NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number(s)	NDA 220320
Priority or Standard	Standard
Submit Date(s)	05/22/2025
Received Date(s)	05/22/2025
PDUFA Goal Date	03/22/2026
Division/Office	Division of Psychiatry (DP) / Office of Neuroscience (ON)
Review Completion Date	03/20/2026
Established/Proper Name	Atomoxetine Oral Solution, 4mg/mL
(Proposed) Trade Name	Atoncy
Pharmacologic Class	Selective norepinephrine receptor inhibitor (SNRI)
Code name	N/A
Applicant	MAP77 LLC
Dosage form	Oral solution
Applicant proposed Dosing Regimen	• Starting dose in pediatric patients up to 70 kg: 0.5 mg/kg daily. May be increased after a minimum of 3 days to a target daily dose of 1.2 mg/kg. • Starting dose in pediatric patients over 70 kg and adult patients: 40 mg daily. May be increased after a minimum of 3 days to a target daily dose of 80 mg.
Applicant Proposed Indication(s)/Population(s)	Treatment of attention-deficit/hyperactivity disorder (ADHD)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	406506008 | Attention deficit hyperactivity disorder (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of attention-deficit/hyperactivity disorder
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	406506008 | Attention deficit hyperactivity disorder (disorder)

Recommended Dosing Regimen

Body Weight	Starting Dosage	Titration Interval	Target Dosage[1]	Maximum Total Daily Dose[1]
Weigh less than 70 kg	0.5 mg/kg/day	Minimum of 3 days	1.2 mg/kg/day	1.4 mg/kg/day or 100 mg (whichever is less)
Weigh 70 kg or more	40 mg/day	Minimum 3 days	80 mg/day	100 mg/day

[1] Administer either as once daily dosage in the morning or as evenly divided twice daily dosage in the morning and late afternoon/early evening

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Signatures

See archived signatory memos for each discipline.

Glossary

AC	advisory committee
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
AR	adverse reaction
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	serotonin norepinephrine reuptake inhibitor

SOC	standard of care
TEAE	treatment emergent adverse event
WBC	white blood cell

1 Executive Summary

1.1. Product Introduction

MAP77 LLC, the Applicant, has submitted a 505(b)(2) application for atomoxetine oral solution for the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients 6 years of age and older. The Applicant proposes to rely on the Agency's previous findings of safety and effectiveness for the listed drug (LD), Strattera (atomoxetine) 60-mg capsules (NDA 021411, initial approval November 26, 2002). The Applicant anticipates that this product may be useful for patients with swallowing difficulties. Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI). The exact mode of therapeutic action in ADHD is unknown.

The Applicant plans to supply the drug product as a 4 mg/mL, clear, colorless solution supplied as a 100-mL amber glass bottle with a 10-mL calibrated oral dosing syringe and bottle adaptor. The proposed dosage regimens are identical to the LD. The recommended starting dosage in pediatric patients up to 70 kg is 0.5 mg/kg daily, and the recommended starting dosage in pediatric patients over 70 kg and adult patients is 40 mg daily. Dosage may be increased after a minimum of 3 days to a target daily dose of 1.2 mg/kg day (pediatric patients up to 70 kg) or 80 mg day (pediatric patients over 70 kg or adult patients). Although no benefit was demonstrated for doses higher than the equivalent of 1.2 mg/kg daily, the maximum daily dose for pediatric patients up to 70 kg is 1.4 mg/kg daily. The maximum daily dose for pediatric patients over 70 kg or adult patients is 100 mg daily. Doses may be administered as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the treatment of ADHD is provided by the Agency's previous findings of effectiveness for the LD and the establishment of an acceptable scientific bridge between the LD and atomoxetine oral solution using pharmacokinetic (PK) data from a comparative bioavailability study.

A three-treatment, three period, crossover study (Study 145-23) in healthy human adult subjects demonstrated adequate scientific bridge between the oral solution formulation of atomoxetine (4 mg/mL) and the LD (60 mg). Atomoxetine oral solution is expected to have the same effectiveness and safety for the treatment of ADHD in pediatric patients 6 years and older and adults as the approved atomoxetine (Strattera) capsules.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This 505(b)(2) NDA for atomoxetine oral solution (Atoncy, 4mg/mL) relies on the Agency's previous findings of effectiveness and safety for the listed drug (LD) atomoxetine capsules (Strattera; NDA 021411) and the acceptable pharmacokinetic (PK) bridge established between the LD and the proposed product. The effectiveness and safety of atomoxetine oral solution are expected to be similar to the LD. No new safety issues were identified from the Applicant's PK studies, including the pivotal bioavailability study. The benefit-risk profile of atomoxetine oral solution is not expected to differ from the LD. This assessment supports the marketing approval of atomoxetine oral solution for the treatment of ADHD in pediatric patients 6 years and older and adults and may provide an easier-to-swallow formulation option for children and patients with swallowing difficulty.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ADHD is a chronic, neurodevelopmental condition involving a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains. • ADHD is the most common neurodevelopmental disorder of childhood and frequently persists into adulthood. • ADHD has been associated with poor educational and occupational outcomes, as well as depression, suicidal behavior, and substance abuse.	ADHD is a serious disorder associated with increased morbidity and mortality and high social and economic costs.
Current Treatment Options	• Multiple treatment options are available for ADHD, including stimulant and non-stimulant medications. • Atomoxetine is one of two selective norepinephrine reuptake inhibitors marketed for the treatment of ADHD. • Although several stimulant ADHD medications are available as oral suspension or solution (e.g., methylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate), there are no available non-stimulant oral liquid formulations.	There are currently no non-stimulant oral solution or suspension medications for ADHD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Atomoxetine oral solution provides a liquid formulation of a non-stimulant medication for ADHD. • Atomoxetine oral solution has demonstrated scientific bridge to atomoxetine oral capsules (Strattera). • Atomoxetine has proven efficacy for the treatment of ADHD from the prior 2002 NDA approval of Strattera for ages 6 and up.	Atomoxetine oral solution may provide a non-stimulant medication option for patients with ADHD and difficulty swallowing; this formulation may be particularly useful in the pediatric population where the condition is most prevalent.
Risk and Risk Management	• Atomoxetine's most common adverse reactions per most recent labeling include nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence in pediatric patients and constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation in adults. • Warnings and precautions from the Strattera label include severe liver injury, serious cardiovascular events, anaphylaxis, urinary hesitancy and retention, priapism, increased heart rate and blood pressure, emergent psychotic or manic symptom, aggressive behavior and hostility, and growth effects. • No significant safety differences from atomoxetine oral solution and the LD were seen in the comparative bioavailability study submitted with this 505(b)(2) NDA.	Atomoxetine oral solution shows comparable safety risks to the LD, Strattera.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

ADHD is a chronic, neurodevelopmental condition marked by a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains. ADHD is the most common neurodevelopmental disorder of childhood, with prevalence in the pediatric population estimated to be approximately 11% (Danielson et al., 2024). ADHD may persist into adulthood and has an estimated 6% prevalence in adults (Staley et al., 2024). Symptoms must persist for at least 6 months and at least some symptoms must have been present prior to the age of 12 years (American Psychiatric Association 2013) to meet diagnostic criteria. Symptom presentation differs between pediatric and adult patients. Pediatric patients with this disorder often experience difficulty with school performance, difficulty interacting with peers, and may participate in dangerous activities due to impulsivity. Adults with ADHD may experience impairment in their workplace, social relationships, and with completing tasks. Many individuals with ADHD obtain symptom reduction with appropriate medication treatment, resulting in significant decreases in impairment in daily tasks and functioning.

2.2. Analysis of Current Treatment Options

Although patients with ADHD may benefit from nonpharmacologic interventions such as behavioral therapy, parent guidance, and educational modifications, data suggest that pharmacological treatment results in greater short-term symptomatic improvement than intensive behavioral therapy (Molina et al., 2009). Research on long-term benefits and risks of pharmacological treatment for ADHD are more limited and frequently confounded; however, data suggest that pharmacological treatment may also result in a lower risk of substance use disorders and injuries (Chang et al., 2019).

Stimulants are often first-line pharmacologic treatments for ADHD; however, these medications carry potential risks of blood pressure and heart rate increases, psychiatric adverse reactions, growth suppression, lowered seizure threshold, insomnia, and decreases in appetite and weight. Stimulants are also Schedule II controlled substances with significant human abuse liability potential, which lead to concerns of abuse, misuse, and diversion.

Patients who are unable to tolerate the adverse effects of stimulant medications or in situations where stimulants are not appropriate (e.g., because of potential for abuse or patient preference), may benefit from nonstimulant treatment options. These agents are not controlled substances. Four nonstimulant medications are currently approved for the treatment of ADHD: guanfacine extended-release, clonidine extended-release, viloxazine, and atomoxetine. Guanfacine extended-release and clonidine extended-release are centrally acting α2-adrenergic receptor antagonists that are indicated for the treatment of ADHD as monotherapy or as adjunctive therapy to stimulant medications. Atomoxetine and viloxazine

are norepinephrine reuptake inhibitors indicated for the treatment of ADHD in pediatric and adult patients. Atomoxetine labeling includes a boxed warning regarding the potential for SI/B, and warnings and precautions such as severe liver injury, serious cardiovascular events, anaphylaxis, urinary hesitancy and retention, priapism, increased heart rate and blood pressure, emergent psychotic or manic symptom, aggressive behavior and hostility, and growth effects.

Bupropion, immediate-release guanfacine and clonidine, tricyclic antidepressants, venlafaxine, and modafinil have also been used as off-label pharmacological treatments for ADHD. Pediatric data on the use of these medications for ADHD are limited.

Although multiple pharmacological options are available for treatment of ADHD, most are solid tablets or capsules. Atomoxetine is not currently available in the United States as an oral liquid formulation.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Agency approved atomoxetine (oral capsules) as Strattera in November 2002 under NDA 21411 for the acute treatment of ADHD. A maintenance treatment indication for ADHD was also approved in May 2008. As of early 2024, the original manufacturer (Eli Lilly) plans to stop marketing Strattera in the United States; the product was not discontinued for safety/ effectiveness reasons.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant used the 505(b)(2) regulatory pathway to rely, in part, on the Agency's previous findings of safety and effectiveness for the LD, Strattera (NDA 021411). The following list summarizes key milestones under IND 175483:

- February 13, 2025 – The Applicant submitted an initial Pediatric Study Plan (iPSP).

- March 11, 2025 – Type B (Pre-IND) meeting to obtain Division concurrence on the acceptability of the proposals for general/regulatory, chemistry, manufacturing and controls, bioavailability, clinical, nonclinical, and labeling.
  - The Division indicated that the Applicant's proposal to submit via 505(b)(2) pathway relying on Strattera as the LD, was reasonable.
  - The Division stated that the device constituent is not exempt from cGMP requirements and that the facility that manufactures the combination product must comply with 21 CFR Part 4 regarding CGMPs for combination product.
  - The Division indicated that the proposed product will be subject to Pediatric Research Equity Act (PREA) requirements, given a novel dosage form of atomoxetine and acknowledged receipt of the iPSP.

- May 15, 2025 – Issued Pediatric Written Response
  - The Division disagreed with the Applicant's proposed plan to request a (b) (4) and advised to include a plan to request a partial waiver for pediatric patients from birth to 4 years of age, a plan to request a deferral in pediatric patients 4 to younger than 6 years of age, and a plan to submit an assessment for pediatric patients 6 to 17 years of age.

- January 21, 2026: The Division communicated an anticipated Post-Marketing Requirement (PMR) in the 8-Week PMR Communication Letter.
  - Under the PREA (21 U.S.C. 355c), the atomoxetine oral solution development program is required to contain an assessment of the safety and effectiveness of the product in pediatric patients ages 4 to <6 years old.
  - The requested PMR requires the conduct of a two-part study to 1) evaluate the

pharmacokinetics (PK) of atomoxetine oral solution in pediatric patients ages 4 to <6 years old with ADHD, and 2) conduct an adequately powered, double-blind, placebo-controlled, efficacy and safety study of atomoxetine oral solution in pediatric patients ages 4 to <6 years old with ADHD.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance (OSIS)

The Office of Study Integrity and Surveillance (OSIS) was consulted for an inspection of the clinical (Ecron AcuNova, Ltd., Karnataka, India) and bioanalytical ((b) (4)) sites of the pivotal relative bioavailability study (145-23).

The OSIS determined that inspections are not needed for the following reasons:

- The Office of Inspections and Investigations (OII) conducted an inspection of the clinical site in February 2025. The inspection was conducted under the submission of ANDA (b) (4). After review of the discussion items and the site's response, OSIS concluded that the discussion items had no impact on data reliability or human subject protection.

- OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the submission of ANDA NON-RESPONSIVE. OSIS concluded that data from the reviewed studies were reliable.

For additional information, refer to the inspection memo archived on 08/08/2025.

4.2. Product Quality

The Applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product, atomoxetine oral solution (4 mg/mL). The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. Refer to the Office of Product Quality (OPQ) review for additional information.

4.3. Clinical Microbiology

Not applicable to this product.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this product.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This NDA relies on the Agency's previous findings of safety and efficacy of the LD, atomoxetine (Strattera) 60-mg capsules (NDA 021411, initial approval November 26, 2002). There were no nonclinical studies or data submitted for review, and the chemistry and manufacturing information did not identify any issues that needed safety evaluation from a nonclinical perspective. There were no proposed labeling changes to the nonclinical portions of the label compared to the LD because there was no change to the doses approved for the LD.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of atomoxetine oral solution (4 mg/mL) for the treatment of attention-deficit/hyperactivity disorder (ADHD). Atomoxetine is a selective norepinephrine reuptake inhibitor. The proposed oral solution formulation of atomoxetine relies on the Agency's previous findings of safety and effectiveness of the LD, atomoxetine hydrochloride capsules (Strattera; NDA 021411) for the treatment of ADHD in pediatric patients 6 years and older, and adults. Strattera capsules are available in seven strengths, and each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine.

The Applicant submitted a three-treatment, three period, crossover study (Test-Fasting, Test-Fed, and Reference-Fasting) to establish a pharmacokinetic (PK) bridge between the oral solution formulation of atomoxetine (4 mg/mL) and LD (60 mg), under fasting state, and to evaluate the effects of food on the PK of atomoxetine oral solution.

The Office of Clinical Pharmacology (OCP) review finds that the PK bridge between the proposed product, atomoxetine oral solution and LD under fasted state is adequate. Therefore, the proposed drug product, atomoxetine oral solution (4mg/mL) can rely on safety and effectiveness of the LD. The high-fat meal did not appreciably the PK of atomoxetine oral solution.

OCP recommends the approval of atomoxetine oral solution (4 mg/mL) for the treatment of ADHD in pediatric patients 6 years and older, and adults.

6.2. Summary of Clinical Pharmacology Assessment

- In a single-dose, relative bioavailability study in healthy adults, the PK of atomoxetine was compared between atomoxetine oral solution (4 mg/mL) and the LD (60 mg), under fasted conditions, and between atomoxetine oral solution under fasted and fed conditions. As the LD showed dose proportional PK characteristics up to 120 mg, the selection of 60-mg dose of the LD for product comparison appears reasonable. The results showed that the peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUCinf) for atomoxetine oral solution 4 mg/mL were similar to the LD, and the geometric mean ratio (GMR) and 90% confidence intervals around the GMR of PK parameters, Cmax and AUCinf were within the acceptable range of (80% to 125%) of the LD, under fasted conditions. The median time to reach Cmax (Tmax) for atomoxetine oral solution and the LD was 1 hour. The results demonstrate that the PK bridge between the formulations is adequate. Thus, atomoxetine oral solution can rely on the safety and effectiveness of the LD for the treatment of ADHD in pediatric patients 6 years and older and adults.

- Compared to fasted conditions, the AUCinf for atomoxetine oral solution was similar and Cmax was about 21% lower under high-fat meal fed conditions. The magnitude of reduction (i.e., 21%) in Cmax for the atomoxetine oral solution under fed state was smaller than that seen for the LD under fed conditions (37% reduction in Cmax). Therefore, the 21% reduction in Cmax is deemed clinically not meaningful for the atomoxetine oral solution. The median Tmax was delayed from 1 hour under fasted state to 2.25 hours under fed state for the oral solution formulation, and 1 hour under fasted state to 4 hours under fed state for the LD. As atomoxetine is intended for the chronic treatment of ADHD, the difference in Tmax between atomoxetine oral solution and the LD, under fed conditions, is not expected to be clinically significant. Therefore, the proposed atomoxetine oral solution formulation can be administered with or without food as similar to the LD.

- Based on OSIS's recommendation, the clinical and bioanalytical sites for the pivotal relative BA study (145-23) are acceptable.

6.2.1. Clinical Pharmacokinetics

Parameter		CYP2D6 Other Metabolizer Types[a]	CYP2D6 Poor Metabolizers[b]
Absorption			
Dose proportionality		10-120 mg	
Accumulation		1.1-fold	3.3-fold
Absolute bioavailability		63%	94%
T_{max} median		1 hr	2.25 hr
Effect of Food		AUC: Unchanged; Cmax: Decreased 21%	
Distribution			
Protein Binding		98%	
Volume of distribution		0.85 L/kg	
Elimination			
Atomoxetine half-life		5.2 hours	21.6 hours
Atomoxetine apparent oral clearance		0.35 L/hr/kg	0.03 L/hr/kg
4-Hydroxyatomoxetine half-life		6 to 8 hours	-
N-Desmethylatomoxetine half-life		6 to 8 hours	34 to 40 hours
Metabolism			
Primary metabolic pathways	CYP2D6	Other CYPs	
4-Hydroxyatomoxetine[c] concentration		1% of atomoxetine	0.1% of atomoxetine[d]
N-Desmethylatomoxetine[e] concentration		5% of atomoxetine	45% of atomoxetine

Parameter	CYP2D6 Other Metabolizer Types[a]	CYP2D6 Poor Metabolizers[b]
Excretion		
Urine	Greater than 80% of the administered dose excreted as 4-hydroxyatomoxetine-O-glucuronide; Less than 3% as unchanged drug	
Feces	Less than 17% of the administered dose	

Abbreviations: $C_{max,ss}$= maximum plasma concentration at steady state; T_{max} = time to peak concentration
[a] In this analysis, CYP2D6 normal metabolizers are defined as individuals who are not CYP2D6 poor metabolizers.
[b] CYP2D6 poor metabolizers are defined as individuals with two nonfunctional alleles (e.g., *CYP2D6*3/*4, CYP2D6*5/*5*), and as a result no CYP2D6 enzyme activity.
[c] Primarily formed by CYP2D6.The major oxidative metabolite formed, regardless of CYP2D6 metabolizer status, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter.
[d] 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes.
[e] Formed by CYP2C19 and other cytochrome P450 enzymes but has substantially (20-fold) less pharmacological activity compared with atomoxetine.
Source: Clinical Pharmacology Reviewer created based on data from the Applicant.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing
Since the exposures to atomoxetine were similar to the LD under fasted conditions, the information relevant to dosing and therapeutic individualization of atomoxetine oral solution can rely upon the LD.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Are the exposures of atomoxetine oral solution 4 mg/mL similar to the LD, atomoxetine capsules, 60 mg under fasted conditions?

A three-treatment, three period, crossover study (Test-Fasting, Test-Fed, and Reference-Fasting) was conducted in healthy human adult subjects to establish a PK bridge between the oral solution formulation of atomoxetine (4 mg/mL) (test product) and the LD (60 mg) (reference product). The study also evaluated the effects of food on the PK of atomoxetine oral solution. The study scheme is shown in Table 1.

Table 1. Study Schema for Study 145-23

Study Treatment Allocation			
No. of subjects	**Period 1**	**Period 2**	**Period 3**
12	Treatment (1)	Treatment (2)	Treatment (3)
12	Treatment (2)	Treatment (3)	Treatment (1)
12	Treatment (3)	Treatment (1)	Treatment (2)
Treatment 1: Atomoxetine oral solution 4 mg/mL [Test Product (A)] (Dose: 60 mg/ 15 mL) of Rubicon Research Private Limited., India under fasting conditions. **Treatment 2:** STRATTERA® atomoxetine capsules 60 mg [Reference Product (B)] of Lilly USA, LLC, Indianapolis, IN 46285, USA under fasting condition. **Treatment 3:** Atomoxetine oral solution 4 mg/mL [Test Product (A)] (Dose: 60 mg/ 15 mL) of Rubicon Research Private Limited., India under fed condition.			

Source: Clinical study report for Study 145-23, Table-5, p. 37.

The GMR and 90% confidence intervals of the PK parameters, Cmax, and $AUC_{0-\infty}$ of test product administered were within 80% to 125% range of the reference product administered under fasted conditions (Table 1). The median Tmax for both, atomoxetine oral solution and the LD, was 1 hour under fasted state. The results demonstrate that the PK bridge between the proposed product, atomoxetine oral solution and LD, Strattera, is adequate. Therefore, the proposed product an rely on the Agency's previous findings of safety and effectiveness of the LD for the ADHD indication.

Table 2. Summary of Statistical Comparisons of Plasma Atomoxetine Pharmacokinetic Parameters after Single Oral Dose Administrations of Strattera Capsules, 60 mg (Reference Product) and Atomoxetine Oral Solution 4 mg/mL (Test Product) under Fasted Conditions

GeoMean of PK Parameters	Strattera Capsule (Ref)	Ref n	Oral Solution (Test)	Test n	GeoMean Ratio% (90%CI)
AUC_{last} (µg*h/mL)	3425.79	32	3502.37	32	102.37 (97.96, 106.98)
AUC_{inf} (µg*h/mL)	3719.25	32	3807.69	32	102.23 (98.13, 106.50)
C_{max} (µg/mL)	603.29	32	564.85	32	93.62 (85.71, 102.27)

Values in Strattera Capsule (Ref) and Oral Solution (Test) columns represent geometric mean values.
AUC=area under the curve; C_{max}=peak plasma concentration; GeoMean=Geometric mean; CI=confidence interval
Source: Clinical Pharmacology Reviewer's analysis.

See Section 15.3 Clinical Pharmacology at the Appendices for additional information.

What is the effect of food on the exposures of atomoxetine oral solution? Does this product require specific dosing instruction regarding food?

In the randomized, open-label, balanced, three-treatment, three-period, crossover, oral comparative bioavailability study, the test product, atomoxetine oral solution 4 mg/mL, was administered under high-fat meal fed and fasted conditions. The results showed that the Cmax decreased by 21% under fed conditions, while the AUC was similar between fed and fasted states. The median Tmax was delayed from 1 hour under fasted conditions to 2.25 hours under

fed conditions. Based on the prescribing information for the LD, the magnitude of reduction in Cmax of oral solution formulation of atomoxetine under high-fat diet was smaller than that seen with the LD (21% vs 37% reduction). The AUCinf of the LD under fasted and fed conditions were similar and the median Tmax of the LD was delayed from 1 hour under fasted conditions to 4 hours under fed conditions. Therefore, approximately 21% reduction in Cmax of oral solution formulation of atomoxetine is considered clinically not meaningful. Further, as the proposed product is intended for chronic treatment of ADHD, the shorter delay in Tmax by 1.25 hours under fed state is also not expected to be clinically meaningful. The food effect assessment suggests that atomoxetine oral solution can be administered with or without food as similar to the LD. Comparison of the PK parameters of atomoxetine oral solution formulation between fed state (Test) and fasting state (Ref) is shown below in Table 3.

Table 3. Summary of Statistical Comparisons of Plasma Atomoxetine Pharmacokinetic Parameters after Single Oral Dose Administrations of Atomoxetine Oral Solution 4 mg/mL under Fed and Fasted Conditions

GeoMean of PK Parameters	Fasted (Ref)	Ref n	Fed (Test)	Test n	GeoMean Ratio% (90%CI)
AUC_{last} (µg*h/mL)	3502.37	32	3558.35	32	101.59 (97.52, 105.83)
AUC_{inf} (µg*h/mL)	3807.69	32	3965.14	32	104.13 (99.65, 108.82)
C_{max} (µg/mL)	564.85	32	445.64	32	78.89 (72.22, 86.18)

Values in Fasted (Ref) and Fed (Test) columns represent geometric mean values.
AUC=area under the curve; C_{max}=peak plasma concentration; GeoMean=Geometric mean; CI=confidence interval
Source: Reviewer's analysis.

See Section 15.3 Clinical Pharmacology in the Appendices for additional information.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The clinical development program for atomoxetine oral solution consists of one randomized, open-label, balanced, three-treatment three-period, three-sequence, crossover clinical pharmacology study (Study 145-23). Study 145-23 was designed to compare the relative bioavailability and food effect of atomoxetine oral solution (4 mg/mL) to atomoxetine (Strattera) capsules in healthy adult subjects. Study details are summarized below.

Table 4. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
145-23	N/A	Randomized, open-label, balanced, three-treatment, three-period, three-sequence, crossover relative bioavailability and food effect study	Single dose of: Atomoxetine oral solution (4 mg/mL), 15 mL (60 mg), fasting Atomoxetine oral solution (4 mg/mL), 15 mL (60 mg), fed Atomoxetine (Strattera) 60 mg capsule	Assess bioavailability and bioequivalence of atomoxetine oral solution (4 mg/mL) compared to Strattera; Characterize the relative bioavailability of atomoxetine following administration of atomoxetine oral solution under fasting conditions; Characterize the effects of food on the rate and extent of absorption of atomoxetine oral solution (4 mg/mL)	Three single doses	36 enrolled 32 completed	Healthy subjects	Single center

7.2. Review Strategy

The Applicant did not conduct efficacy and safety studies. Therefore, efficacy and safety of patients with ADHD were inferred from the known efficacy and safety of the LD, Strattera capsules, after a relative BA study (Study 145-23) established a PK bridge to the proposed product. No clinical efficacy data were presented in this application.

The review focused on serious adverse events (SAEs), premature discontinuations, the incidence of all adverse events (AEs) and the reported changes in vital signs from Study 145-23 to assess for any potential major new safety findings associated with atomoxetine oral solution administration compared to the LD. The Clinical Reviewer also reviewed laboratory parameters, although this study was a three-way crossover design of single doses of atomoxetine oral solution or the LD, and the brief duration of exposure was unlikely to reveal any substantial effects related to laboratory parameters or other clinically relevant factors.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable. No clinical efficacy trials were conducted to support this application. Refer to Sections 6 and 16.3 for additional Clinical Pharmacology review of Study 145-23.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of this application is primarily based on analyses of the comparative bioavailability Study 145-23. The Clinical Reviewer reviewed the Clinical Study Report (CSR) for Study 145-23 for deaths, other serious adverse events, dropouts secondary to adverse experiences, and adverse events. The safety sample included subjects who received at least one dose of study drug and had at least one post-baseline safety evaluation.

8.2.2. Review of the Safety Database

Overall Exposure

Study 145-23 was a single-dose, crossover study (n=36) with a short duration of exposure to either atomoxetine oral solution (4 mg/mL), 15 mL with and without food or the LD, Strattera capsules, 60 mg.

Adequacy of the Safety Database

The Applicant's submission contains one small comparative bioavailability study (n=36) with limited dose exposure to the drug. Because the safety of atomoxetine oral solution (4 mg/mL) relies on the LD, the application's safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application was submitted in eCTD format in which both ADAM and SDTM data were provided. Because of a landslide on a railway track, nine subjects were unable to report to the clinical facility for the period 2 check-in. Those subjects completed periods 2 and 3 on rescheduled dates to maintain a washout period of 7 days between each study period. During the study, there was one incident where well-being inquiries for two subjects were missed at the 8-hour post-dose interval. However, assessments were conducted as scheduled at the time points before (6 hours) and after (12 hours). Neither subject experienced any AE outcome. These actions are not expected to significantly impact the safety conclusions from this study. The submission is of acceptable quality.

Categorization of Adverse Events

The datasets included reported term, dictionary term, body system or organ class. The CSR reported that the Medical Dictionary for Regulatory Activities (MedDRA) coding was not mandatory. Thus, I reviewed the AEs as the reported terms. Reported AEs were relatively simply defined (e.g., vomiting, increase in laboratory parameter) and easy to understand.

Routine Clinical Tests

During Study 145-23, AEs were documented, and other safety monitoring consisted of the following:

- Laboratory tests were assessed at Screening and at the end-of-study safety evaluation
- Urine toxicology and pregnancy testing were conducted before check-in of each study period
- Vital signs (blood pressure, pulse, respiratory rate, temperature) and well-being were assessed prior to dosing, and at 2, 4, 6, 8, and 12 hours after dosing in each study periods, during check-out of each study period, and during post-study assessments.
- Adverse events were continuously monitored.

Given the known safety profile of atomoxetine and the single-dose administration of study drug in each of the three periods of the study, the safety monitoring is considered adequate.

8.2.4. Safety Results

Deaths

No deaths occurred in the single study of this development program.

Serious Adverse Events

No SAEs occurred in the study.

Dropouts and/or Discontinuations Due to Adverse Effects

Four subjects were withdrawn from the study following single occurrences of vomiting. Although the vomiting events were considered mild, subjects were withdrawn due to the single-dose, three-period crossover study design. At least one vomiting event happened during each treatment arm (atomoxetine oral solution, Strattera capsule, atomoxetine oral solution in fed condition). Nausea and vomiting are commonly reported AEs associated with atomoxetine, as indicated in the LD's Prescribing Information (PI). In addition, subjects were administered single doses of 60 mg atomoxetine without initial titration from the recommended adult starting dose of 40 mg daily, which could have impacted tolerability leading to this AE.

Significant Adverse Events

No significant AEs were reported in Study 145-23.

Treatment Emergent Adverse Events and Adverse Reactions

Eleven total AEs were reported in ten subjects; all were considered mild. Four of the AEs were occurrences of vomiting (as discussed above) which occurred during one of the three study periods. The remaining seven AEs were reported following post-study clinical laboratory assessments. The Applicant reported nine of the events subsequently resolved, with two subjects experiencing an AE being lost to follow-up. Refer to the Laboratory Findings section below for further details on these events. Refer to Table 5 below for a listing of AEs by treatment period.

Table 5. Incidence of Adverse Events and Laboratory Abnormalities, Study 145-23

	Reported Incidence by Treatment Groups			
Adverse Event	Treatment 1 (Atomoxetine oral solution (4 mg/mL), 15 mL)	Treatment 2 (Atomoxetine capsule (Strattera), 60 mg)	Treatment 3 (Atomoxetine oral solution (4 mg/mL), 15 mL in fed state)	Post Study Safety Laboratory Abnormality/Safety Population
N	34	34	35	36
Vomiting	2 (6%)	1 (3%)	1 (3%)	0
Post Study Safety Assessments				
Elevated ALT Level	-	-	-	3 (8%)
Elevated AST Level	-	-	-	1 (3%)
Elevated Total Cholesterol	-	-	-	1 (3%)
Elevated WBC Count	-	-	-	1 (3%)
Elevated ESR Level	-	-	-	1 (3%)
Total	2 (6%)	1 (3%)	1 (3%)	7 (19%)

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; ESR= erythrocyte sedimentation rate; n/a not applicable; WBC= white blood cell
Note: Post-study safety evaluations were conducted for all 36 subjects. Post-study safety values cannot be ascribed to any one treatment.
Source: Applicant's Clinical Study Report, p. 55.

Laboratory Findings

With the exception of the laboratory findings in Table 5, pre- and post-laboratory assessments

were within reference ranges. Laboratory abnormalities included three ALT level elevations, one AST level elevation, one total cholesterol level elevation, one elevated white blood count, and one high ESR level. Laboratory level elevations were considered mild in nature, and the Applicant reported that no clinical interventions were required. Significant long-term changes in laboratory parameters are not anticipated following three single doses of atomoxetine separated by a 1-week period. The mild elevations in ALT, AST, cholesterol, white blood count, and ESR are not concerning in a general sample of healthy volunteers over time, and of unclear relationship to three single therapeutic-level doses of study drug administered with an approximate 7-day washout between doses. The LD labeling contains a warning and precaution for liver injury, and three subjects experienced increases in ALT values. However, no value was greater than two times the upper limit of reference range. Refer to Table 6 for details.

Table 6. Abnormal Laboratory Values Listing, Screening and Post-Study Assessments, Study 145-23

Laboratory Parameter	Number (%) of Subjects	Subject	Screening	Post-Study	Outcome
ALT	3 (8)	(b) (6)	35 U/L	79 U/L	Lost to Follow-Up
			37 U/L	88 U/L	Resolved
			21 U/L	54 U/L	Lost to Follow-Up
AST	1 (3)		32 U/L	49 U/L	Resolved
ESR	1 (3)		35 mm/hr	53 mm/hr	Resolved
Total Cholesterol	1 (3)		206 mg/dL	275 mg/dL	Resolved
WBC Count	1 (3)		10.6 $x10^3/\mu L$	11.5 $x10^3/\mu L$	Resolved

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; ESR= erythrocyte sedimentation rate; WBC= white blood cell
Note: post-study repeat assessments were completed when subjects were available; not all assessments reverted to reference ranges before subjects were lost to follow-up
Source: Applicant's Clinical Study Report, p. 56.

Vital Signs

The Applicant reported that there were no significant vital signs findings during the study and that the study drugs were well-tolerated from vital signs perspective. No additional data was provided by the Applicant.

Electrocardiograms (ECGs)

Because of the single-dose, three-period crossover study of this well-known drug, electrocardiograms (ECGs) were only conducted at Screening. No subjects with overt ECG abnormalities were included in the study.

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable; no analyses were conducted for a BA/BE PK study.

8.2.6. Safety Analyses by Demographic Subgroups

Given the small sample sizes in the comparative bioavailability study, no analyses were conducted as they would not be meaningful.

8.2.7. Specific Safety Studies/Clinical Trials

No additional safety studies were conducted.

8.2.8. Additional Safety Explorations

No additional safety explorations were indicated or performed.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

This product has not yet been marketed. The safety concerns identified for atomoxetine through postmarket experience with the LD are outlined in Section 6.2 of the LD's Prescribing Information and include the following adverse reactions: cardiovascular symptoms (QT prolongation, syncope), peripheral vascular effects (Raynaud's phenomenon), general disorders and administration site conditions (lethargy), musculoskeletal system (rhabdomyolysis), nervous system disorders (hypoesthesia, paresthesia in pediatric patients, sensory disturbances, tics), psychiatric disorders (depression and depressed mood, anxiety, libido changes), seizures, skin and subcutaneous tissue disorders (alopecia, hyperhidrosis), and urogenital system (male pelvic pain, urinary hesitation in pediatric patients, urinary retention in pediatric patients).

Expectations on Safety in the Postmarket Setting

Due to the lack of treatment options for the preschool age group with ADHD (as stimulants now have a class-wide limitation of use for that group) and the greater ease of use of an oral solution, the Applicant must conduct a two-part PK and efficacy and safety study of atomoxetine in pediatric patients with ADHD between 4 and 6 years of age. This study will be conducted as a PMR (see Section 13). From a clinical point of view, the product is expected to be reasonably safe in the postmarketing environment for the labeled patient population of patients ages 6 years of age and older, given the LD's existing indication for this group.

8.2.10. Integrated Assessment of Safety

The safety data derived from the small study in this development program revealed no new, clinically significant safety signals that require further study or a major labeling revision. The safety data are consistent with the known safety profile of atomoxetine. Although the study only involved single-dose administration of the drug to healthy adults and are incapable alone of providing adequate safety data to support clinical use, the established PK bridging to a marketed product and extensive clinical experience with atomoxetine over the past two decades support its overall safety for the indicated patient populations.

8.3. Statistical Issues

Not applicable.

8.4. Conclusions and Recommendations

The safety profile of atomoxetine oral solution is consistent with the known safety profile of the LD. Clinically, the Clinical Reviewer expects this product to be reasonably safe and recommends approval.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting occurred, as there were no significant issues to discuss for this 505(b)(2) application. No external consultations were necessary.

10 Pediatrics

The Applicant requested a partial waiver in pediatric patients from birth to <4 years old, because studies in this age group are impossible or highly impracticable. The Division had interpreted the iPSP language to infer that the Applicant intends to conduct pediatric assessments in patients ages 6 through <18 years old, and to request a deferral of studies in pediatric patients between 4 and <6 years old.

On January 21, 2026, the Division sent the Applicant an 8-Week Postmarketing Requirement Communication letter outlining an anticipated postmarketing requirement (PMR) to be required under the Pediatric Research Equity Act (PREA; 21 U.S.C 355c); see Section 13 for more information.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

Labeling for atomoxetine oral solution is generally consistent with that of the LD. Pertinent differences between the labels for this product and the LD are described below.

3 DOSAGE FORMS AND STRENGTHS

This section was revised to describe the dosage forms and strengths of atomoxetine oral solution.

12.3 PHARMACOKINETICS

Contents in this section have been reorganized and revised to include relevant PK measures and parameters that are important for the safe and effective use of atomoxetine oral solution per the clinical pharmacology labeling guidance.

16 HOW SUPPLIED/STORAGE AND HANDLING

This section was revised to describe how atomoxetine oral solution is supplied and provide instructions for how it can be stored and handled.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS was required for this product; none exists for the listed drug.

13 Postmarketing Requirements and Commitment

On January 21, 2026, the Division sent the Applicant an 8-Week Postmarketing Requirement Communication Letter outlining an anticipated PMR to be required under the Pediatric Research Equity Act (PREA; 21 U.S.C 355c). The PMR contained in the Approval letter is:

Conduct a two-part study to 1) evaluate the pharmacokinetics (PK) of atomoxetine oral solution in pediatric patients ages 4 to <6 years old with attention deficit/hyperactivity disorder, and 2) conduct an adequately powered, double-blind, placebo-controlled, efficacy and safety study of atomoxetine oral solution in pediatric patients ages 4 to <6 years old with attention deficit/hyperactivity disorder with the proposed timeline:

Final Protocol Submission: November 30, 2026
Study Completion: October 31, 2028
Final Report Submission: March 31, 2029

14 Division Deputy Director (Clinical) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15 Appendices

15.1. References

Danielson ML, Claussen AH, Bitsko RH, Katz SM, Newsome K, Blumberg SJ, Kogan MD, Ghandour R. ADHD Prevalence Among U.S. Children and Adolescents in 2022: Diagnosis, Severity, Co-Occuring Disorders, and Treatment. J Clin Child Adolesc Psychol. 2024;53(3):343-60. doi: 10.1080/15374416.2024.2335625

Staley BS, Robinson LR, Claussen AH, Katz SM, Danielson ML, Summers AD, Farr SL, Blumberg SJ, Tinker SC. Attention-Deficit/Hyperactivity Disorder Diagnosis, Treatment, and Telehealth Use in Adults—National Center for Health Statistics Rapid Surveys System, United States, October-November 2023. Morbidity and Mortality Weekly Report. 2024;73(40):890-5.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 145-23

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Clinical Pharmacology

Bioanalysis

Atomoxetine in human plasma samples was quantitated using a validated liquid chromatography-tandem mass spectrometry (validation report: (b) (4)/BABE/AL/ATM/145-23/SR-01). The bioanalytical method validation results are shown in Table 7.

Table 7. Performance of Bioanalytical Method (b) (4)/BABE/AL/FMV/ATM-01, in Study 145-23

Analyte		Atomoxetine
Internal Standard (IS)		Atomoxetine D7
Matrix		Human plasma
Transition Monitored, Multiple Reaction Monitoring (MRM) (m/z)		Atomoxetine: 256.05 -> 44.00 Atomoxetine D7: 263.00 -> 44.00
Retention Time (min)		Atomoxetine: 2.76 min Atomoxetine D7: 2.76 min
Calibration	Range (ng/mL)	4.931 to 1479.300 ng/mL
	#Conc. points	4.931, 9.862, 73.965, 147.930, 295.860, 591.720, 887.580, 1183.440, 1479.300 ng/mL
	%CV (precision)	<15 %
	%RE (bias)	-2.95 to 0.58 %
Quality Control	Concentrations (µg/mL)	LLOQ: 5.000 ng/mL LQC: 12.500 ng/mL MQC: 750.000 ng/mL HQC: 1350.000 ng/mL
	%CV	<15 %
	%Bias	1.79 to 9.54 %
	Dilution Factor	4-fold
Long-term Stability in Matrix Validated		58 days at -20±5°C 56 days at -70±10°C

Short-term Stability in Matrix Validated	LQC and HQC at room temperature for 07 hrs and 30 mins.
Longest storage period	32 days at -70±10°C
Date Range of Bioanalytical Assays	13 days (23 July 2024 to 04 August 2024).

Abbreviations: CV- Coefficient of Variation; HQC- High Quality Control; LLOQ- Lower Limit of Quantification; LQC- Low Quality Control; RE: Relative Error
Source: Adapted from the bioanalytical report for Study 145-23, Report No.: (b)(4)/BABE/AL/ATM/145-23/SR-01.

Out of 2202 samples, 215 samples were selected for incurred sample reanalysis (ISR), in which 95.81% of samples were found to have concentrations within ± 20% of the mean of initial concentrations.

Carryover of atomoxetine peaks was less than 20% of lower limit of quantitation (LLOQ) following upper limit of quantitation (ULOQ) and is acceptable. Freeze-thaw stability was established with five cycles of freeze at -70°C ± 10°C.

The bioanalytical methods satisfy the criteria for "method validation" and "application to routine analysis" set by the guidance for industry, *Bioanalytical Method Development* (May 2018), and are acceptable.

Individual Study Report

Title:
A randomized, open label, balanced, three-treatment, three-period, three-sequence, cross over,
relative bioavailability study and food effect study of atomoxetine oral solution 4 mg/ml in normal healthy males and females, general population.

Primary Objectives:
- Compare the single dose bioavailability of atomoxetine from atomoxetine oral solution 4 mg/mL (Test Product (A)) with Strattera capsules, 60 mg (Reference Product), in healthy human adult subjects under fasted conditions.
- Evaluate the effect of food on the pharmacokinetics of atomoxetine oral solution 4 mg/mL (Test Product) in healthy human adult subjects.

Study Design:
- A randomized, open label, balanced, three-treatment, three-period, three-sequence, cross over, relative bioavailability study and food effect study in 36 healthy human (four female and 32 male) adult subjects.

- Study scheme:

Study Treatment Allocation			
No. of subjects	**Period 1**	**Period 2**	**Period 3**
12	Treatment (1)	Treatment (2)	Treatment (3)
12	Treatment (2)	Treatment (3)	Treatment (1)
12	Treatment (3)	Treatment (1)	Treatment (2)
Treatment 1: Atomoxetine oral solution 4 mg/mL [Test Product (A)] (Dose: 60 mg/ 15 mL) of Rubicon Research Private Limited., India under fasting conditions. **Treatment 2:** STRATTERA® atomoxetine capsules 60 mg [Reference Product (B)] of Lilly USA, LLC, Indianapolis, IN 46285, USA under fasting condition. **Treatment 3:** Atomoxetine oral solution 4 mg/mL [Test Product (A)] (Dose: 60 mg/ 15 mL) of Rubicon Research Private Limited., India under fed condition.			

Source: Clinical study report for Study 145-23, Table 5, p. 37.

Treatments Administered:

- **Reference Product:** Strattera capsules, 60 mg (Eli Lilly & Co.).

- **Test Product:** Atomoxetine oral solution 4 mg/ mL (Manufactured by: Rubicon Research Pvt. Ltd., India.)

Pharmacokinetic Sampling:
Blood samples were collected pre-dose and post-dose at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.17, 1.33, 1.5, 1.67, 1.83, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, and 24.0 hours after each treatment period.

Subject Disposition:

Randomized/Completed/Discontinued due to AE	36/32/4
Mean Overall Age (±SD) years	35.1 ± 5.6
Male/Female	32/04
Race (Caucasian/Black/Other)	Asian
Overall, Weight (± SD) kg	68.1 ± 10.3

Subjects (b) (6) *did not complete the study and were excluded from PK analysis. The reason(s) for not completing the study are as follows:*

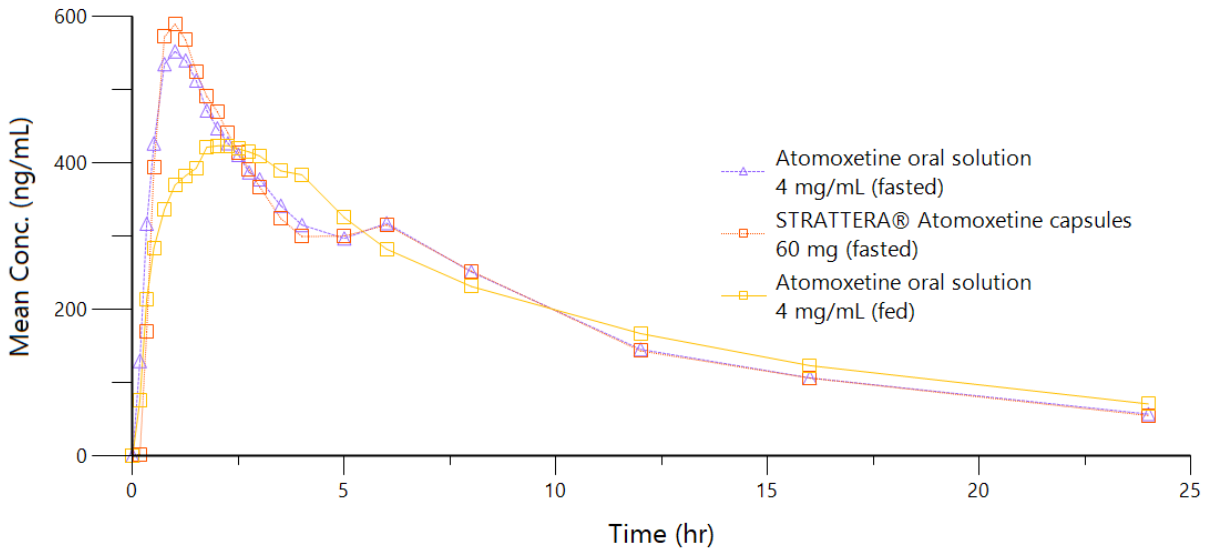
- *EID* (b) (6) *: Subject experienced an adverse event (vomiting) after period 1 dosing, hence withdraw from the study.*
- *EID* (b) (6) *Subject experienced an adverse event (vomiting) after period 3 dosing, hence withdraw from the study.*
- *EID* (b) (6) *Subject experienced an adverse event (vomiting) after period 1 dosing, hence withdraw from the study.*
- *EID* (b) (6) *Subject experienced an adverse event (vomiting) after period 2 dosing, hence withdraw from the study*

Results:

The mean plasma concentration-time profile following a single oral dose administration of the reference product (fed condition) and test product (fed and fasted condition) is shown below in Figure 1. The PK parameters after a single oral dose administration of the reference product

(fed condition) and test product (fed and fasted condition) are shown below and in Table 8, Table 9, and Table 10, respectively.

Figure 1. Mean Plasma Atomoxetine Concentration-Time Profiles after Single Oral Dose Administrations of Strattera Capsules, 60 Mg (Reference Product) Under Fasted State, and 15 mL of Atomoxetine Oral Solution 4 mg/ mL (Test Product) under Fed and Fasted States



Source: Reviewer's analysis.

Table 8. Plasma Pharmacokinetic Parameters of Atomoxetine in Plasma after Single Oral Dose Administrations of Strattera capsules 60 mg (Reference Product) under Fasted Conditions

Pharmacokinetic parameters of Atomoxetine (ng/mL) for Reference Product (Treatment 2):

Parameters	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	t_{half} (hr)	K_{el} (1/hr)
N	32	32	32	32	32	32
Mean	1.0163	653.5203	4684.2616	5584.7528	5.4071	0.1649
Standard Deviation	0.40628	260.32599	3994.05428	5697.86350	3.37745	0.06748
Minimum	0.500	281.698	1003.198	1028.170	2.575	0.046
Median	1.000	609.507	2610.666	2689.433	4.353	0.159
Maximum	2.000	1240.391	14538.442	21636.986	15.191	0.269
CV%	39.98	39.83	85.27	102.03	62.46	40.92
Geometric Mean	0.943	603.298	3425.757	3725.333	4.684	0.148

Source: Applicant's study report for Study 145-23, p. 8.

Table 9. Plasma Pharmacokinetic Parameters of Atomoxetine in Plasma after Single Oral Dose Administrations of Atomoxetine Oral Solution 4 mg/mL (Test Product) under Fasted Conditions

Pharmacokinetic parameters of Atomoxetine (ng/mL) for Test Product (Treatment 1):

Parameters	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	t_{half} (hr)	K_{el} (1/hr)
N	32	32	32	32	32	32
Mean	1.3644	610.7887	4736.6967	5698.6893	5.5074	0.1652
Standard Deviation	1.56858	254.00290	4052.53324	5901.45543	3.56443	0.06921
Minimum	0.330	224.695	1202.028	1226.478	2.662	0.045
Median	1.000	538.908	2722.424	2782.330	4.073	0.170
Maximum	8.000	1350.607	15324.510	21512.039	15.238	0.260
CV%	114.97	41.59	85.56	103.56	64.72	41.91
Geometric Mean	1.011	564.853	3502.831	3811.958	4.713	0.147

Source: Applicant's study report for Study 145-23, p. 8.

Table 10. Plasma Pharmacokinetic Parameters of Atomoxetine in Plasma after Single Oral Dose Administrations of Atomoxetine Oral Solution 4 mg/mL (Test Product) under Fed Conditions

Pharmacokinetic parameters of Atomoxetine (ng/mL) for Test Product (Treatment 3):

Parameters	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	t_{half} (hr)	K_{el} (1/hr)
N	32	32	32	31	31	31
Mean	2.3775	485.4643	4763.3959	5557.1072	5.8792	0.1512
Standard Deviation	2.05011	213.59865	4106.32231	6274.95129	3.88210	0.05863
Minimum	0.330	191.730	1363.619	1401.174	2.792	0.034
Median	2.250	424.754	2827.244	2692.372	4.106	0.169
Maximum	12.000	1043.909	15605.055	27422.663	20.096	0.248
CV%	86.23	44.00	86.21	112.92	66.03	38.79
Geometric Mean	1.831	445.646	3558.497	3734.145	5.080	0.136

AUC=area under the curve; C_{max}=peak plasma concentration; T_{max}=time post dose to reach peak plasma concentration; K_{el}=elimination rate constant; $t1/2$=half life
Source: Applicant's study report for Study 145-23, p. 8.

The study design of the comparative bioavailability study and data analyses were acceptable. The Clinical Pharmacology Reviewer was able to reproduce the Applicant's results and concurs that the PK of atomoxetine oral solution 4 mg/mL is similar to that of Strattera capsules 60 mg under fasted state. Compared to fasting conditions, the high-fat meal showed ~21% reduction of Cmax and delayed the Tmax from 1.0 h to 1.3 h. However, no food effect on AUCinf observed. The extent of effect of high-fat meal on Cmax of the proposed product is lower than that of Strattera (37% reduction in Cmax; refer to the prescribing information for Strattera). However, the food effect on AUCinf (i.e., no change in exposure) is similar between the proposed product and Strattera. The proposed product can be administered with or without food, similar to Strattera.

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