study Stratified by CYP2D6 status	Atomoxetine: n=141 (M:91; F:50) Pbo: n=139 (M:87; F:52) By genotype: PM: atomox: n= 10 Pbo: n=9 Ages: 18-67	Atomox: 60-120 mg/day (bid)
LYAO	Double-blind, placebo-controlled, 10 week study Stratified by CYP2D6 status	Atomoxetine: n=129 (M:83; F:46) Pbo: n=127 (M:87; F:40) Ages: 18-76	Atomox: 60-120 mg/day (bid)

C. Postmarketing Experience

As of October 12, 2001, atomoxetine is not marketed anywhere in the world according to the original NDA submission.

D. Literature Review

The sponsor submitted eight literature articles in which atomoxetine was discussed. Anorexia was observed as a significant adverse event in patients treatment with atomoxetine compared with placebo (Allen, 2001), and a dose related loss of weight was observed in a pediatric study (Michelson, in press at time of submission). Other adverse events reported in patients taking atomoxetine included insomnia, anxiety, constipation, headache, sweating, palpitations, tremors agitation, abdominal spasms, and rash which recurred upon rechallenge (Chouinard, 1984; Kratochvil, 2001). Three other articles were located from a MedLine search of which the abstracts did not contain any new information.

V. Clinical Review Methods

A. How the Review was Conducted

The sponsor states that they have conducted a total of 14 studies in patients diagnosed with ADHD of which 3 of these studies are ongoing, and the data was not included in the original submission. Of the eleven studies submitted in patients with ADHD, there were seven placebo controlled studies and four open label studies.

There were seven placebo-controlled efficacy studies submitted, of which five were conducted in the pediatric population, and two studies included only adults. The **five pediatric** studies included three short term placebo-controlled studies with twice daily dosing (HFBD, HFBK, LYAC), one short term placebo controlled study with once daily dosing (LYAT), and one relapse prevention study with twice daily dosing (HFBE). The **two adult** studies were both short term placebo- controlled with twice daily dosing (LYAA, LYAO). Study HFBE, a year long, placebo controlled relapse prevention study, had negative results and was not reviewed, because the study did not support any of the claims which the sponsor has requested in this current submission.

This review is primarily concerned with the efficacy of atomoxetine. Please refer to the review by Dr. Gerald Boehm (HFD-120) for the safety review for atomoxetine.

B. Overview of Materials Consulted in Review

The materials used in this review included the following:

Original NDA Submission: October 11, 2001

Statistical Review by Ning Li, Ph.D. (6/14/02)

Office of Clinical Pharmacology and Biopharmaceutics Review by Hong Zhao, Ph.D. (6/19/02)

C. Overview of Methods Used to Evaluate Data Quality and Integrity

According to a correspondence from the sponsor (2/14/02, there were documentation errors identified at Site #21 (Dr. Scott West in Orlando, FL). The sponsor conducted an internal audit of Study HFBD and identified documentation errors including omissions on case report forms of adverse events and concomitant medications, incorrect dates, and incomplete verification of physician notes by the site monitor. This site was also involved in studies LYAC and LYAD. The individual studies were re-analyzed with this site omitted (please refer to the individual studies below), and the results did not appear to have changed the statistical significance of the efficacy studies.

From DSI correspondences (3/25/02), it appeared that other inspection sites were acceptable based on on-site investigations.

D. Evaluation of Financial Disclosure

The sponsor submitted financial disclosure information for the following studies: HFBD, HFBK, LYAC, LYAA, LYAO, LYAT, LYAL, LYAZ, LYAD, LYAZ, LYAB, and LYAB.

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Medical Director of the Atomoxetine Product Team signed the Form 3454 testifying that, to his knowledge, there was no financial arrangement made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). The Medical Director of the Atomoxetine Product Team also signed Form 3455 which itemizes the following individuals as having significant disclosures of financial interests:

VI. Integrated Review of Efficacy

A. Conclusions and Critical Differences from Sponsor's Proposed Label Claims

The review of the efficacy data supports the sponsor's claim that atomoxetine demonstrated effectiveness in the treatment of ADHD in the pediatric and adult population. The sponsor also provided sufficient data to support a claim that atomoxetine was effective when administered in once daily dosing or in two divided doses.

Unfortunately, the sponsor did not assess doses between the 0.5 mg/kg/dose and 1.2 mg/kg/dose for a better picture of the lowest effective dose in the pediatric population. Results at the 0.5 mg/kg/day dosing did not support efficacy at this dose. Effectiveness was established for the doses of 1.2 mg/kg/day and 1.8 mg/kg/day, but the 1.8 mg/kg/day dose was not associated with any efficacy benefit over the 1.2 mg/kg/day dose.

Because of the results from Study LYAC in which there appeared to be little difference in the efficacy findings between the 1.2 and 1.8 mg/kg/day dose (in fact, the 1.2 mg/kg/day group had better numerical improvement), it might be prudent for the physician to consider whether or not it is appropriate to recommend dosing as high as 1.8 mg/kg/day. This issue becomes even more important and concerning if the patient is also genotypically a CYP2D6 poor metabolizer (PM) and is already receiving 10 times the drug exposure than an extensive metabolizer receives. An increase in dose for a PM could not only expose the patient to the risk of unnecessary adverse events, but also would provide no benefit. It is recommended that when physicians are considering an increase to 1.8 mg/kg/day, they consider characterizing their patient's CYP2D6 status prior to increasing the dose.

B. General Approach to Review of the Efficacy of the Drug

This review will address six of the seven placebo controlled studies. The seventh study, Study HFBE was a 48 week double-blind placebo controlled discontinuation study; it was not reviewed, because the results were negative and did not support any of the claims which the sponsor had based this current submission. Many of the individual study designs included other portions or periods beyond the placebo-controlled portion (please see Appendix C for the sponsor's schematic of individual study designs); however, the only periods discussed in this review are the placebo controlled period.

There were four pediatric studies reviewed, Studies HFBD, HFBK, LYAC and LYAT. Studies HFBD and HFBK were both 8 week placebo controlled studies conducted in the pediatric population in patients diagnosed with ADHD aged 7-12 years olds; dosing was twice daily. Study LYAC had an 8 week placebo controlled portion in patients diagnosed with ADHD aged 8-18 year olds; dosing was twice daily. Study LYAT was the only single dose study, and was conducted in the pediatric population aged 6-16 year olds in an 8 week placebo controlled design.

There were two studies submitted to support the efficacy of atomoxetine for the treatment of ADHD in adults, studies LYAA and LYAO. Studies LYAA and LYAO both had a 10 week placebo controlled period in adult patients (age ranged from 18-76) diagnosed with ADHD. Dosing was twice daily for both of these studies.

This review will discuss only the primary efficacy variables of each study. The pediatric studies utilized The ADHDRS-IV-Parent: Inv (see Appendix A) as the primary efficacy variable of the pediatric studies. The sponsor used a novel approach to an old instrument. The ADHDRS-IV-Parent: Inv is a modified version of the ADHDRS-IV-Parent scale, an 18 item scale in which each item describes a DSM-IV criteria of the ADHD diagnosis (0=rarely/never, 3=very often) that can each be scored ranging from zero to three by parents. The sponsor revised the ADHDRS-IV-Parent rating scale by having the investigator score the ADHDRS-IV-Parent:Inv. based on interviews with parents about their children's behavior at weekly visits.

The adult studies utilized the Conners Adult ADHD Rating Scale-Investigator rated: Screening Version (CAARS-INV:SV) as the primary efficacy variable. Please see Appendix B for a copy of this 30 item scales which assesses the symptoms of ADHD.

C. Detailed Review of Trials

1. Study HFBD

Investigators/Location

This study was conducted at 7 centers in the United States including 9 principle investigators. Please refer to the sponsor's study report of HFBD Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to determine the safety and efficacy of atomoxetine in treating pediatric patients aged 7-12 years old diagnosed with ADHD.

Population

Patients chosen for this study were physically healthy, aged 7-12 years old, and diagnosed with ADHD according to the DSM-IV criteria. Required for participation was a score on the ADHDRS-IV-Parent above 1.5 standard deviations for the age/gender norm, in addition to an IQ score ≥ 80 . Excluded from the study were CYP2D6 poor metabolizers and patients with a history of bipolar I or II disorder, psychosis, seizure disorder, alcohol/drug abuse, or glaucoma. Sexually active females were required to use medically accepted forms of birth control.

Design

This was a 7 site, 9 week, randomized, double blind, placebo and comparator (methylphenidate) controlled study. Patients were stratified according to prior use of methylphenidate. The study was preceded by a washout/screening phase, and concluded with a week long single blind discontinuation phase (please see Appendix C for the sponsor's schematic of the entire study plan). Stimulant-naïve patients were randomized to one of the following 3 treatment groups: 1) **atomoxetine** (5-90 mg/day bid before and after school with placebo given during school hours), 2) **methylphenidate** (5-60 mg/day bid before and during school with placebo given after school), or 3) **placebo**. Patients with prior exposure to stimulants were randomized to treatment with either **atomoxetine** (5-90 mg/day bid before and after school) or **placebo**. Psychotropic medications and sympathomimetic medications were not permitted during the study. Diphenhydramine was permitted to be used prn insomnia.

Screening included a history and physical, ECG, routine labs, pregnancy test (for sexually active females), urinalysis, and CYP2D6 and DRD4*7 genotyping. Vital signs were monitored weekly; ECGs and laboratory analyses were obtained monthly throughout the study.

Analysis Plan

The primary efficacy variable was the change from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score (see Appendix A for a copy of the ADHDRS-IV-Parent:Inv). The ADHDRS-IV-Parent:Inv is a modified version of the ADHDRS-IV-Parent scale, an 18 item scale in which each item describes a DSM-IV criteria of the ADHD diagnosis (0=rarely/never, 3=very often) that can each be scored ranging from zero to three by parents. The sponsor revised the ADHDRS-IV-Parent rating scale by having the investigator score the ADHDRS-IV-Parent:Inv. based on interviews with parents about their children's behavior at weekly visits.

The primary efficacy analysis used was an analysis of variance (ANOVA) model to assess treatment differences of atomoxetine and placebo. The sponsor included methylphenidate in the stimulant-naïve stratum for study validation, but did not use results from patients assigned to methylphenidate in the primary analysis. Secondary efficacy variables included the ADHDRS-IV-Parent:Inv subscale scores, CTRS-R:S subscale scores, CRPS-R:S subscale scores, CGI-ADHD-S, and RAS measures.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 199 patients entered, 147 patients were screened and randomized into double-blind treatment which included 77 stimulant naïve patients and 70 patients with prior stimulant exposure. Reasons given for ineligibility included lost to follow-up (n=5), personal conflict (n=15), entry criteria not met (n=28), and physician decision (n=4).

Of the 77 patients in the stimulant naïve group, 20 (26%) discontinued and 57 (74%) completed the study; of this stratum, completion rates were as follows for each group: atomoxetine 73.3%, methylphenidate 55%, placebo 88.9%. For the stimulant prior exposure stratum, the study was completed by 50 (71.4%) of patients including 77.1 % in the atomoxetine group and 65.7 % in the placebo group. Reasons for early withdrawal included the following: adverse events, lack of efficacy, lost to follow up, moved, protocol violation, personal conflict and sponsor's decision (further elaboration was not provided). Table 2 below elaborates on the percentages of patients who dropped out for each reason within the atomoxetine, methylphenidate and placebo groups. A total of 107 patients completed the study (atomoxetine: n=49, placebo: n=47, methylphenidate: n=11).

Table 2 Reasons for withdrawal during Study HFBD (combined strata)

Reasons for Withdrawal	Atomoxetine N=65	Placebo N=62	Methylphenidate n=20
Adverse events	4 (6%)	3 (5%)	2 (10%)
Lack of efficacy	6 (9)	7 (11)	4 (20)

Lost to f/u	1 (2)	1 (2)	1 (5)
Moved	1 (2)	2 (3)	0
Protocol violation	1 (2)	0	0
Personal conflict	3 (5)	1 (2)	2 (10)
Sponsor's decision	0	1 (2)	0
Total withdrawal	16 (25)	15 (24)	9 (45)
Total completed	49 (75)	47 (76)	11 (55)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males comprised of 119 boys (81%) and 28 girls (19%) with a mean age of 9.71 years (range 7.03 to 12.92). The population consisted of 122 (83%) Caucasians, 12 (8.2%) African-Americans, 7 (4.8%) Hispanics, 1 (0.7%) Asian, and 5 (3.4%) "other." Seventy-seven (52.4%) of patients were stimulant naïve. The sponsor did not find a statistically significant difference in baseline demographics between the placebo and atomoxetine groups for the combined strata. However, for the stimulant-naïve stratum, the only statistically significant difference identified in baseline demographics was the percentages of male patients (% of male patients: atomoxetine: 66.7%, placebo 85.2%, and methylphenidate 95.0%; $p=0.035$).

Concomitant Medications

Concomitant medications used most frequently included emla cream (29 patients or 24%), albuterol (8 patients or 6.6%), benadryl (10 patients or 8.3%), and tylenol (10 patients or 8.3%). There were no notable differences in the treatment group. Table 3 below is a breakdown of select concomitant medications according to treatment group.

Table 3 Selected concomitant medications used in Study HFBD

	Tomoxetine N=62	Placebo N=58
Emla cream	12	17
Albuterol	6	2
Benadryl	7	3
Tylenol	4	6
Ativan	0	2
Dexedrine	1	0
Welbutrin	1	0
Ritalin	0	3

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference ($p=0.001$ for LOCF) when comparing the change from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score of the atomoxetine and placebo treatment groups including both strata (i.e. stimulant naïve and stimulant prior exposure). In the **stimulant-naïve stratum**, atomoxetine was shown to have a statistically significant greater mean reduction in the ADHDRS-IV Parent:Inv total score than placebo ($p=0.0015$). The methylphenidate treatment group also demonstrated a statistically significant greater reduction in ADHDRS-IV-Parent:Inv total score than the placebo group ($p=0.0003$), and had a numerically higher mean change than the atomoxetine group which does not appear to be statistically significant. For the **stimulant prior exposure stratum**, the sponsor demonstrated that there is a statistically significant difference ($p=0.0091$) between the atomoxetine and placebo groups for the change in ADHDRS-IV-Parent:Inv scores.

The following sponsor table presents a summary of these findings.

Table 4: Study HFBD: ADHRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint (sponsor's table from HFBD Study Report Table HFBD.11.4)

	n	Baseline		Endpoint		Change		p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	
Combined								
Tomoxetine	64	41.2	8.9	25.6	14.6	-15.6	13.7	0.0001
Placebo	61	41.4	7.9	35.9	13.3	-5.5	11.6	---
Stimulant-Naïve Stratum								
Tomoxetine	30	39.4	9.0	24.3	13.9	-15.1	11.8	0.0015
Placebo	27	39.6	8.3	35.4	12.6	-4.2	10.8	---
Methylphenidate ^b	20	38.6	6.5	21.3	13.5	-17.3	14.2	0.0003
Prior-Exposure Stratum								
Tomoxetine	34	42.8	8.7	26.9	15.3	-16.0	15.3	0.0091
Placebo	34	42.9	7.4	36.3	14.1	-6.6	12.3	---

^a Between treatment group p-Values are from pairwise tests of treatment differences in mean change from baseline to endpoint (last visit carried forward) scores versus placebo using least squares means from an ANOVA model with terms for investigator and treatment (in each strata) or terms for investigator, treatment and strata (combined group).

^b P-Value for Tomoxetine versus Methylphenidate comparison in the Stimulant-Naïve stratum is 0.4219.

Source Data: program: locf.sas

As discussed above (Section V: C. Overview of Methods Used to Evaluate Data Quality and Integrity), there was one study site (Site #21: Investigator; Scott West in Orlando, Florida) in which some data was not properly recorded according to an internal audit. In his review, Dr. Li, FDA statistician, reanalyzed the data omitting patients from this site; results continued to show that the atomoxetine group showed a statistically significant improvement over placebo (p=0.013); although, the results were not as robust as when this site was included (p=0.0001).

Conclusions

The results from study HFBD support the claim that atomoxetine, when prescribed twice a day, is effective in the treatment of ADHD in pediatric patients aged 7-12 years old (p=0.0001).

2. Study HFBK

Investigators/Location

This study was conducted at 10 centers in the United States including 13 principle investigators. Please refer to the sponsor's study report of HFBK Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to determine the safety and efficacy of atomoxetine in treating pediatric patients aged 7-12 years old diagnosed with ADHD.

Population

Please refer to Study HFBD which had the same entrance criteria.

Design

This was a 10 site, randomized, double blind, placebo and comparator (methylphenidate) controlled study. Patients were stratified according to prior use of methylphenidate. The details of this study’s design were identical to Study HFBD (please refer to Study HFBD for more information). Please see Appendix C for the sponsor’s schematic of the entire study plan.

Analysis Plan

As with Study HFBD, the primary efficacy variable was the change from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score. The details of this study’s design were identical to Study HFBD (please refer to Study HFBD for more information).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 210 patients entered, 144 patients were screened and randomized into double-blind treatment which included 70 stimulant naive patients and 74 patients with prior stimulant exposure. Reasons given for ineligibility included lost to follow-up (n=2), personal conflict (n=13), entry criteria not met (n=48), sponsor’s decision (n=1) and physician decision (n=2).

Of the 69 patients in the stimulant naive group, 13 (19%) discontinued and 56 (81%) completed the study; of this stratum, completion rates were as follows for each group: atomoxetine 81%, methylphenidate 88%, placebo 77%. For the stimulant prior exposure stratum, the study was completed by 57 (of 74 or 71.4%) patients including 84 % in the atomoxetine group and 69 % in the placebo group. Reasons for early withdrawal included the following: adverse events, lack of efficacy, moved, protocol violation, and personal conflict. Table 5 below elaborates on the percentages of patients who dropped out for each reason within the atomoxetine, methylphenidate and placebo groups. A total of 113 patients completed the study (atomoxetine: n=53, placebo: n=45, methylphenidate: n=15).

Table 5 Reasons for withdrawal during Study HFBK (combined strata)

Reasons for Withdrawal	Atomoxetine N=64 (%)	Placebo N=62 (%)	Methylphenidate n=18 (%)
Adverse events	2 (3%)	0	0
Lack of efficacy	4 (6)	10 (16)	0
Moved	1 (2)	0	0
Protocol violation	2 (3)	3 (5)	2 (11)
Personal conflict	2 (3)	4 (7)	1 (6)
Total withdrawal	11 (17)	17 (27)	3 (16)
Total completed	53 (83)	45 (73)	15 (83)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males comprised of 117 boys (81%) and 27 girls (19%) with a mean age of 9.9 years (range of 7.0 to 12.8). The population consisted of 116 (80%) Caucasians, 13 (9 %) African-Americans, 7 (5 %) Hispanics, 1 (1%) Asian, and 7 (5%) “other.” For the combined strata, the only statistically significant difference at baseline identified was that the atomoxetine

group had statistically significantly lower mean Wechsler Intelligence Scale for Children (WISC-III-R) total score (atomoxetine: 101.4, placebo 107.7, $p=.018$) and Wide Range Achievement Test 3 (WRAT3) arithmetic standard scores (atomoxetine 91.0, placebo 97.5, $p=.007$) than the placebo treatment group. In the stimulant-naïve stratum, the only statistically significant differences were found for the percentage of patients with phobias determined by the DICA-IV (atomoxetine 37.5%, placebo 28%, and methylphenidate 66.7%; $p=.04$); however, the sponsor notes that the percentages of patients with phobias as determined by clinical assessment did not differ between the groups. Otherwise, the treatment groups at baseline were comparable.

Concomitant Medications

The most frequently used medications were EMLA cream, Tylenol, Claritin, and Benadryl. Please see Table 6 for a listing of select concomitant medications used in Study HFBK. There were no statistically significant differences between treatment groups in terms of concomitant medications used during the study.

Table 6 Selected concomitant medications used in Study HFBK

	Atomoxetine N=64 (%)	Placebo N=58
Emla cream	31 (46)	17 (29)
Benadryl	3 (5)	7 (12)
Claritin	5 (8)	7 (12)
Tylenol	11 (17)	11 (19)
Ritalin	1 (2)	1 (2)
Adderall	0	1 (2)
Remeron	0	1 (2)

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Efficacy Results

For the primary efficacy variable, a statistically significant difference was observed when comparing the change from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score of the atomoxetine and placebo treatment groups combining both strata (stimulant-naïve and stimulant prior exposure); the sponsor reported a p -value=0.0003 for LOCF, while Dr. Li, FDA statistician, calculated a p -value=0.0005. In the stimulant-naïve stratum, the atomoxetine group showed a greater mean reduction in the ADHDRS-IV Parent:Inv total score than the placebo, but this was not statistically significant when compared with placebo ($p=0.0936$); however, the methylphenidate treatment group demonstrated a statistically significant greater reduction in ADHDRS-IV-Parent:Inv total score than the placebo group ($p=0.0071$). For the stimulant prior exposure strata, there was a statistically significant difference ($p=0.0059$) observed when comparing the atomoxetine and placebo treatment groups. Please Table 7 (below) for a summary of these results.

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Table 7 Study HFBK: ADHDRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint

(Table adapted from FDA statistical review by Dr. Ning Li).

Treatment	Baseline		Endpoint		Change		p-value vs. placebo
	n	Mean SD	Mean SD	Mean SD	Mean SD		
Combined:							
TMX	63	37.8 7.9	23.3 14.3	-14.4	13.0	0.0005	
Placebo	60	37.6 8.0	31.7 14.4	-5.9	13.0		
<i>Stimulant-Naïve stratum</i>							
TMX	25	36.6 7.4	18.6 14.9	-18.0	13.2	0.094	
Placebo	24	35.9 7.0	26.8 14.0	-9.1	11.7		
MPH	17	37.9 11.2	14.7 13.7	-23.2	16.4	0.0071	
<i>Prior-Exposure stratum</i>							
TMX	38	38.6 8.2	26.5 13.1	-12.1	12.4	0.0059	
Placebo	36	38.7 8.5	35.0 13.9	-3.7	13.5		

Conclusions

The results from study HFBK support the claim that atomoxetine, when prescribed twice a day, is effective in the treatment of ADHD in pediatric patients aged 7-12 years old (p=0.005). It is noted that in this study, a statistically significant difference was not observed in the stimulant-naïve stratum when comparing the atomoxetine group and the placebo group (p=0.094); however, the trend was toward a greater improvement in the atomoxetine group.

3. Study LYAC

Investigator(s)/Location

This study was conducted at 13 centers in the United States including 13 principle investigators. Please refer to the sponsor’s study report of LYAC Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to determine the safety and efficacy of atomoxetine (at doses of 0.5, 1.2, and 1.8 mg/kg/day) compared to placebo in children aged 8-18 y.o. diagnosed with ADHD.

Population

Patients chosen for this study were physically healthy aged 8-18 years old and diagnosed with ADHD according to DSM-IV criteria. Scores on the ADHDRS-IV-Parent above 1.5 standard deviations for the age/gender norm were required for participation, along with IQ ≥ 80 and weight between 20 to 75 kg. Excluded from the study were patients who were not responsive to an adequate trial of methylphenidate (at least 1.2 mg/kg/day for at least 2 weeks) and patients with a history of bipolar I or II disorder, psychosis,

seizure disorder, or alcohol/drug abuse. Sexually active females were required to use medically accepted forms of birth control; pregnant females were excluded from the study.

Design

This was a 13 site, 8 week, randomized, double blind, placebo controlled study with an optional one year extension for treatment responders (please see Appendix C for the sponsor's schematic of the entire study plan). For the purposes of this NDA submission, the sponsor only reported on the acute 8 week phase of this study. Patients were randomized to one of the following 4 treatment groups with dosing administered twice daily: 1) atomoxetine 0.5 mg/kg/day, 2) atomoxetine 1.2 mg/kg/day, 3) atomoxetine 1.8 mg/kg/day, and 3) placebo. Patients were stratified according to CYP2D6 status (i.e. extensive or poor metabolizers); only extensive metabolizers were also stratified according to whether or not they had a prior history of psychostimulant use.

Screening included a history and physical, ECG, routine labs, pregnancy test (for sexually active females), urinalysis, urine drug screen, and CYP2D6 and DRD4*7 genotyping. Vital signs were monitored weekly; ECGs and laboratory analyses were obtained twice during the study.

Analysis Plan

The primary efficacy variable is the change from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score (see Appendix A for a copy of the ADHDRS-IV-Parent:Inv). The ADHDRS-IV-Parent:Inv is a modified version of the ADHDRS-IV-Parent scale, an 18 item scale in which each item describes a DSM-IV criteria of the ADHD diagnosis (0=rarely/never, 3=very often) that can each be scored ranging from zero to three by parents. The sponsor utilized the ADHDRS-IV-Parent rating scale by having the investigator score the ADHDRS-IV-Parent:Inv. based on interviews with parents about their children's behavior at weekly visits.

The primary analysis was the intent-to-treat utilizing 2-sided, 0.05 significance level. Only the mid (1.2 mg/kg/day) and high (1.8 mg/kg/day) dose groups were compared to placebo to assess for efficacy.

Study Conduct/Outcome

Patient Disposition

Of the 383 patients entered into the study, 297 patients were screened and randomized into double-blind treatment which included 85 (28.6%) stimulant naïve patients and 212 (71.4%) patients with prior stimulant exposure. Reasons given for ineligibility included lost to follow-up (n=6), personal conflict (n=17), entry criteria not met (n=59), sponsor's decision (n=1), physician decision (n=1), and protocol violation. Patients were randomized to one of the following 4 treatment groups: 1) 0.5 mg/kg/day (n=44); 2) atomoxetine 1.2 mg/kg/day (n=84), 3) atomoxetine 1.8 mg/kg/day (n=69), or 4) placebo (n=84). Because patients in the low dose group (0.5 mg/kg/day) were excluded from the efficacy analysis, there were 253 patients included in the efficacy analysis.

Reasons for early withdrawal included the following: adverse events, lack of efficacy, moved, protocol violation, personal conflict, entry criteria not met, physician decision, and protocol violation. Table 8 (below) elaborates on the percentages of patients who dropped out for each reason within the atomoxetine and placebo treatment groups. A total of 248 (83.5%) patients completed the study (atomoxetine total: n=176, placebo: n=72). A comparison of each strata according to prior stimulant exposure was not located in this submission.

Table 8 Reasons for withdrawal during Study LYAC (based on sponsor's table LYAC.10.2)

Reasons for Withdrawal	Atomoxetine 0.5 mg/kg/day n=44 (%)	Atomoxetine 1.2 mg/kg/day n=84 (%)	Atomoxetine 1.8 mg/kg/day n=85 (%)	Placebo N=84 (%)
Adverse events	1 (2.3)	2 (2.4)	4 (4.7)	0
Lack of efficacy	3 (6.8)	2 (2.4)	1 (1.2)	4 (6.5)
Lost to f/u	3 (6.8)	1 (1.2)	2 (2.4)	4 (4.8)
Moved	0	1	0	0
Protocol violation	0	0	2 (2.4)	0
Personal conflict	3 (6.8)	6 (7.1)	4 (4.7)	4 (4.8)
Entry criteria not met	0	0	1 (1.2)	0
Physician decision	0	1 (1.2)	0	0
Protocol Violation	0	2 (2.4)	0	0
Total withdrawal	12 (23%)	15 (18)	13 (14)	14 (14)
Total completed	34 (77)	69 (82)	73 (86)	72 (86)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males comprised of 212 boys (71%) and 85 girls (29%) with a mean age of 11.1 years (range of 8.0 to 17.5). The population consisted of 225 (76%) Caucasians, 53 (17.8 %) African-Americans, 6 (2 %) Hispanics, 3 (1%) Asian, and 10 (3.4%) "other." The majority of patients, as expected, were extensive cytochrome P4502D6 (CYP2D6) metabolizers; there were a total of 17 (5.7%) poor CYP2D6 metabolizers of which 11 were evenly distributed amongst the atomoxetine treatment groups. There were a total of 212 (71%) patients previously exposed to stimulants and 85 (29%) stimulant naïve; there appeared to be an even distribution of prior exposures amongst all of the treatment groups.

Concomitant Medications

The most frequently used medications were EMLA cream, Tylenol, 17.5%, and Benadryl. Please see Table 9 for a listing of select concomitant medications used in Study LYAC. There were no statistically significant differences between treatment groups in terms of concomitant medications used during the study.

Table 9 Selected concomitant medications used in Study LYAC (based in table LYAC 11.28)

	Atomoxetine 0.5 mg/kg/day N= 44 (%)	Atomoxetine 1.2 mg/kg/day N=84 (%)	Atomoxetine 1.8 mg/kg/day N=84 (%)	Placebo N=83 (%)
Emla cream	11 (25)	20 (24)	27 (32)	23 (28)
Tylenol	8 (18)	9 (11)	10 (12)	15 (18)
Benadryl	4 (10)	5 (6)	9 (11)	8 (10)
Albuterol	1 (2.3)	3 (3.6)	2 (2.4)	1 (1.2)
Proventil	1 (1.2)	2 (2.4)	1 (1.2)	1 (1.2)
Adderall	0	0	0	1 (1.2)
Proventil	0	1 (1.2)	0	0
Trazadone	0	1 (1.2)	0	0

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference ($p < 0.001$ for LOCF) when comparing the change from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score of the two higher dose atomoxetine (1.2 and 1.8 mg/kg/day) and placebo treatment groups. The mean improvement for the 0.5 mg/kg/day atomoxetine group was not statistically significantly better than the placebo group for the primary efficacy variable. Table 10 (below) does not suggest an increase in efficacy with increasing dose, and that the 1.2 mg/kg/day actually has a numerical score slightly higher than the 1.8 mg/kg/day. The sponsor has suggested that there is a possible leveling off of efficacy at doses above 1.2 mg/kg/day. Because the 0.5 mg/kg/day did not demonstrate a statistically significant difference when compared to placebo, it could be inferred that the lowest effective dose was somewhere in the range of 0.5 to 1.2 mg/kg/day.

Table 10: Study LYAC: ADHDRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint (sponsor's table from LYAC Study Report Table LYAC.11.5)

Treatment	n	Baseline		Endpoint		Change		p-val* vs Pla Adj. (UnAdj.)
		Mean	SD	Mean	SD	Mean	SD	
Placebo	83	38.3	8.9	32.5	13.8	-5.8	10.9	
TMX0.5	43	40.2	9.6	30.3	15.2	-9.9	14.6	(.155)
TMX1.2	84	39.2	9.2	25.5	13.8	-13.6	14.0	<.001 (<.001)
TMX1.8	82	39.7	8.7	26.2	14.8	-13.5	14.5	<.001 (<.001)

Conclusions

The results of Study LYAC provides evidence that atomoxetine is effective in the treatment of children aged 8-17 diagnosed with ADHD. From the results of this study, the 1.2 and 1.8 mg/kg/day atomoxetine doses appear to be equally effective compared to placebo, suggesting a plateau of dose response at these higher doses; the dose of 0.5 mg/kg/day atomoxetine was not shown to be efficacious compared to placebo. It would be helpful if the sponsor could further define a dose response within the dose ranges of 0.5 to 1.2 mg/kg/day.

4. Study LYAT

Investigator(s)/Location

This study was conducted at 9 centers in the United States including 9 principle investigators. Please refer to the sponsor's study report of LYAT Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to assess the safety and efficacy of atomoxetine administered as a single-daily dose in children diagnosed with ADHD.

Population

Patients chosen for this study were aged 6 to 16 years old, physically healthy, and diagnosed with ADHD according to DSM-IV criteria. Patients were required to have an IQ \geq 80, weigh between 20 to 70 kg at study entry, and have a symptom severity threshold of 1.5 standard deviations above age and sex norms on the ADHDRS-IV-Parent:Inv. Excluded from the study were patients with a history of Bipolar I or II, psychosis, pregnant females, seizure disorder, hyper/hyperthroidism, alcohol or drug abuse (within past 3 months of study), and hypertension.

Design

This was a 9 site, double blind, 6 week, placebo-controlled trial (please see Appendix C the sponsor's schematic of the entire study plan). Patients were randomized to either the atomoxetine or placebo treatment group. For patients randomized to treatment with atomoxetine, dosing began at 0.5 mg/kg/day for 3 days, then 0.75 mg/kg/day, and, if tolerated, further titration increased the dose to 1.0 mg/kg/day at the next visit. Dosing was increased if symptomatology persisted up to 1.5 mg/kg/day. Dosing was to be administered once daily in the morning with no instructions regarding food intake. Concomitant psychotropic medications were forbidden during the study. Also prohibited was daily use of medications that would have sympathomimetic activity (e.g. albuterol, inhalation aerosols, and pseudoephedrine).

Screening included a history and physical, ECG, routine labs, pregnancy test (females of child bearing potential), CYP2D6 genotyping, and urinalysis. Vital signs were monitored weekly; ECGs were monitored at after one week on study drug and at the end of the study. Also at the completion of the study, the sponsor observed an ECG, routine labs, and urinalysis.

Analysis Plan

The protocol states that the primary efficacy variable is the comparison of the atomoxetine group and the placebo group scoring on the ADHDRS-IV-Parent:Inv total score (see Appendix A for a copy of the ADHDRS-IV-Parent:Inv). The ADHDRS-IV-Parent:Inv is a modified version of the ADHDRS-IV-Parent scale, an 18 item scale in which each item describes a DSM-IV criteria of the ADHD diagnosis (0=rarely/never, 3=very often) that can each be scored ranging from zero to three by parents. The sponsor utilized the ADHDRS-IV-Parent rating scale by having the investigator score the ADHDRS-IV-Parent:Inv. based on weekly interviews with parents about their children's behavior at weekly visits.

The change from baseline was computed for all patients with a baseline and at least 1 post-baseline score. The primary efficacy analysis variable was the total score of the 18 items in the ADHDRS-IV-Parent:Inv. Differences between the treatment groups were assessed using a repeated measures mixed model. The model contained fixed class effect terms for treatment, investigator, visit, and an interaction term between treatment and visit. The model also included a random subject effect and baseline ADHDRS-IV-Parent:Inv total score as a covariate.

Study Conduct/Outcome

Patient Disposition

Of the 197 patients entered, 171 patients were screened and randomized into double-blind treatment. Reasons given for ineligibility included lost to follow-up (n=1), personal conflict (n=9), and entry criteria not met (n=16). Of the 171 patients in the intent-to-treat population, 23 (13.5%) discontinued and 148 (86.5%) completed the study. Table 11 (below) summarizes the reasons for early withdrawal. A total of 148 patients completed the study (atomoxetine: n=73; placebo: n=75). As can be seen from Table 11, there was no statistically significant difference between the atomoxetine and the placebo groups with regard to reasons for early withdrawal.

Table 11: Reasons for early withdrawal (sponsor's table LYAT 10.2 p. 61 of study report)

Primary Reason for Discontinuation	ATOMOX (N=85) n (%)	PLACEBO (N=86) n (%)	Total (N=171) n (%)	p-Value*
Adverse event	2 (2.4)	1 (1.2)	3 (1.8)	.621
Lack of efficacy, patient perception	1 (1.2)	1 (1.2)	2 (1.2)	1.00
Lack of efficacy, patient and physician perception	0	1 (1.2)	1 (0.6)	
Unable to contact patient (lost to follow-up)	4 (4.7)	2 (2.3)	6 (3.5)	.443
Personal conflict or other patient decision	3 (3.5)	5 (5.8)	8 (4.7)	.720
Physician decision	1 (1.2)	0	1 (0.6)	
Protocol Violation	1 (1.2)	1 (1.2)	2 (1.2)	1.00
Study Period II completed	73 (85.9)	75 (87.2)	148 (86.5)	.826

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males comprised of 120 boys (71%) and 50 girls (29%) with a mean age of 10.3 years (range of 6.0 to 16.2). The population consisted of 134 (79%) Caucasians, 21 (12 %) African-Americans, 7 (4 %) Hispanics, 2 (1%) Asian, and 6 (4%) "other." Although the sponsor did not stratify according to prior exposure of stimulant or CYP2D6 metabolizer status, 44.7% of patients were stimulant naïve, and 3% of patients determined to be CYP2D6 poor metabolizers. There did not appear to be any statistically significant differences in demographics between treatment groups at baseline.

Concomitant Medications

Concomitant medications used most frequently included emla cream (51 patients or 30%), albuterol (8 patients or 4.7%), Ritalin (8 or 4.7%), benadryl (7 patients or 4.1%), Adderall (4 or 2.4%), and tylenol (24 patients or 4.1%). There were no notable differences in the treatment group. Table12 (below) summarizes select concomitant medications according to treatment group administered during the course of the study. Although there were psychotropic medications used which were prohibited by the protocol, these appear to have been used with a similar frequency in both the placebo and the treatment group.

Table 12: Selected concomitant medications used in Study LYAT

	Tomoxetine N=85	Placebo N=85
Emla cream	25	17
Tylenol	11	13
Ritalin	4	4
Albuterol	4	4
Benadryl	4	3
Ventolin	1	2
Concerta	1	1
Imipramine	0	1
Dexedrine	0	1
Welbutrin	1	0
Ritalin-SR	1	0

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Efficacy Results

The sponsor was able to demonstrate a statistically significant result using a repeated measures mixed model ($p < 0.001$). Please refer to Table 13 below for the sponsor's table of results.

Table 13: Study LYAT: ADHRS-IV-Parent:Inv Total Score Repeated Measures Least Squares Means (sponsor's table LYAT 11.5)

Atomoxetine Visit	Placebo			Treatment Difference					
	LS Mean	SE	p-val ^a	LS Mean	SE	p-val ^a	LS Mean	SE	p-val ^b
3	28.91	0.94	<.001	33.09	0.95	<.001	-4.18	1.27	.001
4	25.52	1.14	<.001	32.00	1.15	<.001	-6.48	1.56	<.001
5	24.45	1.22	<.001	31.29	1.23	<.001	-6.84	1.69	<.001
6	23.81	1.31	<.001	31.75	1.32	<.001	-7.94	1.82	<.001

95% Confidence Interval on Change from Baseline to Visit 6
 { -15.93 , -10.74 } { -8.00 , -2.79 }

Summary of Model Parameters	F-Value	P-Value ^c
Baseline	103.20	<.001
Treatment	21.01	<.001
Visit	7.73	<.001
Investigator	1.50	.161
Treatment*Visit	2.17	.094

Results based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

- ^a P-values are from tests for a nonzero least squares mean at the given visit.
- ^b P-values are from tests for a treatment difference in least squares means at the given visit.
- ^c P-values are from F-tests for a nonzero coefficient estimate.

FDA statistician, Dr. Ning Li, was able to conduct an analysis using an LOCF method which confirmed the efficacy findings observed with the mixed model. As can be seen in Table 14 (below), the atomoxetine group showed a statistically significant improvement over placebo using the LOCF method ($p < 0.001$).

Table 14: ADHD Rating Scale IV-Parent Version: Investigator Scored (ADHDRS-IV-Parent:Inv) Total Score Change from Baseline to Endpoint, LOCF for Study HFBE

(Table extracted from FDA statistical review by Dr. Ning Li: 6/14/02)

Treatment	Baseline		Endpoint		Change		p-value TMX v.s. placebo
	n	Mean SD	Mean SD	Mean SD	Mean SD		
TMX	84	37.5 9.4	24.8 13.7	-12.8	12.4	<0.001	
PLACEBO	83	36.7 8.8	31.8 12.8	-4.95	10.4		

Both the placebo and atomoxetine groups demonstrated significant improvement during this study. The treatment group did, however, demonstrate an improvement that was statistically significantly larger than the placebo group.

Conclusions

The results of Study LYAT provide evidence that atomoxetine is effective in the treatment of children aged 6-16 diagnosed with ADHD when administered once a day. The treatment group demonstrated a greater improvement than the placebo group that was statistically significant. It is noted that both the placebo and atomoxetine groups demonstrated statistically significant improvement comparing endpoint to baseline.

5. Study LYAA

Investigator(s)/Location

This study was conducted at 17 centers of which 14 were in the US and 3 were in Canada. There were 17 principal investigators involved in this study. Please refer to the sponsor's study report of LYAA Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to determine the safety and efficacy of atomoxetine (at doses of 60-120 mg) compared to placebo in adults 18 years and older diagnosed with ADHD.

Population

Patients chosen for this study were ≥ 18 years of age, physically healthy, and diagnosed with ADHD according to DSM-IV criteria. At baseline, patients were required to have a CGI-ADHD-S score of 4 (moderate symptoms) and a score of at least 2 (of 6) items of either the inattentive or hyperactive core subscales of the CAARS. Excluded from the study were patients with a history of bipolar disorder, psychosis, organic brain disorder, seizure disorder, hyper/hyperthyroidism, alcohol or drug abuse (within past 3 months of study), hypertension, and pregnant or breast feeding females.

Design

This study was a 17 site, double blind, 5 week, placebo-controlled trial, followed by a 4 week double-blind discontinuation phase in which patient were either abruptly discontinued or tapered slowly (please see Appendix C for the sponsor's schematic of the entire study plan). During the placebo-controlled portion of the study, patients were randomized to either the atomoxetine or placebo treatment group. For patients randomized to treatment with atomoxetine, dosing began at 30 mg bid. If an adequate response (CGI-S < 3) was not obtained after two weeks, then titration would continue up to 45 mg bid, and, if needed, be further increased to a maximum dose of 60 mg. Concomitant medications were prohibited during the study. However, diphenhydramine could be used intermittently as needed for insomnia.

Screening included a history and physical, ECG, routine labs, pregnancy test (females of child bearing potential), CYP2D6 genotyping, and urinalysis. Vital signs were monitored weekly; ECGs and labs were monitored during the study and at discontinuation.

Analysis Plan

The primary efficacy scale was the Conner's Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). The primary efficacy variable was the sum of the 18 DSM-IV Total ADHD Symptoms from the CAARS-Inv:SV. Assessment of differences in treatment effect utilized a repeated measures mixed model using the CAARS-INV:SV Total ADHD Symptoms as the dependent variable. The model contains fixed class effect terms for treatment, investigator, visit, CYP2D6 status, and an interaction term between treatment and visit. Comparisons were made between the atomoxetine and the placebo groups at the end of the placebo controlled phase.

Study Conduct/Outcome

Patient Disposition

Of the 448 patients entered, 280 patients were screened and randomized into double-blind treatment. Reasons given for ineligibility included lost to follow-up (n=13), personal conflict (n=21), adverse event (n=3), entry criteria not met (n=119), protocol violation (n=5), physician decision (n=4), sponsor's decision (n=2), and patient perception (n=1). Of the 280 patients in the intent-to-treat population, 271 (25%) discontinued and 209 (74.6%) completed the placebo controlled portion of the study. Table 15 (below) summarizes the reasons for early withdrawal. A total of 209 patients completed the study (atomoxetine: n=102; placebo: n=107). As can be seen from Table 15, there was no statistically significant difference between the atomoxetine and the placebo groups with regard to reasons for early withdrawal.

Table 15: Reasons for early withdrawal (sponsor's table LYAA 10.2 p. 103 of study report)

Primary Reason for Discontinuation	ATOMOXI (N=141) n (%)	PLACEBO (N=139) n (%)	Total (N=280) n (%)	p-Value*
Adverse event	11 (7.8)	6 (4.3)	17 (6.1)	.317
Lack of efficacy, patient perception	2 (1.4)	3 (2.2)	5 (1.8)	.683
Lack of efficacy, patient and physician perception	1 (0.7)	0	1 (0.4)	
Unable to contact patient (lost to follow-up)	11 (7.8)	11 (7.9)	22 (7.9)	1.00
Personal conflict or other patient decision	11 (7.8)	7 (5.0)	18 (6.4)	.466
Sponsor's decision	1 (0.7)	1 (0.7)	2 (0.7)	1.00
Physician decision	1 (0.7)	0	1 (0.4)	
Protocol Violation	1 (0.7)	4 (2.9)	5 (1.8)	.212
Study Period II completed	102 (72.3)	107 (77.0)	209 (74.6)	.411

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males with a mean age of 40 years old (range of 18 to 67). The population consisted of 178 men (64%) and 50 women (36%) of which there were 245 (88%) Caucasians, 10 (4 %) African-Americans, 13 (5 %) Hispanics, 6 (2%) Asian, and 3 (1%) "other." As expected, the majority of patients were extensive cytochrome P4502D6 metabolizers; there were a total of 18 (6%) patients determined to be CYP2D6 poor metabolizers, of which 10 patients were randomized to the atomoxetine treatment group. Stimulant naïve patients made up 53.6% of the patients participating in the study. There did not appear to be any statistically significant differences in demographics between treatment groups at baseline.

Concomitant Medications

Concomitant medications used most frequently included multivitamins and various NSAIDs (including ibuprofen, Advil, aspirin, Tylenol, Aleve). There were two notable differences between the treatment groups: 1) Viagra was used in 5 (3.5%) patients in the atomoxetine group while no patients in the placebo group took Viagra, and 2) Proventil was used in 5 (3.8%) patients in the placebo group, but no patients in the atomoxetine treatment group. Otherwise, there were no notable differences in the treatment group. Table 16 below is a breakdown of select concomitant medications according to treatment group.

Table 16: Select concomitant medications used in Study LYAA

	Atomoxetine N=141	Placebo N=138
Multivitamin	26	32
Ibuprofen	25	17
Advil	15	20
Asprin	16	19
Tylenol	15	16
Synthroid	7	5
Viagra	5	0
Proventil	0	5
Albuterol	6	2
Atenolol	3	4
Benadryl	5	4
Ambien	3	2

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Efficacy Results

The sponsor was able to demonstrate a statistically significant result using a repeated measures mixed model ($p < 0.001$). As can be seen in Table 17 (below), the atomoxetine group had a statistically significant difference in improvement over placebo for all weeks, other than week 5.

Table 17: Study LYAA: ADHRS-IV-Parent:Inv Total Score Repeated Measures Least Squares Means

Visit	Atomoxetine			Placebo			Treatment Difference		
	LS Mean	SE	p-val a	LS Mean	SE	p-val a	LS Mean	SE	p-val b
4	28.82	0.90	<.001	30.76	0.93	<.001	-1.94	0.82	.020
5	27.67	0.99	<.001	28.62	1.02	<.001	-0.95	1.00	.342
6	25.23	1.00	<.001	28.18	1.03	<.001	-2.94	1.02	.004
7	23.90	1.10	<.001	27.44	1.12	<.001	-3.54	1.21	.004
8	23.88	1.13	<.001	27.60	1.15	<.001	-3.72	1.24	.004

95% Confidence Interval on Change from Baseline to Visit 8
(-12.04 , -7.57) (-8.35 , -3.81)

Summary of Model Parameters	F-Value	P-Value c
Baseline	210.55	<.001
Treatment	9.33	.004
Visit	15.06	<.001
Investigator	1.25	.290
Treatment*Visit	2.27	.063
CYP2D6 Status	0.12	.730

Results based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

- a P-values are from tests for a nonzero least squares mean at the given visit.
- b P-values are from tests for a treatment difference in least squares means at the given visit.
- c P-values are from F-tests for a nonzero coefficient estimate.

(sponsor's table LYAA 11.5)

FDA statistician, Dr. Ning Li, was able to conduct an analysis using an LOCF method which confirmed the efficacy findings observed with the mixed model. As can be seen in the table below (Table 18), the atomoxetine group showed a statistically significant improvement over placebo using the LOCF method ($p = 0.006$).

Table 18: Conner's Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) Total Score Change from Baseline to Endpoint, LOCF for Study LYAA (Table extracted from FDA statistical review by Dr. Ning Li: 6/14/02)

Treatment	n	Baseline		Endpoint		Change		p-value TMX v.s. placebo
		Mean	SD	Mean	SD	Mean	SD	
TMX	133	33.6	7.2	24.1	11.2	-9.5	10.1	0.006
PLACEBO	134	33.2	7.8	27.2	10.6	-6.0	9.3	

Conclusions

The results of Study LYAA provide evidence that atomoxetine is effective in the treatment of adults diagnosed with ADHD when administered twice a day.

6. Study LYAO

Investigator(s)/Location

This study was conducted at 14 centers. There were 15 principal investigators involved in this study. Please refer to the sponsor's study report of LYAA Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to determine the safety and efficacy of atomoxetine (at doses of 60-120 mg) compared to placebo in adults 18 years and older diagnosed with ADHD.

Population

Please refer to Study LYAA which had the same entrance criteria.

Design

This was a 10 site, randomized, double blind, placebo and comparator (methylphenidate) controlled study. Patients were stratified according to prior use of methylphenidate. The details of this study's design were identical to Study LYAA (please refer to Study LYAA for more information).

Analysis Plan

As with Study LYAA, the primary efficacy scale is the Conner's Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). The primary efficacy variable is the sum of the 18 DSM-IV Total ADHD Symptoms from the CAARS-Inv:SV. Assessment of differences in treatment effect will utilize a repeated measures mixed model using the CAARS-INV:SV Total ADHD Symptoms as the dependent variable. The model contains fixed class effect terms for treatment, investigator, visit, CYP2D6 status, and an interaction term between treatment and visit.

Comparisons were made between the atomoxetine and the placebo groups at the end of the placebo controlled phase.

Study Conduct/Outcome

Patient Disposition

Of the 388 patients entered, 256 patients were screened and randomized into double-blind treatment. Reasons given for ineligibility included lost to follow-up (n=16), adverse event (n=2), entry criteria not met (n=63), protocol violation (n=3), physician decision (n=7), sponsor's decision (n=6), personal conflict (n=32), lack of efficacy (n=2) and patient moved (n=1). Of the 256 patients in the intent-to-treat population, 85 (33%) discontinued and 171 (67%) completed the placebo controlled portion of the study. The sponsor table XX (below) summarizes the reasons for early withdrawal. A total of 171 patients completed the study (atomoxetine: n=82; placebo: n=89). As can be seen from Table 19, discontinuations due to adverse events in the atomoxetine group were statistically significantly higher than adverse events observed in the placebo group. Otherwise, there was no statistically significant difference between the atomoxetine and the placebo groups with regard to reasons for early withdrawal.

Table 19: Reasons for early withdrawal (sponsor's table LYAO 10.2 p. 103 of study report)

	ATOMOXETIN E (N=129) n (%)	PLACEBO (N=127) n (%)	TOTAL (N=256) n (%)	p-value*
Adverse event	12 (9.3)	3 (2.4)	15 (5.9)	.030
Lack of efficacy, patient perception	3 (2.3)	6 (4.7)	9 (3.5)	.332
Lack of efficacy, patient and physician perception	2 (1.6)	0	2 (0.8)	.498
Unable to contact patient (lost to follow-up)	8 (6.2)	4 (3.1)	12 (4.7)	.376
Patient moved	0	1 (0.8)	1 (0.4)	
Personal conflict or other patient decision	7 (5.4)	5 (3.9)	12 (4.7)	.769
Sponsor's decision	13 (10.1)	15 (11.8)	28 (10.9)	.693
Physician decision	1 (0.8)	1 (0.8)	2 (0.8)	1.00
Protocol violation	1 (0.8)	3 (2.4)	4 (1.6)	.368
Study Period II completed	82 (63.6)	89 (70.1)	171 (66.8)	.290

* p-value between atomoxetine and placebo are based on the Fisher exact test.

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males with a mean age of 43 years old (range of 18 to 76). The population consisted of 83 men (64%) and 46 women (36%) of which there were 124 (96%) Caucasians, 1 (1%) African-American, 3 (2%) Hispanics, and 1 (1%) Asian. The majority of patients, as expected, were extensive cytochrome P4502D6 (CYP2D6) metabolizers; there were a total of 13 (5.2%) patients determined to be CYP2D6 poor metabolizers, of which 6 patients were randomized to the atomoxetine treatment group. Stimulant naïve patients made up 53% of the patients participating in the

study. There did not appear to be any statistically significant differences in demographics between treatment groups at baseline.

Concomitant Medications

Table XX Selected concomitant medications used in Study LYAO

	Atomoxetine N=141	Placebo N=138
Multivitamin	25	15
Ibuprofen	20	25
Advil	12	12
Aspirin	15	14
Tylenol *	15	17
Synthroid *	5	2
Afrin	3	0
Guanfenesin	3	0
Tylenol PM	3	0
Viagra	1	2
Proventil	3	0
Albuterol	3	3
Benadryl *	2	5
Ambien	1	0
Ritalin	1	0
Trazadone	0	1
Valium	1	0
Welbutrin	1	0
Zoloft	0	1

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Efficacy Results

The sponsor was able to demonstrate a statistically significant result using a repeated measures mixed model ($p < 0.001$). Please refer to Table 20 below for the sponsor's table of results. As can be seen in Table 20, the atomoxetine group had statistically significant difference in improvement over placebo for all weeks, other than week 5.

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Table 20: Study LYAO: ADHRS-IV-Parent:Inv Total Score Repeated Measures Least Squares Means

(sponsor's table LYAO 11.5)

Visit	Atomoxetine			Placebo			Treatment Difference		
	LS Mean	SE	p-val a	LS Mean	SE	p-val a	LS Mean	SE	p-val b
4	28.81	1.17	<.001	31.43	1.14	<.001	-2.62	0.95	.006
5	26.61	1.24	<.001	29.80	1.22	<.001	-2.19	1.12	.052
6	24.87	1.29	<.001	28.74	1.27	<.001	-3.97	1.23	.002
7	23.89	1.34	<.001	27.89	1.31	<.001	-4.01	1.32	.003
8	22.63	1.37	<.001	27.23	1.33	<.001	-4.60	1.37	<.001

95% Confidence Interval on Change from Baseline to Visit 8
 (-14.57, -9.19) (-9.90, -4.65)

Summary of Model Parameters	F-Value	P-Value c
Baseline	151.23	<.001
Treatment	12.15	<.001
Visit	17.71	<.001
Investigator	1.91	.030
Treatment*Visit	1.05	.382
CTP2D6 Status	0.20	.653

Results based on a mixed model with a term for visit, (treated as a class variable), baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.
 a. P-values are from tests for a nonzero least squares mean at the given visit.
 b. P-values are from tests for a treatment difference in least squares means at the given visit.
 c. P-values are from F-tests for a nonzero coefficient estimate.

FDA statistician, Dr. Ning Li, was able to conduct an analysis using an LOCF method which confirmed the efficacy findings observed with the mixed model. As can be seen in the table below (Table 21), the atomoxetine group showed a statistically significant improvement over placebo using the LOCF method (p=0.002).

Table 21: Conner's Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) Total Score Change from Baseline to Endpoint, LOCF for Study LYAA (Table extracted from FDA statistical review by Dr. Ning Li: 6/14/02)

Treatment	Baseline		Endpoint		Change		p-value TMX v.s. placebo
	n	Mean SD	Mean SD	Mean SD	Mean SD		
TMX	124	34.9 6.9	24.4 11.21	-10.5	10.9	0.002	
PLACEBO	124	34.2 7.5	27.5 11.40	-6.7	9.3		

Conclusions

The results of Study LYAA provide evidence that atomoxetine is effective in the treatment of adults diagnosed with ADHD when administered twice a day.

VII. Integrated Review of Safety

Please refer to the review by Dr. Gerald Boehm (HFD-120) for the safety review for atomoxetine.

VIII. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor conducted a gender analysis for the adult studies (combining LYAA and LYAO) and a separate gender analysis combining the pediatric studies (HFBD, HFBK, and LYAC---the short term placebo controlled twice daily dosing studies). The sponsor found no statistically significant gender or therapy-by-gender interaction effects in either the pediatric and the adult populations.

B. Evaluation Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor conducted a subgroup analysis by age for the pediatric population by combining data from the short term placebo controlled twice daily dosing studies (HFBD, HFBK, and LYAC); a comparison was made between the age groups of children aged < 12 years old and adolescents aged 12 to 17 years old. The sponsor found no statistically significant age or therapy-by-age interaction effects in their analysis. For study LYAT, the short term placebo controlled once daily dosing study, the sponsor found no statistically significant effects when comparing children aged < 12 years old and adolescents aged 12 to 17 years old.

The subgroup analysis by age for adults compared patient's above and below the mean age of 42. The sponsor did not find any statistically significant age or therapy-by-age interaction effects.

There was insufficient exposure to characterize ethnic variations in this data base of this submission.

C. Evaluation of Pediatric Program

The sponsor has submitted five pediatric studies with a placebo controlled portion, of which four have supported their efficacy claims. Their program for the pediatric population appears to be adequate; although, the sub-population of CYP2D6 poor metabolizers is under represented in the exposed population.

D. Comments on Data Available or Needed in Other Population (Renal, Hepatic Compromised Patients, or Use in Pregnancy).

The sponsor has tested this drug in patients with renal and hepatic compromise. The safety of use in pregnancy has not been assessed. To date, the exposure of patients who are genotypically CYP2D6 poor metabolizers is quite small in this NDA data base.

IX. Conclusions and Recommendations

A. Conclusions

Atomoxetine has been shown to be effective in the treatment of ADHD in the pediatric and adult population. The sponsor also provided evidence to support effectiveness of atomoxetine for both once and twice daily dosing.

Unfortunately, the sponsor did not assess doses between the 0.5 mg/kg/dose and 1.2 mg/kg/dose for a better picture of the lowest effective dose in the pediatric population. Results at the 0.5 mg/kg/day dosing did not

support efficacy at this dose. Effectiveness was established for the doses of 1.2 mg/kg/day and 1.8 mg/kg/day, but the 1.8 mg/kg/day dose was not associated with any efficacy benefit over the 1.2 mg/kg/day dose.

Safety

Please refer to the review by Dr. Gerald Boehm (HFD-120) for the safety review for atomoxetine.

Labeling

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

B. Recommendations

In terms of the efficacy data submitted, it is recommended that this NDA receive an "approvable" action.

Of concern is that the sponsor has collected only a small number of patients who are genotypically CYP2D6 poor metabolizers with too few individuals exposed to determine an accurate efficacy or safety profile. Also, the sponsor has not identified a lowest effective dose, and has only identified the high end dosage range (the 1.2 mg/kg/day and 1.8 mg/kg/day showed similar results). It is recommended that the sponsor consider these issues as they enter Phase IV of drug development.

The one relapse prevention study submitted demonstrated negative findings. It is recommended that the sponsor continue to assess efficacy for long term use, as well as generate safety data extending beyond one year

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XI. Appendices

Appendix A

The ADHDRS-IV-Parent: Inv is a modified version of the ADHDRS-IV-Parent scale. This instrument was used the pediatric placebo controlled studies as the primary efficacy instrument.

ADHD RATING SCALE-IV : PARENT VERSION - INVESTIGATOR SCORE

INFORMATION NOT OBTAINED

Date of assessment _____
DD MM Y Y Y Y

Rater's initials _____ (Use Information Provider Number from the Information Provider page.)
First Middle Last

List all the information providers present at this interview _____

Was the primary caregiver in the last week present at this interview? 1 Yes 2 No 97 Unkn

Check or box (✓) the box that <u>best describes</u> the child's behavior over the <u>past week</u> .	Never or Rarely (None)	Sometimes (Mild)	Often (Moderate)	Very Often (Severe)
1. Fails to give close attention to details or makes careless mistakes in schoolwork.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
2. Fidgets with hands or feet or squirms in seat.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
3. Has difficulty sustaining attention in tasks or play activities.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
4. Leaves seat in classroom or in other situations in which remaining seated is expected.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
5. Does not seem to listen when spoken to directly.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
6. Runs about or climbs excessively in situations in which it is inappropriate.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
7. Does not follow through on instructions and fails to finish work.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
8. Has difficulty playing or engaging in leisure activities quietly.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
9. Has difficulty organizing tasks and activities.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
10. Is "on the go" or acts as if "driven by a motor."	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| 11. Avoids tasks (eg. schoolwork, homework) that require sustained mental effort. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Talks excessively. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Loses things necessary for tasks or activities. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Blurts out answers before questions have been completed. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Is easily distracted. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Has difficulty awaiting turn. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Is forgetful in daily activities. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Interrupts or intrudes on others. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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Appendix B

Conners Adult ADHD Rating Scale-Investigator rated: Screening Version (CAARS-INV:SV) Used in Protocols LYAA and LYAO (placebo controlled studies in adults)

CAARS - INVESTIGATOR : SCREENING VERSION : (CAARS - INV:SV)

INFORMATION NOT OBTAINED

Listed below are items concerning behaviors or problems sometimes experienced by adults. Read each item carefully and decide how much or how frequently each item describes the person recently. Indicate your response for each item by circling the number that corresponds to your choice. Use the following scale: 0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; and 3 = Very much, very frequently.

The person being described:	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently	(DNDE) ADHD Symptom Score
1. loses things necessary for tasks or activities (e.g., to-do lists, pencils, books, or tools).	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
2. talks too much.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
3. is always on the go as if driven by a motor.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
4. gets rowdy or boisterous during leisure activities.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
5. has a short fuse/hot temper.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
6. leaves seat when not supposed to.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
7. throws tantrums.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
8. has trouble waiting in line or taking turns with others.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
9. has trouble keeping attention focused when working or at leisure.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
10. avoids new challenges because of lack of faith in his/her own abilities.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
11. appears restless inside even when sitting still.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
12. is distracted by sights or sounds when trying to concentrate.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
13. is forgetful in daily activities.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
14. has trouble listening to what other people are saying.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
15. is an underachiever.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	X
16. is always on the go.	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	

CAARS - INVESTIGATOR : SCREENING VERSION : (CAARS - INV:SV)

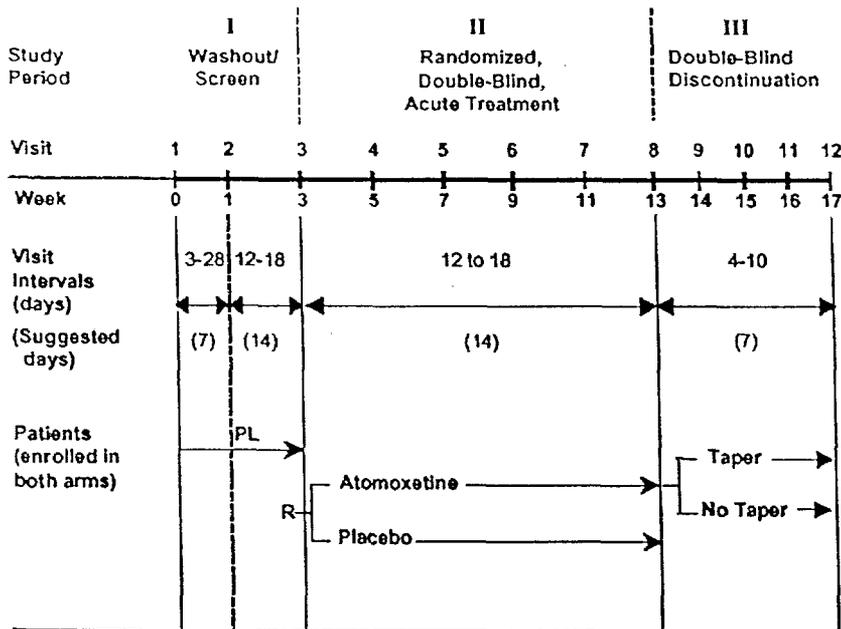
	Not at all never	Just a little once in a while	Pretty much often	Very much all the time	(DNDE) ADHD Symptom Score
17. can't get things done unless there is an absolute deadline.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
18. fidgets (with hands or feet) or squirms in seat.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19. makes careless mistakes or has trouble paying attention to detail.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
20. intrudes on others' activities.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
21. doesn't like academic studies/work projects where effort at thinking a lot is required.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
22. is restless or overactive.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
23. sometimes overfocuses on details, at other times appears distracted by everything going on around him/her.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
24. can't keep his/her mind on something unless it's really interesting.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
25. gives answers to questions before the questions have been completed.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
26. has trouble finishing job tasks or schoolwork.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
27. interrupts others when they are working or busy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
28. expresses lack of confidence in self because of past failures.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
29. appears distracted when things are going on around him/her.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
30. has problems organizing tasks and activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

(DNDE)
ADHD Symptom Score Total _____

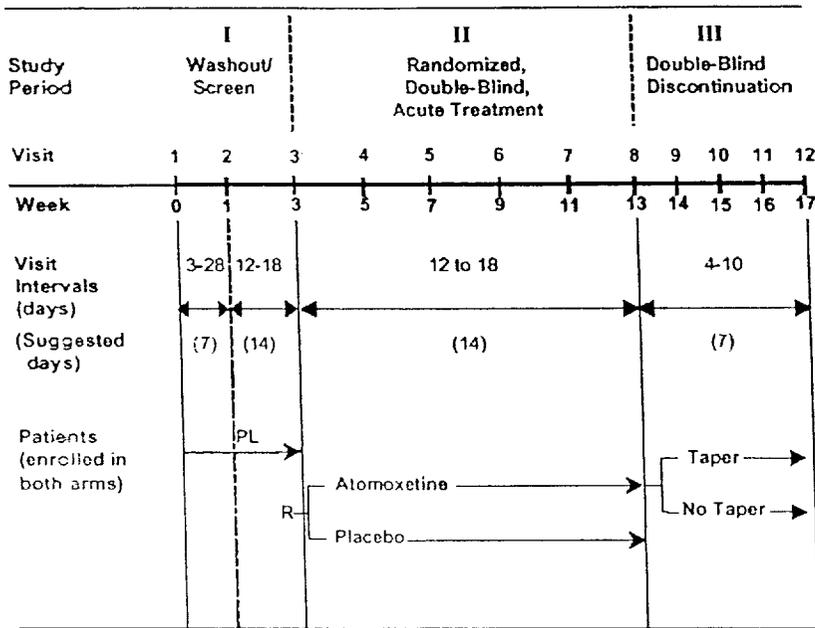
Sponsor's Study Schematic for HFBE

I - Screen/ Washout	II - Randomized Open-Label		III - Randomized, Double-Blind, Variable Discontinuation						IV - Ran Double-Bl and Disc Vis	
	V1	V2	V12	V14	V15	V16	V21	V22		V26
Visit Interval	V1-V2 7-28 days	V2-V12 Weekly Visits ~14 days	V12-V16 Biweekly Visits 1-16 days				V16-V26 Monthly Visits 1-35 days			V26-V28 Weekly Visits 1-14 days
(Suggested Intervals)	7/14 days	(7 days)	(14 days)				(28 days)			(7 days)
		Atomoxetine				Atomoxetine		Atomoxetine		Taper
						Atomoxetine		Placebo		No Taper
						Atomoxetine		Atomoxetine		Taper
						Atomoxetine		Placebo		No Taper
						Placebo				
		Methylphenidate				Placebo				

Sponsor's Study Schematic for LYAA



Sponsor's schematic for Study LYAO



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/s/

Roberta Glass
6/30/02 02:34:04 PM
MEDICAL OFFICER

Thomas Laughren
7/19/02 07:59:11 AM
MEDICAL OFFICER

I agree that this NDA is approvable; see memo
to file for more detailed comments.--TPL

REVIEW OF CLINICAL DATA

NDA	21-411
Brand name (generic name)	Strattera (atomoxetine)
Sponsor	Eli Lilly
Materials reviewed	Responses to reviewer questions dated 6/11/02, 6/19/02
Reviewer	Gerard Boehm, MD, MPH
Date Completed	7/23/2002

Background

This document reviews the sponsor's submissions addressing the safety experience of atomoxetine subjects exposed to a CYP2D6 inhibitor, and providing additional information for subjects with convulsion AEs.

Atomoxetine/metabolic inhibitor analysis

Atomoxetine's metabolism is influenced by the CYP2D6 genotype of the treated individual as well as by concomitant use of drugs that inhibit CYP2D6. In the atomoxetine ISS and safety update, the sponsor reviewed the safety experience of atomoxetine treated subjects who were poor metabolizers based on genotype, and the safety experience of atomoxetine subjects who took a CYP2D6 inhibitor to create phenotypic poor metabolizers, and then started atomoxetine. In these cases, the poor metabolizer phenotype was present prior to dosing atomoxetine.

I had concerns about patients titrated to tolerable doses of atomoxetine and subsequently started on a CYP2D6 inhibitor. This group could potentially experience sudden increases in drug plasma levels resulting in unique safety concerns not explored in the sponsor's submitted analyses. I asked the sponsor to identify subjects administered atomoxetine and subsequently started on a CYP2D6 inhibitor and to summarize the safety experience for these individuals.

The sponsor focused on patients who took moderate (celecoxib, fluvoxamine, sertraline) or potent (terbinafine, fluoxetine, paroxetine) CYP2D6 inhibitors. For these subjects, the sponsor produced individual timeline summaries that identified when the inhibitor was started, subsequent AEs, vital signs, and laboratory data.

The sponsor identified a total of 312 subjects who took at least one CYP2D6 inhibitor but most of these took either CYP2D6 substrates or weak inhibitors. Forty subjects were identified who added a moderate or potent CYP2D6 inhibitor to their atomoxetine regimen. I reviewed the summaries provided by the sponsor for all forty of these subjects. Fifteen subjects had fluoxetine added to atomoxetine, 14 had celecoxib, 4 had terbinafine, 3 had paroxetine, 3 had sertraline and 1 had fluvoxamine added to atomoxetine.

There were no patterns of AEs or adverse vital sign changes in the forty identified subjects who had a moderate or strong CYP2D6 inhibitor added to an atomoxetine regimen. In many cases the inhibitor was started about the same time as atomoxetine, preventing us from observing the true circumstance of interest.

Discussion

This post-hoc analysis did not provide affirmative evidence of increased risk for adverse outcomes when a CYP2D6 inhibitor was added to a regimen of atomoxetine but this

analysis has limitations. There were few subjects in the database who had a CYP2D6 inhibitor added to atomoxetine. The data from subjects who started the inhibitor at the same time as atomoxetine was of little additional value since data from subjects with similar circumstances were included in the ISS and NDA.

Atomoxetine/convulsion cases

During the atomoxetine safety review, I identified two serious AEs and four non-serious AEs coded as convulsions. While the sponsor provided details for the SAE cases, both narratives acknowledged that they did not have all relevant diagnostic test results for these events. There was little information provided about the non-serious convulsion cases. Since drug-related seizure events would be a concerning finding, I asked the sponsor to provide additional information for the serious cases and to summarize information for the non-serious cases. The sponsor's response to this request was dated 6/4/02.

The sponsor searched their safety database for all adverse events that included the terms seizure, generalized convulsions and epilepsy. They identified the same six cases that I identified during my review. The sponsor commented that several of these cases did not appear to represent true seizures. The sponsor found no consistent pattern for the six cases and no evidence of dose response. CYP2D6 did not appear to be a risk factor since none of the subjects with convulsions were poor metabolizers. Time to event since beginning treatment varied and some cases included rechallenge or continued treatment without event recurrence.

The sponsor provided narratives for the six convulsion AE cases. Those narratives are provided below.

LYAB-57-5333: Events related to this patient were described in the NDA, and the text from the NDA is presented below. This patient had new onset seizures while on atomoxetine, which continued after drug discontinuation. A history of significant birth trauma is most likely the etiology of his attention-deficit/hyperactivity disorder (ADHD) and epilepsy. It is not uncommon for seizures to begin long after the initial brain insult, and the events described here occurred only after approximately 8 months of atomoxetine therapy, and did not occur at the maximum drug dose. Further, as noted below, seizures also occurred after atomoxetine was stopped at a time when plasma concentrations of atomoxetine would have been expected negligible, as this patient is a CYP2D6 extensive metabolizer.

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LYAI-88-8570: It is likely that this patient had a syncopal episode, which may have included seizure-like activity. The event followed a dental procedure which included blood loss and anesthesia, and the patient's medication had not been administered on the day of the event. Since he is an extensive metabolizer, the plasma atomoxetine concentration would have been very low at the time of the event. A sleep electroencephalogram (EEG) done as part of the evaluation of this episode was normal. It seems likely that factors other than atomoxetine are primarily responsible for these events. Approval was given for this patient to continue therapy, and at the time of the NDA submission it was thought that this was done. Dosing records indicate that atomoxetine was not restarted.

HFBF-17-1649: A single 15 second event described as a psychomotor seizure was reported. On 30 May 2002, the investigator called the patient's mother and reported: "The mother recalls the incident on January 27th 2000 as follows: She was watching — out of the corner of her eye and saw him fall down. He was shaky and attempted to slowly sit up. She thought that he was playing and asked him to stop it and sit up. He did get up into a sitting position and appeared to stare for a few seconds. He "snapped out of it" right away. There was not loss of his bladder or mental confusion postictally. He sent him to school immediately following." An EEG was normal, and the patient has been treated with atomoxetine for 2 more years. At the time of the event, the patient was on a minimal dose of atomoxetine (<0.5 mg/kg/day) and subsequently was administered much higher doses with no further similar episodes. A causal relationship between atomoxetine and the seizure can not be definitively excluded, but seems unlikely given the very low dose of atomoxetine and the absence of further episodes while on drug. Records from the pediatrician and the EEG report have been requested.

LYAB-56-5309: Although the episodes described (staring, unresponsiveness, inappropriate giggling, and drooling) could be accounted for by seizures, their etiology is unclear and no further evaluation was done. At the time of the event the patient was on a minimal dose of atomoxetine (<0.5 mg/kg/day). The patient continued atomoxetine therapy for another 3 months at doses considerably higher than that at which these events occurred (up to a maximum of 1.71 mg/kg/day) without recurrence of such events, and a causal relationship to atomoxetine therefore seems unlikely.

LYAB-59-5416: This patient had a long history of staring spells, and an EEG suggestive of epilepsy. The history suggests that partial seizures were present prior to the initiation of atomoxetine treatment. Developmental delay and ADHD are consistent with an underlying brain insult which is the likely cause of the epilepsy.

LYBB-19-8942: An event described as convulsive syncope in conjunction with a vasovagal episode was reported after phlebotomy. It was recommended that the patient lie down while having blood drawn. Atomoxetine therapy continued for an additional 13 months at higher doses without recurrence. These events do not appear to represent seizures and do not appear to be related to atomoxetine therapy.

Discussion

The information presented by the sponsor does not strongly suggest a relationship between atomoxetine and convulsions. In several of the cases, the diagnosis of convulsions was not clearly made and alternative diagnoses that can result in temporary loss of consciousness such as vasovagal syncope should have been considered. In many of the cases, atomoxetine was continued without additional episodes, despite use of higher atomoxetine doses. None of these events occurred in poor metabolizers. There did not appear to be a pattern with respect to time to event.

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/s/

Jerry Boehm
7 25/02 07:05:51 AM
MEDICAL OFFICER

Judith Racoosin
7 29/02 02:38:21 PM
MEDICAL OFFICER