NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Prior Approval
Application Number(s)	NDA 021323/S-055; NDA 021365 S-039
Priority or Standard	Standard
Submit Date(s)	July 12, 2022
Received Date(s)	July 12, 2022
PDUFA Goal Date	May 12, 2022
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	April 20, 2022
Established/Proper Name	Escitalopram oxalate
(Proposed) Trade Name	LEXAPRO
Pharmacologic Class	Selective serotonin reuptake inhibitor (SSRI)
Code name	N/A
Applicant	Allergan Sales, LLC
Dosage form	Tablets (021323); Oral solution (021365)
Applicant proposed Dosing Regimen	10 mg once daily 20 mg once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of generalized anxiety disorder (GAD) in patients 7 to 17 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	21897009 Generalized anxiety disorder
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of generalized anxiety disorder (GAD) in patients 7 to 17 years of age
Recommended SNOMED CT Indication Disease Term for each Indication	21897009 Generalized anxiety disorder
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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Valerie Magda, PharmD
Nonclinical Reviewer	Yongbin Zhang, DVM, PhD
Nonclinical Team Leader	Antonia Dow, PhD / Ikram Elayan, PhD
Office of Clinical Pharmacology Reviewer(s)	Praveen Balimane, PhD; Michael Bewernitz, PhD
Office of Clinical Pharmacology Team Leader(s)	Atul Bhattaram, PhD; Venkateswaran Chithambaram Pillai, PhD
Clinical Reviewer	Cathy Southammakosane, MD
Clinical Team Leader	Valentina Mantua, MD, PhD.
Statistical Reviewer	Yang (Kelly) Yang, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Valentina Mantua, MD, PhD.
Division Director (signatory)	Tiffany R. Farchione, MD

Additional Reviewers of Application

Office of Pharmaceutical Quality	Lin Qi, PhD, Gurpreet Gill-Sangha, PhD
Office of Prescription Drug Promotion	Annette Egbonim, PharmD Aline Moukhtara, RN, MPH
Office of Scientific Investigations	Elena Boley, MD; Phillip Kronstein, MD
Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis	Loretta Holmes, BSN, PharmD Madhuri Patel, PharmD
Division of Pediatric and Maternal Health	Ndidi Nwokorie, MD; Mona Khurana, MD
Division of Medical Policy Programs (Patient Labeling Team)	Laurie Buonaccorsi, PharmD Wendy Lubarsky, PharmD Ruth Mayrosh, PharmD

Signatures

See archived signatory memos for each discipline.

Glossary

AACAP	American Academy of Child and Adolescent Psychiatry
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGAS	Children's Global Assessment Scale
CI	confidence interval
CSR	clinical study report
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FOB	functional observation battery
GAD	generalized anxiety disorder
IND	Investigational New Drug
IRS	interactive response system
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LSM	least squares mean
LSMD	least squares mean difference
MAR	missing at random
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MNAR	missing not at random
MINI	Mini International Neuropsychiatric Interview for Children and Adolescents
mITT	modified intent to treat
NDA	new drug application
OSI	Office of Scientific Investigation
PARS	Pediatric Anxiety Rating Scale
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SD	standard deviation

SI/B	suicidal ideation and behavior
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment emergent adverse event
WBC	white blood cells

1 Executive Summary

1.1. Product Introduction

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) developed by Allergan, a subsidiary of AbbVie. Escitalopram was approved in the United States as Lexapro for the treatment of major depressive disorder (MDD) in adults, on August 14, 2002 (NDA 021323), and in adolescents 12 to 17 years of age on March 19, 2009 (NDA 021323/S-031; NDA 021365/S-022). It was approved for the treatment of generalized anxiety disorder (GAD) in adults on December 18, 2003 (NDA 021323/S-003). The dosage strengths of escitalopram are 10 mg and 20 mg. With this supplemental application, the Applicant proposes to expand the indication to the treatment of GAD in pediatric patients 7 to 17 years of age. The Agency issued a postmarketing requirement (PMR) study under the Pediatric Research Equity Act (PREA) and Study SCT-MD-60 was conducted to fulfill this requirement (PMR # 2975-1). Study SCT-MD-60, included in this submission, evaluated the safety, efficacy, and pharmacokinetics (PK) of escitalopram at a daily dosage of 10 to 20 mg in pediatric subjects (7 through 17 years of age) for the treatment of GAD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In Study SCT-MD-60, a randomized, double-blind, placebo-controlled, flexible-dose, 8-week study evaluating pediatric subjects 7 to 17 years of age with GAD, treatment with escitalopram was associated with improvement in symptoms. The treatment effect observed on the primary endpoint, the pediatric anxiety rating scale (PARS), was statistically significantly superior to placebo. The PARS is considered by the Division of Psychiatry to be a suitable outcome measure to assess symptoms of anxiety in the pediatric population. The dose regimen is supported by the submitted escitalopram efficacy data and mirrors that for pediatric MDD. Therefore, results of Study SCT-MD-60, together with partial extrapolation from escitalopram's known efficacy in the treatment of adult GAD, form the basis of substantial evidence of effectiveness for escitalopram in the treatment of GAD in pediatric patients ages 7 to 17 years.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Escitalopram is an SSRI currently approved for the treatment of generalized anxiety disorder (GAD) in adults. Although clinical practice guidelines commonly recommend serotonergic drugs for pediatric GAD, only one serotonin-norepinephrine reuptake inhibitor (SNRI) is approved for this indication and no SSRIs are approved for pediatric GAD. The Applicant has submitted an efficacy study, SCT-MD-60, that demonstrates benefit in pediatric patients 7 to 17 years of age with GAD: the primary efficacy analysis showed statistically significant and clinically meaningful superiority to placebo in the change from Baseline to Week 8 on the pediatric anxiety rating scale (PARS). The safety evaluation of escitalopram for pediatric GAD is consistent with the known safety profile for pediatric use of escitalopram including risks for suicidal ideation and behavior (SI/B) and decreased appetite with potential impact on growth—these are adequately described in current labeling. The benefits of this product for pediatric patients 7 to 17 years of age with GAD outweigh the risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric GAD is often a chronic illness with a prevalence of 2%. • Pediatric GAD is characterized by excessive, uncontrollable worry and other associated symptoms and may impact various aspects of a patient's life. • Diagnosis is clinical and based upon DSM-5 criteria.	• Pediatric GAD is frequently a chronic condition that can be impairing without treatment.
Current Treatment Options	• The only drug approved for the treatment of pediatric GAD is duloxetine, an SNRI. • Cognitive behavioral therapy and SSRIs are also recommended first-line interventions for pediatric GAD.	• Despite extensive literature supporting the use of SSRIs, approved effective treatments available for the treatment of pediatric GAD are limited to behavioral therapy and one SNRI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant submitted Study SCT-MD-60, a randomized, double-blind, placebo-controlled, flexible-dose, 8-week study to evaluate efficacy of escitalopram in pediatric subjects 7 to 17 years of age with GAD. • Subjects began with a 10 mg/day dose of escitalopram (taken orally) and could have a dose escalation to 20 mg/day of escitalopram. • The proposed dose regimen is supported by the submitted escitalopram efficacy data and mirrors that for pediatric MDD. • The primary efficacy outcome measure was the PARS, which is considered a suitable measure for a pediatric GAD study, and also supported the approval of duloxetine for the same indication. • A statistically significant treatment effect for escitalopram versus placebo was observed at Week 8 for the PARS severity score; the MMRM least squares mean (LSM) change from baseline was -7.81 for the escitalopram group versus -6.38 for the placebo group for a treatment difference of -1.42 [95% CI: (−2.69, −0.15); p=0.0281]. This difference is clinically meaningful.	• The Applicant submitted data to demonstrate that escitalopram is effective in reducing pediatric GAD symptoms in a single short-term flexible-dose efficacy study in pediatric subjects 7 to 17 years of age. • The primary efficacy analysis, which demonstrated superiority to placebo, was change from Baseline to Week 8 on the PARS. • The proposed dosing regimen is acceptable for this product, which can be titrated to effect based on clinical assessments and is supported by the submitted efficacy data. • Escitalopram is a new treatment option for the treatment of pediatric GAD.
Risk and Risk Management	• Important risks with SSRIs are SI/B, serotonin syndrome, discontinuation symptoms, seizures, activation of mania/hypomania, hyponatremia, abnormal bleeding, interference with cognitive and motor performance, angle closure glaucoma, and sexual dysfunction. • Adverse reaction information for pediatric patients currently included in the product label was collected in a double-blind placebo-controlled study in 576 pediatric patients 6 to 17 years of age, (286 escitalopram, 290 placebo) with MDD. The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies. However, the following adverse reactions were reported at an incidence of at least 2% in subjects taking escitalopram in MDD clinical trials and greater than	• The clinical safety of escitalopram in the pediatric population is informed by short- and long-term studies in MDD. • The clinical safety in pediatric patients with GAD is informed by findings from the short-term pediatric GAD Study SCT-MD-60. • The adverse events that occurred in Study SCT-MD-60 are consistent with the known safety profile of escitalopram in the pediatric population (e.g., suicidal ideation and behavior (SI/B) and decreased appetite

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo: back pain, urinary tract infection, vomiting, and nasal congestion. • The safety database also relies upon an open-label study in pediatric MDD for long-term findings. Because important safety differences are not expected between pediatric MDD and GAD populations, it is reasonable to consider the long-term MDD data supportive of the safety assessment for escitalopram in pediatric GAD. • In Study SCT-MD-60 there were no deaths; there were three serious adverse events (SAEs) not related to the study drug. Overall, the adverse events leading to discontinuation were known potential drug effects, which do not indicate new safety signals. • The one severe treatment-emergent adverse reaction in Study SCT-MD-60 was anger, which is a known potential drug effect. • The treatment-emergent adverse events associated with escitalopram occurring in >2% of subjects and greater than placebo were nausea, decreased appetite, insomnia, somnolence, diarrhea, abdominal discomfort, anxiety, dizziness, nasopharyngitis, abdominal pain, anger, and irritability.	with potential impact on growth) and do not indicate new safety signals. • Considering the safety profile of escitalopram for pediatric GAD, the benefits of the product outweigh the risks.

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Section 8.1.1
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	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):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Pediatric GAD is a chronic mental illness with a waxing and waning course.[1] Onset is typically during school-age or adolescence, and it is often comorbid with other psychiatric disorders (including other anxiety disorders). The prevalence rate of pediatric GAD is estimated to be up to 2% in national samples.[2] The disease may impact pediatric patients socially, educationally, occupationally, and medically and, particularly when comorbid with depression, may increase the risk of suicide. GAD is characterized by excessive, uncontrollable worry and is associated with one or more of the following: restlessness, easy fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbance.[3] As with adult patients, diagnosis in pediatric patients is made clinically based on these Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria.

2.2. Analysis of Current Treatment Options

The most recent American Academy of Child and Adolescent Psychiatry (AACAP) Clinical Practice Guidelines recommends cognitive behavioral therapy and SSRIs for the treatment of pediatric GAD with SNRIs as potential alternatives. Less than half of pediatric patients with GAD receive treatment.[1] Despite a more extensive literature supporting the use of SSRIs compared to SNRIs, duloxetine, an SNRI, is the only FDA-approved drug for the treatment of GAD in pediatric patients 7 to 17 years of age.

[1] Walter HJ, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders. J Am Acad Child Adolesc Psychiatry. 2020; 59(10):1107-24.
[2] Costello EJ, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. Arch Gen Psychiatry. 1996; 53(12):1129-36.
[3] American Psychiatric Association, 2013, *Diagnostic and statistical manual of mental disorders (DSM-5),* Washington (DC): American Psych Pub.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FDA initially approved escitalopram (Lexapro) tablets (NDA 021323) on August 14, 2002, and escitalopram (Lexapro) oral solution (NDA 021365) on November 27, 2002, for the treatment of MDD. Subsequently, escitalopram tablets and oral solution were approved for the treatment of GAD on December 18, 2003 (NDA 021323 S-003/ NDA 021365 S004). On October 23, 2012, the Applicant was informed that the supplemental application for GAD that was approved in 2003 triggered PREA. The Agency then issued PREA PMRs for pediatric GAD:

2975-1: Deferred pediatric study under PREA to assess the safety and effectiveness of escitalopram oxalate as a treatment of Generalized Anxiety Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata.

2975-2: A juvenile rat study to support use of Lexapro in children less than 12 years of age.

The Applicant conducted Study SCT-MD-60 to fulfill PMR 2975-1.

3.2. Summary of Presubmission/Submission Regulatory Activity

The history of PREA PMR 2975-1 is as follows:

- October 23, 2012: Applicant informed that the supplemental application for GAD (approved on December 18, 2003) triggered PREA (NDA 021323)
- August 05, 2013: Written Responses provided in response to a Type C meeting request. The Applicant sought clarification on the delayed notification of the PREA requirement for studies in GAD, which the Agency provided.
- December 04, 2013: (b) (4) for an observational study in pediatric patients with GAD 7 through 17 years of age (IND 058380)
- September 16, 2014: Submission of request for IND inactivation (IND 058380)
- June 04, 2015: Advice letter sent stating the Applicant would be required to assess safety and efficacy of escitalopram as a treatment for GAD in patients 7 through 17 (NDA 021323)

- September 23, 2015: Applicant committed to completing studies, but proposed adjustment to timelines for PREA requirements (NDA 021323)
- October 16, 2015: PREA PMRs letter issued for 2975-1 (NDA 021323)
- November 30, 2018: Request for IND reactivation submitted (IND 058380)
- January 04, 2019: Reactivation/May Proceed letter issued (IND 058380)
- July 16, 2021: Deferral extension granted letter issued (NDA 021323)

A pre-sNDA meeting was submitted under IND 058380 on January 12, 2022, and subsequently cancelled as the Applicant's questions were sufficiently answered prior to the meeting. The purpose of the meeting was to align with the Division on the sNDA submission plan including content and format of the sNDA, the proposed update to labeling, and to discuss the efficacy and safety results from Study SCT-MD-60. sNDA 021323 S-055 (oral tablets) was submitted on July 12, 2022, and sNDA 021365 S-039 (oral solution) was submitted on July 13, 2022.

During the filing review, a nonclinical review issue was identified and conveyed to the applicant via the Filing Review Issues Identified letter issued September 20, 2022, which asked the Applicant to include the juvenile toxicology study (in rats) in labeling.

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

4.1. Office of Scientific Investigations (OSI)

Drs. Joseph, Mehta, and Knutson were inspected in support of NDA 021323-S55 and NDA 021365-S39. These inspections covered Study SCT-MD-60. Despite some minor protocol deviations, the study overall appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. See the Clinical Inspection Summary archived on March 2, 2022, for additional information.

4.2. Product Quality

No new product quality information was submitted with this supplement.

4.3. Clinical Microbiology

No new microbiology information was submitted with this supplement.

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

A juvenile animal study (JAS) was required to support use of escitalopram in pediatric patients younger than 12 years old. The Agency issued PMR 2975-2 on June 4, 2015, and a JAS was conducted to fulfil this requirement. The Division reviewed the draft protocol of the JAS and provided comments to the Applicant on October 13, 2016. The JAS was submitted under the current efficacy supplement and the findings from the study are discussed here. The label will be updated with the relevant findings from this JAS.

Juvenile rats were treated by oral gavage with escitalopram starting on postnatal day (PND) 21 to PND 69 at doses of 0, 5 (low dose, LD), 40 (mid-dose, MD), 80 (high dose, HD) mg/kg/day once daily for 7 weeks with a recovery period of 7 weeks. Animals were observed and evaluated for effects on general toxicity outcomes (clinical signs, body weight, food consumption, hematology, clinical chemistry, urine analysis, gross pathology, organ weights, and histopathology), ophthalmology, sexual maturation and reproductive function, bone density and length, motor activity and behavioral performance, and learning and memory (Cincinnati water maze).

Escitalopram administration resulted in a delay in sexual maturation (by 1 to 2 days for vaginal opening in females and 2 days for preputial separation in males compared to control group) at doses of 40 and 80 mg/kg/day. The AUC plasma levels at the NOAEL of 5 mg/kg for this observation are less than the clinical exposures. It should be noted that there was no effect on reproductive capacity.

A reversible disruption of learning and memory function was observed in males at the high dose 80 mg/kg/day during the drug treatment in the Path B configuration (which is considered a more complex path). The NOAEL was 40 mg/kg in males which provides a 3.5-fold safety margin relative to the human plasma levels in pediatrics at the maximum recommended human dose (MRHD) of 20 mg/day. There was no effect in females during treatment and there was no effect after the recovery period in males indicating that the effect is reversible.

An increase in motor activity, both in ambulation and fine movements, was observed prior to the daily dosing in females during the treatment period at the MD and HD. The Applicant considered this as a sequela of a postdosing effect that is pharmacological and not adverse in nature. The fact that this effect was still seen the next day prior to dosing should not be ignored and should not be considered simply a pharmacological effect because the drug levels would be at trough at that point. In addition, such an effect was not observed in males. However, this effect was not seen in the recovery group indicating that it is not a long-term effect on motor activity.

There were some histopathological findings observed during treatment such as liver hypercellular hypertrophy in both males and female at MD and HD, tubular epithelial vacuolation in epididymis at HD, minimal increase in hyaline droplet accumulation in kidney at MD and HD in male rats, and minimal-to-mild lymphoid hyperplasia in all treated groups in females. These effects were not observed after the recovery period and therefore are considered reversible. There were no significant adverse treatment-related findings on general toxicity outcomes, ophthalmology, or bone density and length.

In summary, the Applicant conducted a JAS study to support the use of escitalopram in pediatric patients 7 to 12 years of age. The JAS study was conducted based on recommendations from the Division on the study design and the study is deemed adequate. Delays in sexual maturation in both males and females, effects on motor activity in females, and deficits on learning and memory in males will be reflected in the Section 8.4 of the label.

5.2. Toxicology

5.2.1. Other Toxicology Studies

Juvenile Animal Study

A 7-Week Oral Developmental Toxicity Study of Escitalopram in Juvenile Rats with a Recovery Period of at least 7 Weeks/Study No. SCT-TX-101

Key Study Findings

- Rats were treated by oral gavage with escitalopram at doses of 0, 5 (LD), 40 (MD), 80 (HD) mg/kg/day once daily for 7 weeks with a recovery period of 7 weeks.

- Delays in vaginal opening and preputial separation were noted in MD and HD animals.

- The number of errors in Path B configuration in the Cincinnati water maze test for learning and memory function significantly increased in HD males.

- Based on delays in sexual maturations at MD and HD for both males and females, the no observed adverse effect level (NOAEL) was determined to be LD (5 mg/kg/day) with AUC exposures of 80.3 ng*hr/mL (males) and 93.3 ng*hr/mL (females) on PND 21, providing the safety margin of approximately 0.1-fold to the pediatric patient at 20 mg/day (AUC 607.2 ng*hr/ml).

- Based on the learning and memory deficits noted at HD in males, the NOAEL was determined to be 40 mg/kg/day (AUC 1690 ng*hr/mL) for males, and 80 mg/kg/day (AUC 7250 ng*hr/mL) for females, respectively, providing the safety margin of approximately 3-

times in males and 12-times in females to the pediatric patient at 20 mg/day (AUC 607.2 ng*hr/ml).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 5 (LD), 40 (MD), and 80 (HD) mg/kg/day; Once daily from PND 21 to 69
Route of administration:	ORAL GAVAGE
Formulation/Vehicle:	Ultra-pure water
Species/Strain:	Rats/ Sprague Dawley
Number/Sex/Group:	Main Toxicology: 15/sex/dose Recovery: 20/sex/dose Naïve Females: 20/group
Satellite groups:	TK: 6/sex/dose for control; 24/sex/dose for drug treatment groups
Study design:	Dose selection was based on a 14-day oral dose-range finding (DRF) toxicity study in juvenile rats (study number SCT-TX-100). In this DRF study juvenile rats (n=5/sex/group) were treated with 0, 5, 30, 50, and 80 mg/kg/day by oral gavage from PND 21 to 35. Decreases in food consumption and body weight were noted at 50 mg/kg/day and 80 mg/kg/day in both males and females. Based on these effects, doses of 5, 40, and 80 mg/kg/day were selected for the pivotal study. In the pivotal study, rats were treated by oral gavage with escitalopram at doses of 0, 5, 40, 80 mg/kg/day once daily for 7 weeks with a recovery period of 7 weeks. Mortality: F0 generation dams were evaluated twice daily. F1 generation rats were observed for mortality and moribundity twice daily. Clinical Signs: F0 generation dams were observed on Days 15 and 21 of lactation. F1 generation rats were observed daily following arrival, pre-weaning litter

check, and then weekly during the treatment and recovery periods. The rats utilized for evaluation of reproductive functions were observed on days 0, 3, 7, 10, and 13 post coitum for treated females. The naïve females were observed on the day of randomization, day 0, and 13 post coitum.

Body weights were recorded individually on Days 15 and 21 of lactation for F0 generations. Body weights were recorded on 2 days; PNDs 15 and 20, and then twice weekly starting on PND 21 until the end of the study for F1 generations. Food consumption was measured weekly from PND 21 to initiation of cohabitation for mating. Feed consumptions were evaluated at Days 0 to 3, 3 to 7, 7 to 10, and 10 to 13 for mated females.

Ophthalmological evaluations were conducted for main toxicology and recovery animals at the end of the dosage period.

Blood was collected from the abdominal aorta of fasted animals at termination of the study and at the end of the recovery period. The hematology, coagulation and clinical chemistry parameters were measured.

Urine was collected from animals deprived of food and water during the collection procedure, and standard urinalysis parameters were measured.

Sexual Maturation: Females were evaluated once daily for vaginal opening beginning on PND 26. Males were evaluated once daily for preputial separation beginning on PND 35. Body weight was recorded on the day animals attained sexual maturation.

Reproductive Capacity: Estrus cycle of all reproductive subset females was determined by vaginal lavage for 14 days before and during the mating period until the day of positive identification of mating (both treated and naïve). For cohabitation and mating assessment, treated females were placed with a proven breeder

naïve male for 14 days starting at PND 112, and a naïve female with normal estrous cycle was placed with each treated male. A vaginal plug or sperm in vaginal smear from female was used to detect the evidence of the mating. The day of positive identification of spermatozoa or presence of a vaginal plug was defined as Day 0 post coitum or Day 0 of gestation.

The reproductive tract of the reproductive subset and naïve females was dissected from abdominal cavity and the uterus and contents were examined for the number of and distribution of corpora lutea, implantation sites, live and dead embryos, early resorption, and any abnormal placenta.

Male reproductive assessments were used to evaluate the potential toxicity of the test article on the male reproductive system. Sperm motility was evaluated following dispersion into a medium of sperm from the left vas deferens. Sperm concentration was evaluated for two counts of sperm obtained from the left cauda epididymis. Sperm morphology was evaluated for the percentage of abnormal sperm in the sample (a total of at least 200 sperms) and quantitation of abnormal sperm from the two spermatozoa smear obtained from the left cauda epididymis. Spermatogenic cycle assessment was conducted by the evaluation of the tubular stages of spermatogenic cycle from a qualitative examination of the testis section from control and HD animals.

CNS/Neurobehavioral Assessment: The assessment in the report includes a functional observation battery (FOB) test, locomotor activity test, startle habituation test to evaluate the effect on motor and sensory endpoints and learning and memory test. During the treatment period, all the CNS/neurobehavioral assessments were conducted prior to daily dosing.

FOB test was conducted during the dosing period (PND 55) prior to daily dosing and during the recovery period (PND 104). Locomotor activity was evaluated following FOB using a home cage photobeam activity system for

1 hour (6 intervals each for 10 min), once during the dosing period on PND 55 (before the daily dosing) and once during the recovery period on PND 104. Both ambulation and fine movements were evaluated.

The learning and memory test was conducted using Cincinnati Water Maze (CWM) during dosing period (PND 52 to 68) (prior to daily dosing) on main subset animals and during recovery period (PND 106 to 116) in the recovery group. The maze utilizes two paths (Path A and Path B). Path A was used on the first day of testing and each animal was tested twice, this was repeated for additional two days. There was at least 24h separation between the second trial on the first day and the first trial on the second day. The same animals were then tested using Path B, two days after the first set of testing using Path A, and the test was repeated in a similar fashion to that used for Path A. The effect of the treatment on the ability to swim was tested using a straight channel path in both control and treated groups.

Startle habituation was measured during the dosing period (prior to daily dosing), once between PND 60 and 66, and during the recovery period, once between PND 105 and 111. The rats were given a 4-minute acclimation period, and the startle response were measured in 50 identical trials with an 8-second inter-trial interval.

Bone Evaluation: Right femur and tibia dimensions (length and width) were collected and measured at the time of necropsy. Dual Energy X-ray Absorption (DXA) bone densitometry analysis (bone mineral density, bone mineral content, and area) was performed on the right femur (global, proximal, distal, and mid-shaft).

Histopathology: The animals were sacrificed, and the major organs were collected at the end of the study. Tissue samples from these organs were prepared for histopathology. Seven brain levels were prepared and examined.

	Toxicokinetics: Blood was collected at pre-dose and 1-, 2-, 4-, 8-, and 24-hours post-dose by abdominal aorta on PND 21 and by jugular venipuncture on PND 69. The levels of escitalopram, desmethyl citalopram and didesmethyl citalopram were measured and analyzed.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article-related deaths
Clinical Signs	For the F1 generation, abnormal gait was noted in HD males and females on Days 22 to 23 and decreased activity was noted in HD males and females on Days 21 to 25 after treatment. Wet fur was noted in MD males and females on Days 49 to 70 and HD of males and females on Days 38 to 69. Salivation was noted in MD males and females on Days 56 to 70, HD males on Days 24 to 119, and HD females on Days 27 to 84. These findings were pharmacological effects of the test article, which were not considered to be adverse.
Body Weights/Food Consumption	No remarkable findings
Ophthalmoscopy	No test article-related effects
Hematology	No test article-related effects
Clinical Chemistry	• Increases in creatinine level were noted at MD and HD males (up to +29% compared to control) and HD females (up to +19% compared to control). • Increases in glucose level were noted in at HD males (+28%), MD females (34%), and HD females (+24%). • Increases in triglycerides were noted at MD and HD in both males and females (up to 75%). • Decreases in chloride were noted at MD and HD in both males and females (from 98.5 to 99.6 mmol/L); however, they were within the range of historical data (87.7 to 106.6 mmol/L) Due to the small magnitude of changes observed with these findings and the fact that they are within the historical control these findings are considered non-adverse.
Urinalysis	No test article-related effects

Sexual Maturation	See Table 16 in the Appendix. In females, a delay in the day of vaginal opening was seen in animals treated with 80 mg/kg/day (2.1 days) and in animals treated with 40 mg/kg/day (0.8 days) compared to the control group. The values for the 40 and 80 mg/kg/day for vaginal opening exceeded the historical control range for the testing facility (range: PND 31.0 to 34.3 vs. average of 34.7 to 36 in MD and HD, respectively). Body weight was increased in these groups compared to control groups at the time of sexual maturation. Preputial separation was delayed in males treated with 40 and 80 mg/kg/day dose groups compared to the control group (by 2.1 days). The values were outside the historical control range for preputial separation (PND 41.2 to 45.6 vs. average of 45.7 for both MD and HD). There was an increase in body weight at the time of sexual maturation in these groups compared to the control group. The Applicant stated that there were no test article-related effects on reproductive function and related parameters and thus considered these delays to be non-adverse. However, the Reviewer considers the delays in vaginal opening and preputial separation as drug-related and therefore should be described in the label, even though there was no effect on reproductive function.
Reproductive Capacity	No test article-related effects on: • The parental performance including the mean day to mating, mating and fertility indices, and conception rate for the treated males and females mated with untreated animals. • Ovarian and uterine parameters including numbers of corpora lutea, live embryos, dead embryos, early resorptions, and the pre and post implantation losses of the treated females and naïve females mated with treated males. • Sperm motility, morphology, or concentration and spermatogenic cycle assessment.

CNS/ Neurobehavioral Assessment	No remarkable findings for the FOB and startle habituation tests. There were increases (approximately 50%) in ambulation for MD and HD female during treatment period, and a more pronounced effect was noted at intervals 2 and 3. There was an increase in fine movements at multiple intervals in MD (89 to 231%) and HD (103 to 205%) females compared to control group, and the most pronounced effect was noted at intervals 2, 3, and 4. No significant changes in fine movements or ambulation were noted in males during treatment period and for both sexes during the recovery period. The Applicant proposed that the effect seen in females prior to daily dosing are attributed to a sequela of a postdosing effect, that are pharmacological and not adverse in nature. It is not convincing that the increase in the motor activity in females seen prior to dosing are considered a pharmacological sequela, as the Applicant contends. The fact that it was still seen the next day prior to dosing should not be ignored. The treatment appears to have an effect as the animals did not return to normal motor activity the next day prior to dosing, which is what is expected as the drug levels should be at trough at that time. In addition, if the effect was pharmacological in nature, it should have been also seen in males, which was not the case, even though the males had comparable plasma levels. Therefore, this explanation by the Applicant is speculative. There was no difference in the swimming ability of rats in the treated group and the control as indicated by a comparable time to swim a straight channel. There were no treatment-related effects on learning and memory performance in male and female rats when tested in the Path A configuration. However, the number of errors made by HD males in Path B configuration was significantly higher than controls in trials 2 through 4 (see Table 17in Appendix), indicating that learning and memory function was affected in males at HD. In addition, and even though they were not statistically significant, the latencies to find the platform were higher for males treated with the HD during treatment in trials 2-4 (see Table 18 in Appendix). During the post-treatment period (PND 106-116), an effect was still evident on the effect on latencies after the recovery period, even though was not statistically significant (see Table 19 in Appendix). However, the number of errors in Path B configurations were comparable to controls, indicating that the observed adverse effect during treatment phase appears to be reversible. There were no effects observed in females during treatment or after the recovery period. There were no adverse test article-related effects on any of the startle parameters at the end of dosing or at the end of the post dosing period.
Bone Evaluation	No test article-related effects.
Gross Pathology	No test article-related effects.
Organ Weights	Increased liver weights for males and females (up to +17% relative to body weight) at MD and HD. These findings correlated to hepatocellular hypertrophy.

Histopathology Adequate battery: Yes	The histological findings were noted in the treatment groups. •Epididymis: minimal to moderate microvesicular tubular epithelial vacuolation was noted at HD males •Kidney: minimal increase tubular hyaline droplets accumulation at MD (2/10) and HD (4/10) males in treatment group. •Liver: diffuse centrilobular hepatocellular hypertrophy was noted in males at MD (3/10 minimal) and HD (4/10 minimal and 6/10 mild), while none were seen in control. •Lymph node (mandibular): minimal or mild Lymphoid hyperplasia was noted in all treated females. However, these histological findings were not noted in the recovery group, indicating a complete recovery and considered not to be adverse.
Toxicokinetics	TK parameters are summarized in Table 20, Table 21, and Table 22 in Appendix. PND 21 AUC (males): 80.3, 4170, or 14400 ng*hr/ml at LD, MD, or HD AUC (females): 93.3, 4780, or 12200 ng*hr/ml at LD, MD, or HD PND 69 AUC (males): 32.8, 1690, or 5630 ng*hr/ml at LD, MD, or HD AUC (females): 84.0, 2590, or 7250 ng*hr/ml at LD, MD, or HD For escitalopram, mean plasma exposures (Cmax and AUC) increased more than dose-proportional from 5 mg/kg/day to 40 mg/kg/day, and approximately dose-proportional from 40 mg/kg/day to 80 mg/kg/day for both males and females for PND 21 and PND 69. There was no difference in exposure between male and females. Tmax ranges from 1 to 2 hours on PND 21 and PND 69. Half-life of the escitalopram ranges from 1.1 to 3.9 hours. For desmethyl citalopram, mean plasma exposures (Cmax and AUC) increased more than dose-proportional from 5 mg/kg/day to 40 mg/kg/day, and approximately dose-proportional from 40 mg/kg/day to 80 mg/kg/day for Cmax on PND 21 and PND 69 but more than dose-proportional for AUC on PND 21 and dose-proportional for AUC on PND 69. There was no difference in exposure between male and females, except for exposure in males at the doses of 40 mg/kg and 80 mg/kg on PND 69 was higher compared to that in females. Tmax ranged from 1 to 8 hours on PND 21 and PND 69. For didesmethyl citalopram, mean plasma exposures (Cmax and AUC) increased more than dose-proportional from 5 mg/kg/day to 40 mg/kg/day, and approximately dose-proportional from 40 mg/kg/day to 80 mg/kg/day for both males and females on PND 21 and PND 69. There was no difference exposure between male and females. Tmax ranges from 2 to 8 hours on PND 21 and PND 69.

LD: low dose; MD: mid dose; HD: high dose.

6 Clinical Pharmacology

6.1. Executive Summary

This submission includes a clinical study report (SCT-MD-60) to satisfy the PMR-2975-1. Additionally, a population pharmacokinetics (PopPK) and exploratory exposure-response analysis in pediatric patients 7 to 17 years of age with GAD were also submitted.

PopPK analysis suggested that steady state exposures (Cmax and AUCtau) in adolescents receiving 20 mg once daily were similar to those observed in adults. However, steady-state Cmax and AUCtau in younger subjects (7 to 11 years of age) receiving 20 mg once daily were approximately 93% and 86%, respectively, higher than those observed in adults.

No apparent relationship between plasma exposures and primary efficacy endpoint, change in PARS from Baseline to Week 8 was observed in adolescents and children 7 to 11 years of age. Following escitalopram treatment, slightly higher median plasma concentrations were observed in subjects who experienced somnolence or decreased appetite compared to those who did not experience these symptoms. However, relatively similar plasma concentrations were observed between subjects who experienced insomnia or nausea and subjects who did not experience these symptoms.

6.1.1. General Dosing

Dosing in Pediatric Patients (7 through 17 years of age): The recommended dosing for pediatric patients with GAD 7 through 17 years of age is to start with 10 mg once daily and, if warranted by clinical response and tolerability, increase to the maximum recommended dosage of 20 mg once daily no sooner than 2 weeks after initiation. This regimen is identical to the dosing strategy used in efficacy and safety study SCT-MD-60 which included pediatric patients 7 through 17 years of age. The exposures in 7 to 11 years old patients were 86% to 93% higher than those observed in adults and the exposure in 12 to 17 years old patients were similar to adults.

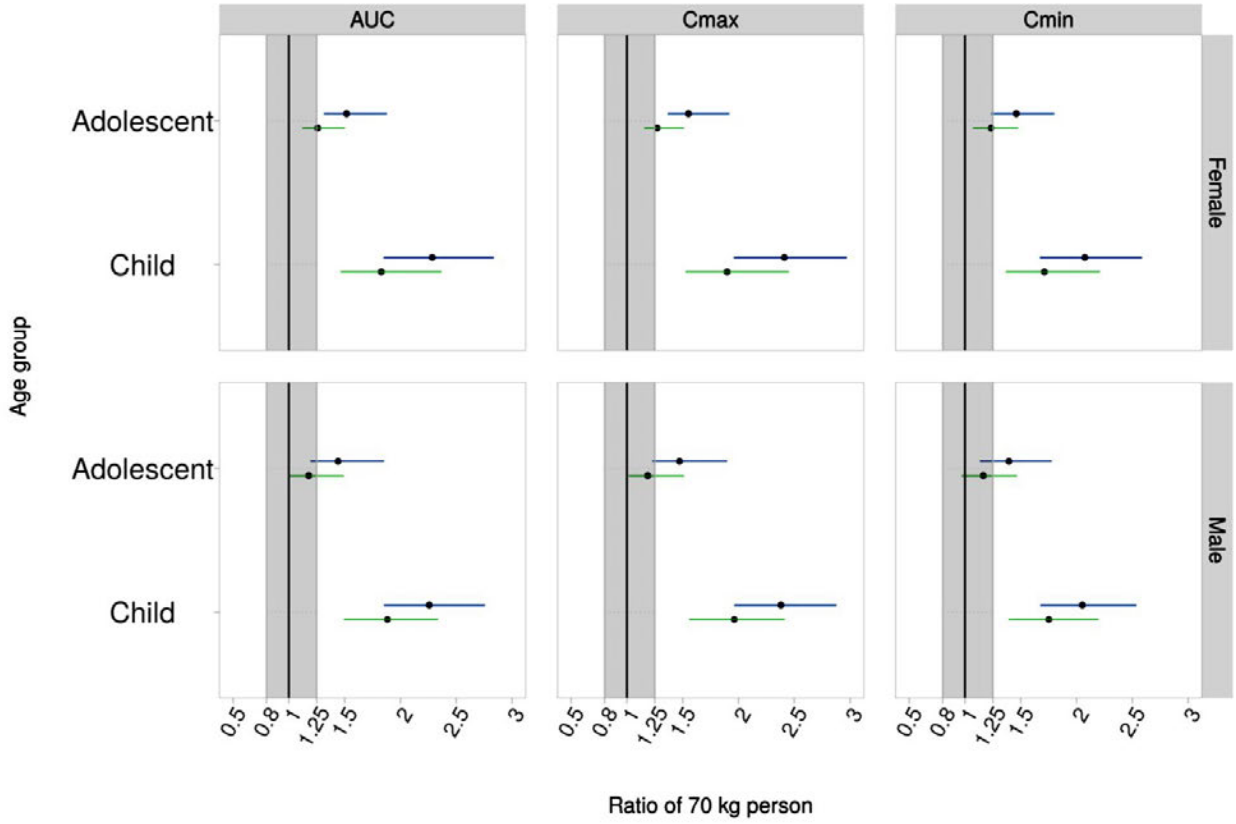
6.2. Clinical Pharmacology Review Questions

6.2.1. What were the PK characteristics in adolescents (12 to 17 years) and children (7 to 11 years) compared to PK in adults?

Sparse PK samples were collected in Study SCT-MD-60. The Applicant utilized population pharmacokinetic (PPK) model to predict escitalopram PK in adolescents and children for comparison with adults. The median weight values as well as the 5^{th} percentile of weight values for male and female pediatric subjects 7 to 17 years were used to generate a virtual pediatric population. A 70 kg weight was used to represent an adult reference. Steady-state PK metrics (Cmin,ss, Cmax,ss, and AUCtau,ss) were simulated for the 20 mg once daily dosing regimen. The

results are presented as the ratio (and 95% CI) of the PK metrics for each pediatric group (adolescent or child) divided by the PK metric for the 70 kg adult reference. For additional details on the PPK modeling and simulation, please refer to the Pharmacometric Analyses section of this review. The simulation results are stratified by male and female pediatric subjects and by the three PK metrics in Figure 1.

Figure 1: Forest Plot of Simulated Steady-State PK in Pediatric Subjects Relative to a 70 kg Adult



Green: Median (50th percentile) subject in age/gender group with 95% confidence intervals.
Blue: 5th percentile body weight subject in age/gender group with 95% confidence intervals
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 55.

The key PK findings in pediatric patients at the median body weight are summarized below:

- **Pediatric patients 7 to 11 years of age**: Based on population PK simulations, following multiple administrations of 20 mg once daily escitalopram, steady-state Cmax and AUCtau of escitalopram were increased by 93% and 86%, respectively, in patients with GAD 7 to 11 years of age compared to adults

- **Pediatric patients 12 to 17 years of age**: The simulation results are consistent with the information present in the version of the Lexapro label available at the time of this

submission. Overall, the median values of steady-state PK for adolescents with GAD are similar to a 70 kg adult.

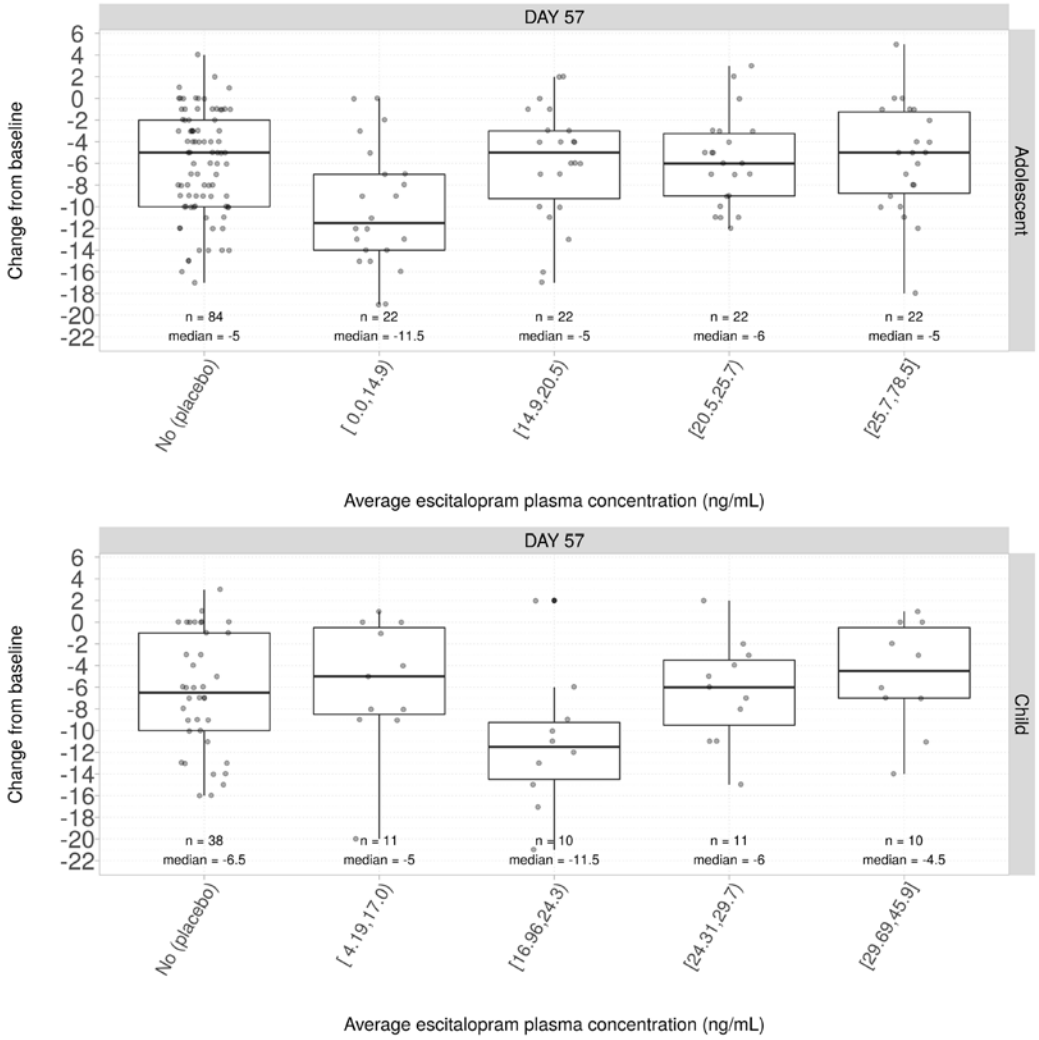
The Office of Clinical Pharmacology (OCP) recommends updating the Lexapro label, Section 12.3 Specific Populations, by including a new heading to describe the PK in pediatric GAD subjects 7 to 11 years of age with respect to a 70 kg adult.

6.2.2. Based on the exposure-response analysis, was there any relationship between exposure and efficacy or safety?

The Applicant provided the results of a graphical analysis of the relationship between the primary efficacy endpoint in SCT-MD-60, change from baseline in PARS at Week 8, and average concentration up to Week 8. The results are presented in

Figure **2**.

Figure 2: Change from Baseline PARS Week 8 vs. Average Plasma Concentration by Pediatric Age Group (Adolescent or Child) in Phase 3 Trial SCT-MD-60



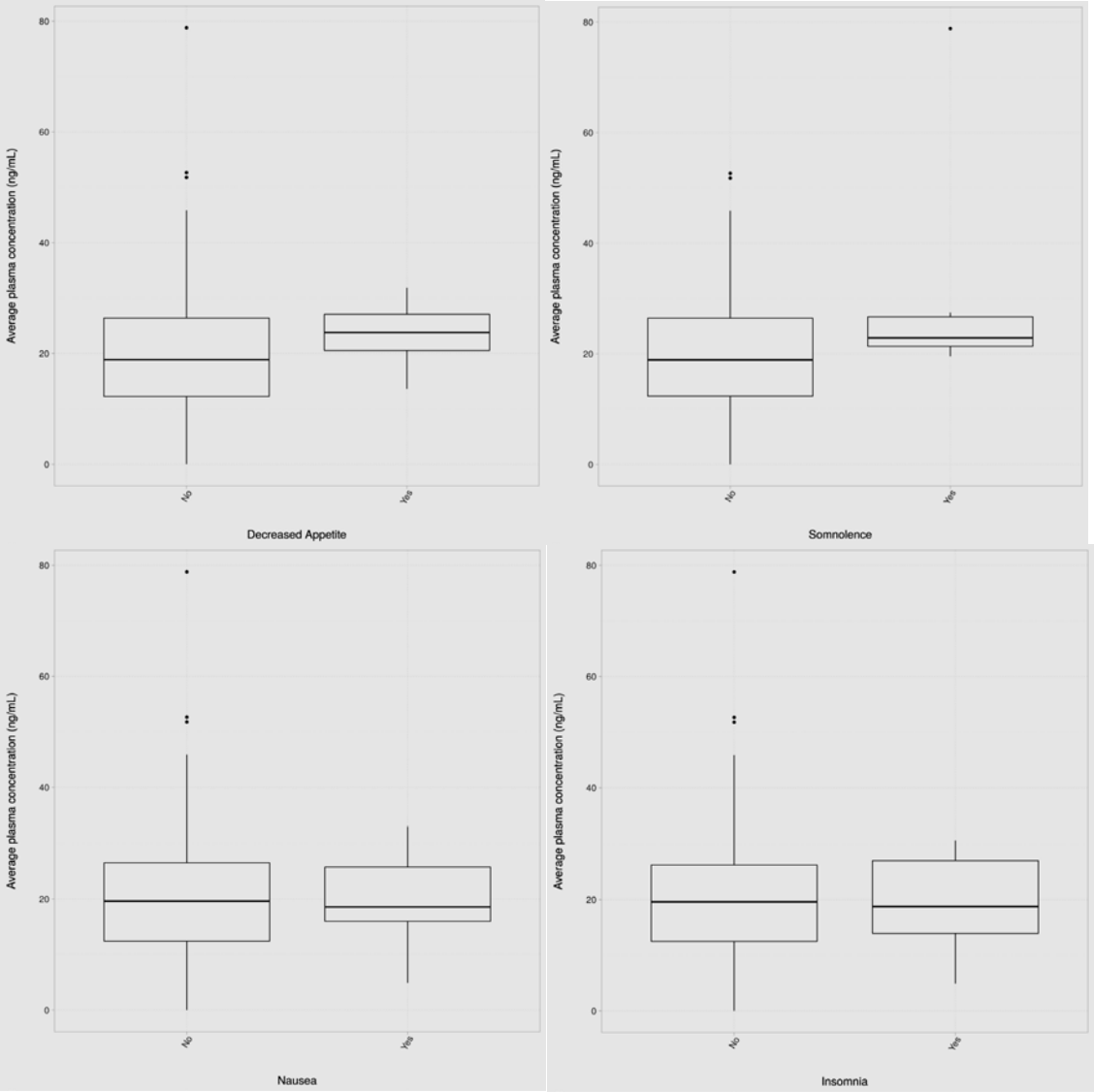
Boxplot shows median, quartiles and whiskers are 1.5 times the inter-quartile range, dots are outliers
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 59.

Overall, the data presented in

Figure **2** do not support the existence of an exposure-response relationship for Week 8 change from baseline on the PARS.

The Applicant assessed the relationship between escitalopram plasma concentration and adverse event risk. The Applicant selected four adverse events that they believe are common. Figure 3 shows a comparison the escitalopram plasma concentration between subjects that experienced an adverse event versus the escitalopram plasma concentration in subjects that did not experience each of the four adverse events.

Figure 3: Average Plasma Concentration in Patients that Received Escitalopram and Did or Did Not Experience the Selected Adverse Event



Boxplot shows median, quartiles and whiskers are 1.5 times the inter-quartile range, dots are outliers.
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, pages 69 to 72.

The analyses in Figure 3 demonstrate that subjects treated with escitalopram who experienced decreased appetite or somnolence also demonstrated numerical higher median plasma concentrations than patients that did not experience these adverse events. The plasma concentrations in subjects experiencing insomnia or nausea were similar to patients that did not experience these adverse events.

The safety reviewer has concluded that there are no safety signals in this submission that preclude approval of this sNDA. See the Integrated Assessment of Safety section for additional details.

6.2.3. Was a Validated bioanalytical method used for the analysis of sparse PK samples from Study SCT-MD-60?

Yes, a validated bioanalytical method was utilized for the analysis of both the parent (escitalopram) and the metabolite (S-desmethyl citalopram) in the plasma samples from Study SCT-MD-60. The performance of the analytical method was successfully demonstrated during the validation and also by the in-study method performance. The analytes were stable under all conditions tested. See the Appendix (Section 0) for details.

6.2.4. What was the formulation/dosage form used for the Study SCT-MD-60 and is a PK bridging study required?

The already-approved tablet formulation of Lexapro was used in the pivotal efficacy study (SCT-MD-60). Thus, no PK bridging study is required.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The clinical development program for escitalopram consisted of one randomized, double-blind, placebo-controlled study (Study SCT-MD-60).

Table 1: Listing of Clinical Trial Relevant to this NDA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. Subjects Randomized	Study Population	No. Centers/ Countries
Controlled Studies to Support Efficacy and Safety								
SCT-MD-60	N/A	Randomized, double-blind, placebo-controlled, flexible dose study	Escitalopram 10 mg oral daily, titrated to 20 mg oral daily per Investigator discretion at Weeks 2 or 4	Primary: Change from Baseline to Week 8 on the PARS Secondary: - Week 8 response rate on PARS - Week 8 remission rate on PARS - Change from baseline to Week 8 on CGI-S - Week 8 remission rate on CGI-S - Change from baseline to Week 8 Children's Global Assessment Scale (CGAS) - Week 8 remission rate on CGAS - COVID-19 impact assessment score at each visit	8-week acute treatment period 1-week down taper period 1-week follow-up period	N=275 Escitalopram n=138 Placebo n=137	Children ages 7 to 11 years and adolescents ages 12 to 17 years with GAD	35 in the United States

Source: Generated by Clinical Reviewer.

7.2. Review Strategy

The Applicant submitted this sNDA to expand their approval for the treatment of GAD in pediatric patients 7 through 17 years of age. Efficacy and safety of escitalopram with regard to the proposed indication of are reviewed below. The efficacy review focuses on Study SCT-MD-60, the short-term trial in pediatric subjects with GAD, with analyses performed by the Applicant and by Office of Biometrics reviewer Dr. Kelly Yang. The Office of Clinical Pharmacology's assessment of dosing and adverse events can be found in Section 6. Clinical Pharmacology. The safety review focuses on Study SCT-MD-60 with a brief review of Study SCT-MD-55, an open-label, 24-week safety study in pediatric subjects 7 to 11 years of age with MDD.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SCT-MD-60: A Randomized, Multicenter, Double-blind, Flexibly-dosed, Efficacy and Safety Study of Escitalopram in the Treatment of Children and Adolescents with Generalized Anxiety Disorder

Trial Design

This study was a randomized, double-blind, placebo-controlled study comparing escitalopram to placebo. Subjects were 7 to 17 years of age and met DSM-5 criteria for GAD.

Objectives:
Primary: To evaluate the safety and efficacy of escitalopram compared to placebo in the acute treatment of children (7 through 11 years of age) and adolescents (12 through 17 years of age) who met DSM 5 criteria for GAD.

Secondary: To characterize the pharmacokinetic (PK) profile of escitalopram in the pediatric population (7 through 17 years of age).

Key inclusion criteria:
- Male or female ages 7 through 17 years
- Met DSM-5 criteria for GAD established by comprehensive psychiatric evaluation and confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents
- Moderate to severe illness defined by the following:
  - Presence of at least four symptoms on the generalized anxiety section of the Pediatric Anxiety Rating Scale (PARS) checklist (two of these symptoms must be “excessive worry” and “dread or fearful anticipation”)
  - PARS severity generalized anxiety section score $\geq$15
  - CGI-S $\geq$4
- Generally healthy

Key exclusion criteria:
- Current diagnosis of MDD
- Lifetime diagnosis of attention deficit hyperactivity disorder, bipolar disorder, psychotic depression, schizophrenia, other psychotic disorder, feeding or eating disorder, posttraumatic stress disorder, panic disorder, pervasive development disorder, or intellectual disability
- Substance use disorder within the past year
- Any secondary DSM-5 disorder requiring pharmacologic treatment or potentially confounding study participation

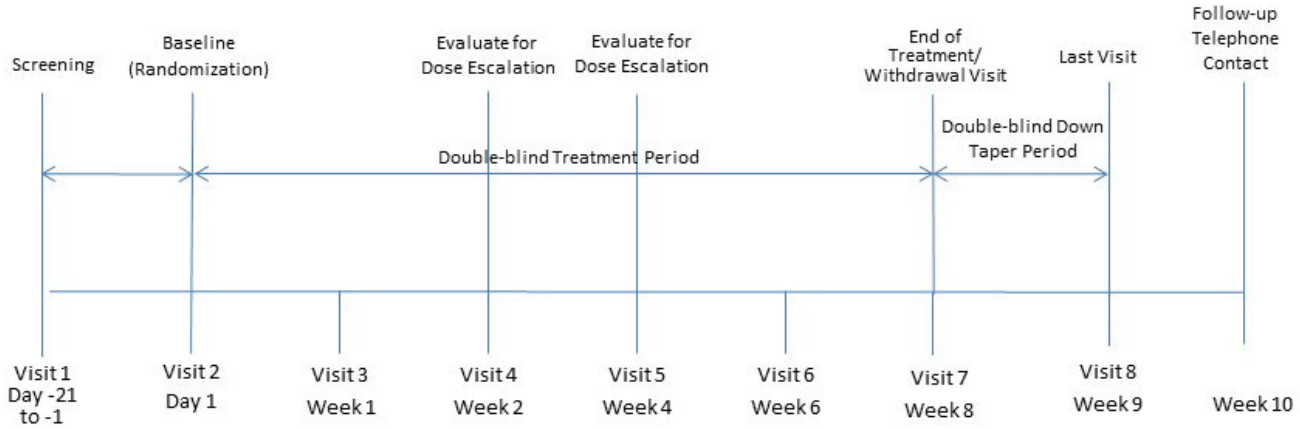
- Current or history of environmental stressor (e.g., abuse, trauma) that might confound study participation
- Unlikely to comply with study requirements or unsuitable for any reason, including any indication the subject may have been significantly impacted by the COVID-19 pandemic
- One or more first-degree relatives with bipolar I disorder
- "Yes" response to C-SSRS Item 3, 4, or 5, a lifetime history of suicidal behavior, or currently considered at risk for suicide based upon investigator judgment
- Treatment failure with adequate trials of two or more antidepressant or antianxiety medications or per investigator judgment
- Suboptimal efficacy with an adequate trial of escitalopram
- Lifetime history of ECT
- Change to psychotherapy in the past 6 weeks
- Serious or unstable medical illness or laboratory or ECG results, including thyroid disease
- Use of biotin greater than 2.5 mg daily within the past week
- Change in hormone therapy in the past 3 months

Clinical Reviewer's Comment: *Subjects with psychiatric comorbidities, SI/B, or history of trauma, or who may have been significantly impacted by COVID-19 were excluded from the study. The effect of these enrollment criteria likely decreased inter-subject variability and improved interpretability of treatment effect, but at the same time it limited the generalizability of the study findings to the patient population. However, these criteria are typical of clinical trial populations. Otherwise, subject enrollment criteria appear reasonable.*

Randomization and Blinding:
Subjects were block-randomized in a 1:1 ratio to either escitalopram or placebo. The randomization schedule was stratified by age at randomization (grouped as 7 to 11 years versus 12 to 17 years) and sex. Subjects were randomized via an interactive response system (IRS). Escitalopram and placebo capsules appeared identical. Study subjects and personnel remained blind to the selected treatment until database lock. The only exception was bioanalytic personnel involved in analysis of PK samples.

Study Schematic:
There was a 3-week screening phase, an 8-week double-blind acute treatment phase, a 1-week double-blind down-taper phase, and a follow-up phase.

Figure 4: Study Design



Source: SCT-MD-60 clinical study report (CSR), Figure 1, page 24.

Dosing:

Subjects began with a 10 mg/day dosage of escitalopram (taken orally) or matching placebo for the first 2 weeks of double-blind treatment. At the end of Week 2, subjects who tolerated the current dosage of 10 mg/day could have a dosage escalation to 20 mg/day of escitalopram or matching placebo. Dose escalation was at the investigator's discretion taking into account the CGI-S score. Subjects who remained on the 10-mg/day dosage of escitalopram or matching placebo were evaluated again at Week 4 for a possible dose escalation to 20 mg/day at the investigator's discretion. Dosage escalations were not to be made at any other time during the study. The dosage could be decreased from 20 mg/day to 10 mg/day after discussion with the medical director if the subject did not tolerate the 20 mg/day dosage.

Clinical Reviewer's Comments: *The dosing regimen for Study SCD-MD-60 was likely selected to mirror the dosing regimen for pediatric MDD studies (SCT-MD-32, SCT-MD-15, SCT-MD-32A, and SCT-MD-55) in subjects ages 6 to 17 years. This is also the approved regimen for adolescents ages 12 to 17 years with MDD and adults with MDD or GAD. As noted in Section 6. Clinical Pharmacology, exposure in adolescents aged 12 to 17 years is similar to that of adults; however, exposure in pediatric subjects 7 to 11 years is higher. From a clinical perspective, I noted that this dose was found to have a similar safety profile in children ages 6 to 11 years with MDD as in older pediatric patients with MDD and adults.*

Per Investigator or Medical Director judgment, dosage titration could occur at Week 2 or 4, and dosage taper was permitted. This dose-optimization study design could have obscured important safety findings. Fixed-dose studies allow for the best interpretation of study safety findings. However, this issue was not broached at the time of protocol review in 2019. Dose-optimization may limit interpretation of study results.

Study Schedule:

Study visits occurred at Screening, Day 1/Baseline, Week 1, Week 2, Week 4, Week 6, Week 8 (end-of-study), and Week 9. Except for the Screening visit and, in females of childbearing potential, the Baseline Visit, these visits could be conducted remotely per local COVID-19 guidance and restrictions. Follow-up at Week 10 was conducted by telephone. The assessment schedule was as follows:

Table 2: Schedule of Assessments

Period	Screening period	Double-blind acute treatment period						Double-blind down-taper period	Follow-up
Visit	1	2/Baseline	3	4	5	6	7/ET[a]	8b	Telephone contact
Day/week	Day −21 to Day −1	Day 1	Week 1[c]	Week 2[c]	Week 4[c]	Week 6[c]	Week 8[c]	Week 9[c]	Week 10[c]
Subject informed consent/assent	X								
Parent informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Medical history	X								
Psychiatric history	X								
Medication history	X								
MINI Kid	X								
Physical examination	X						X		
BMI	X				X		X		
Randomization		X							
Vital signs[d]	X	X	X	X	X	X	X	X	
ECG	X						X		
Urine drug screen	X						X		
Screen for HBsAg, HCVAb, and HIV	X								
Clinical chemistry including thyroid	X[e]						X		
Hematology	X						X		
Urinalysis	X						X		
Pregnancy test[f]	X	X					X		
C-SSRS	X	X	X	X	X	X	X	X	
CGAS	X	X	X	X	X	X	X		
PARS	X	X		X			X		
CGI-S	X	X		X			X		
Global COVID-19 impact assessment[g]	X	X	X	X	X	X	X		

Evaluate for dose escalation[h]				X	X				
PK blood samples[i]					X		X		
Dispense study drug		X[j]	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	
Adverse events	◄						►		
Concomitant medications	◄					►			

Abbreviations: BMI, body mass index; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression of Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ET, End of Treatment; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; MINI Kid, Mini International Neuropsychiatric Interview for Children and Adolescents; PARS, Pediatric Anxiety Rating Scale; PK, pharmacokinetic.
[a] ET or Early Withdrawal.
[b] If a site became aware of any adverse events after study completion (occurring outside of a defined study visit, including any contact up to 30 days after receiving the last dose of study drug), all adverse events reported by the subject or subject representative or observed or otherwise identified by the investigator or other study personnel were documented.
[c] Visit window ±3 days. Refer to Table 2 for visit windows for safety assessments (physical examination, BMI, vital signs, ECG, urine drug screen, clinical chemistry including thyroid, hematology, urinalysis, and pregnancy test) and/or PK assessments missed because of remote visits.
[d] Vital signs (blood pressure, pulse rate, temperature, and respiration rate) were recorded at every visit. Height and weight were recorded at Visit 1 (Screening), Visit 5 (Week 4), and Visit 7 (Week 8/ET) only.
[e] Fasting blood sample.
[f] A serum pregnancy test was performed at Visit 1 (Screening); a urine pregnancy test was performed at Visit 2 (Baseline) and Visit 7 (Week 8/ET) for females of childbearing potential.
[g] Completed last after all other study assessments.
[h] Subjects who tolerated the current dose of 10 mg/day could have a dose escalation to 20 mg/day at the investigator's discretion, taking into account the subject's CGI-S score.
[i] For PK blood sampling for assented/consented subjects at Visit 5 (Week 4) and Visit 7 (Week 8/ET), 2 blood samples per subject were collected at each of these visits for escitalopram and S-desmethylcitalopram analysis at the following times: Visit 5 (Week 4): for subjects receiving dose in the morning, at 0 hours (pre-dose) and ≥1 hour post-dose and for subjects receiving dose in the evening, 2 samples at random times during the visit (i.e., post-dose from the dose received the previous evening), collected at least 2 hours apart from each other; and Visit 7 (Week 8/ET): 2 samples at random times during the visit (i.e., post-dose from the dose received in the morning or the previous evening), collected at least 2 hours apart from each other.
[j] Subjects were to take their first dose of study drug in clinic.
Source: SCT-MD-60 CSR, Table 3, page 36.

Study Discontinuation:

Subjects could be removed from the study for withdrawal of consent, use of nonpermitted concurrent therapy, noncompliance with the study drug or study schedule, being lost to follow-up, an adverse event (AE), investigator request, intercurrent illness, protocol deviation, pregnancy, Sponsor request, lack of efficacy, COVID-19 pandemic, or death. Subjects who discontinued study drug before completion were monitored for symptoms of discontinuation syndrome and were asked to return to their study site and complete the final assessments. Subjects who left the study were not replaced.

Clinical Reviewer's Comment: *Some of these reasons for discontinuation could have confounded study efficacy and safety data interpretation (e.g., discontinuation due to lack of efficacy or AEs).*

Prohibited Medications:
Subjects had to discontinue antidepressant medication at least 14 days prior to randomization, except for fluoxetine, which had to be discontinued at least 28 days prior.

Treatment Compliance:
Subjects were instructed to bring unused medication to each study visit during which study personnel monitored compliance with a capsule count. Subject noncompliance warranting dismissal from the study was at the discretion of the Investigator.

Efficacy Outcome Instruments

- PARS
  This is a clinician-rated scale measuring symptom severity and impairment of GAD, social phobia, and separation anxiety disorder. The instrument comprises a 50-item anxiety symptom checklist and 7 global items. The global items are rated on a 6-point scale: *0=none* and *5=extreme*.

- CGI-S
  This is a clinician-rated scale measuring the subject's global functioning over the past 7 days. It is rated on a 7-point scale: *1= normal, not at all ill, symptoms of disorder not present past 7 days* and *7=among the most extremely ill, pathology drastically interferes in many life functions, may be hospitalized*.

- CGAS
  This is a clinician-rated scale measuring the subject's global functioning and impairment. It is rated on a 100-point scale; higher scores represent better functioning.

- Global COVID-19 Impact Assessment
  This is a clinician-rated instrument measuring the impact of COVID-19 on subject GAD symptom severity over the past 1 week. It is rated on an 8-point scale: *0= not applicable, subject not enrolled in the trial during the pandemic* and *7=extreme impact*. Whether the impact was an improvement or worsening was documented.

- Safety assessments included vital signs, ECG, laboratory tests (serum hematology and chemistry and urinalysis), physical examination, AE, and the C-SSRS.

Clinical Reviewer's Comment: *PARS was the accepted primary efficacy outcome measure for the pediatric GAD study that supported the indication for duloxetine and is also a suitable primary efficacy outcome measure for Study SCT-MD-60.*

Primary Endpoint:

- PARS change from Baseline to Week 8 for escitalopram compared to placebo

Secondary Endpoints:

- Response rate on the PARS at Week 8 for escitalopram compared to placebo
- Remission rate on the PARS at Week 8 for escitalopram compared to placebo
- CGI-S change from Baseline to Week 8 for escitalopram compared to placebo
- Remission rate on the CGI-S at Week 8 for escitalopram compared to placebo
- Children's Global Assessment Scale (CGAS) change from Baseline to Week 8 for escitalopram compared to placebo
- COVID-19 impact assessment score at each visit with escitalopram compared to placebo

Statistical Analysis Plan

The primary efficacy parameter was the change from Baseline to Week 8 in PARS severity score. The PARS severity score for GAD was assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist. The PARS severity score for GAD was derived by summing five of seven severity/impairment/interference items (items 2, 3, 5, 6, and 7). The range of each item is 0 to 5, the range of PARS severity score should be 0 to 25. If any of the items was missing, the severity score was considered missing.

A sample size of 256 subjects (128 subjects in the escitalopram treatment group and 128 subjects in the placebo group) was planned before the pre-specified sample size re-estimation to detect an effect size (treatment group difference of 2.3 units relative to pooled standard deviation (SD) of 5.79) of 0.39 with 85% power based on an MMRM model using a simulation method.[4] The simulation assumed a correlation of 0.7 between the repeated measures, and a common dropout rate of 14%, based on historical data of escitalopram in pediatric subjects.

A sample size re-estimation (blinded interim analysis) was conducted when approximately 75% of randomized subjects had either completed the study or discontinued from the study. The sample size re-estimation was conducted to obtain an estimate of the pooled SD of the change from baseline in the PARS score to Week 8 of the double-blind acute treatment period. The sample size was re-estimated using the estimated pooled SD and dropout rate from subjects included in the sample size re-estimation. If the estimated pooled SD was larger than the assumed pooled SD because of assumption deviation, as well as COVID-19 remote visits, or the dropout rate was increased, the sample size in placebo and escitalopram treatment groups could have been increased to ensure adequate power. Because of the difficulties in recruiting pediatric subjects with GAD, the Applicant capped the number of subjects in each treatment group at 160.

[4] Lu K. Sample size calculations with multiplicity adjustment for longitudinal clinical trials with missing data. Stat Med 2012;31:19-28.

The efficacy analyses are based on the modified intent-to-treat (mITT) population, which was defined as all subjects who were randomized and received at least one dose of study medication and had both baseline and at least one postbaseline primary efficacy measure (i.e., PARS severity score).

The primary estimand was defined by the following:

- Population: The target population was children (7 through 11 years of age) and adolescents (12 through 17 years of age) with GAD and who satisfied the inclusion and exclusion criteria as specified in the protocol. The analysis population was the mITT Population.

- Variable: Change from Baseline to Week 8 in the PARS severity score. The PARS severity score is derived by summing five of seven severity/impairment/interference items (items 2, 3, 5, 6, and 7).

- Intercurrent events: To evaluate the efficacy at Week 8 in the mITT population, subjects were assumed to adhere to the assigned treatment for the duration of the study. As a result, data after the discontinuation from the study treatment due to all reasons were not included in the primary analysis and were assumed as missing at random (MAR).

- Population-level summary: The change from baseline in the PARS severity score at Week 8 in subjects treated with escitalopram compared with the change from baseline in the PARS severity score at Week 8 in subjects treated with placebo.

The Applicant performed the primary analysis using an MMRM with treatment group, age group strata (7 to 11 vs. 12 to 17 years), sex, pooled study center, visit, and treatment group by-visit interaction as the fixed effects and the baseline value and baseline value-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-subject scores. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

The Applicant performed two sensitivity analyses, last observation carried forward (LOCF) and pattern-mixture model on the primary efficacy parameter to assess the impact of the MAR assumption of MMRM.

For the LOCF approach, baseline total score was carried forward only for the missing scores immediately after baseline. If all the postbaseline values were missing, the baseline value would not be carried forward. The LOCF approach was based on an analysis-of-covariance (ANCOVA) model including treatment group and pooled study center as factors and baseline PARS severity score as a covariate.

Another sensitivity analysis using a pattern-mixture model approach was performed to assess the robustness of the primary MMRM results to the possible violation of the MAR assumption.

The pattern for the pattern-mixture model was defined by the subject's last visit with an observed value. The observed PARS severity score at a visit was assumed to have a linear relationship with the subject's prior measurements. The missing values were imputed under the assumption that the distribution of the missing observations differs from that of the observed only by a shift parameter value Δ. The shift parameter served as a penalty and would be applied to only the escitalopram group to explore the resulting treatment difference after adding the penalty to the imputed values in the escitalopram group. The dataset with missing values imputed was analyzed using an ANCOVA model with treatment group and pooled study center as factors and baseline PARS severity score as a covariate for between–treatment group comparisons at Week 8. The imputation of missing values and the analysis was performed multiple times and the inference of this sensitivity analysis was based on the combined estimates using the standard multiple imputation technique. The shift parameter values Δ for the multiple imputation would start at 0 and increase by 1 to 6 or until a tipping point was reached (i.e., the p-value switches from <= 0.05 to > 0.05), whichever was higher.

To assess the impact of COVID-19 on the primary efficacy parameter, the Applicant conducted the respective subgroup analyses by whether subjects were significantly impacted by COVID-19 or not and by whether subjects were randomized before the start of the pandemic (March 17, 2020). Moreover, the respective sensitivity analyses by treating remote visits as missing and by adding a pandemic indicator were conducted.

Protocol Amendments

The original protocol for SCT-MD-60 was dated February 7, 2019. There were two protocol amendments. The first was in alignment with Division recommendations and included the additions of PK assessment and an interim analysis for sample size re-estimation. The second amendment was in response to the COVID-19 pandemic and included subject risk mitigation and quality analysis (i.e., remote visits and global COVID-19 impact assessment).

Clinical Reviewer's Comment: *There are no major concerns that these protocol amendments affected the study results.*

8.1.2. Study Results

Compliance with Good Clinical Practices

An attestation that this study was conducted in accordance with the Declaration of Helsinki, current good clinical practice guidelines, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines, and applicable national and local laws and regulatory requirements and that this study received institutional review board approval was provided in Section 5 of the clinical study report (CSR).

Financial Disclosure

This study was conducted at 35 sites in the United States. The investigators had no financial interests to disclose. See Section 0. Financial Disclosure for details.

Subject Disposition

In Study SCT-MD-60, 442 subjects were screened, 167 (38%) were screen failures mostly due to not meeting subject enrollment criteria (specific criteria were not specified). Of the 275 subjects that were randomized, 233 subjects (85%) completed the study. Two randomized subjects did not receive treatment: one subject randomized to placebo withdrew, and one subject randomized to escitalopram could not swallow capsules. Additionally, in the escitalopram group, 11% of subjects discontinued the study compared to 18% in the placebo group. Withdrawal of consent was the most common reason for discontinuation (7% of all subjects).

Table 3: Subject Disposition (Safety Population)

	Placebo (N=136) n (%)	Escitalopram (N=137) n (%)	Total (N=273) n (%)
Completed double-blind acute treatment period	117 (86.0)	123 (89.8)	240 (87.9)
Prematurely discontinued during the double-blind acute treatment period	19 (14.0)	14 (10.2)	33 (12.1)
Reason for premature discontinuation during the double-blind acute treatment period			
Withdrawal of consent	12 (8.8)	6 (4.4)	18 (6.6)
Adverse event	2 (1.5)	4 (2.9)	6 (2.2)
Lost to follow-up	2 (1.5)	2 (1.5)	4 (1.5)
Noncompliance with the study drug or study schedule	1 (0.7)	0	1 (0.4)
Lack of efficacy	1 (0.7)	0	1 (0.4)
Protocol deviation	1 (0.7)	0	1 (0.4)
Other[a]	0	2 (1.5)	2 (0.7)
Entered double-blind down-taper period	112 (82.4)	123 (89.8)	235 (86.1)
Completed double-blind down-taper period	111 (81.6)	122 (89.1)	233 (85.3)
Prematurely discontinued during the double-blind down-taper period	1 (0.7)	1 (0.7)	2 (0.7)
Prematurely discontinued study	25 (18.4)	15 (10.9)	40 (14.7)
Reason for premature discontinuation for the entire study			
Withdrawal of consent	12 (8.8)	6 (4.4)	18 (6.6)
Lost to follow-up	4 (2.9)	3 (2.2)	7 (2.6)
Adverse event	2 (1.5)	4 (2.9)	6 (2.2)
Noncompliance with the study drug or study schedule	4 (2.9)	0	4 (1.5)
Lack of efficacy	2 (1.5)	0	2 (0.7)
Protocol deviation	1 (0.7)	0	1 (0.4)
Other	0	2 (1.5)	2 (0.7)

Abbreviations: N, number of subjects in the Safety Population; n, number of subjects within a specific category.
[a] For the 2 subjects with reason "Other": 1 subject took a prohibited medication to treat an adverse event and 1 subject stopped taking the investigational product.
Source: SCT-MD-60 CSR, Table 5, page 61.

Clinical Reviewer's Comment: *Overall, the incidence of discontinuations was modest (15%) but was higher for subjects in the placebo group (18%) compared to those in the escitalopram group (11%). The largest proportion of discontinuations were categorized as "withdrew consent" in both groups, with a higher incidence of discontinuations in the placebo group than the escitalopram group. Although it would be expected for the active medication treatment group to have a higher incidence of AEs leading to discontinuation, incidence between the two treatment groups was similar (3% with escitalopram compared to 2% with placebo). See Section 8.3.4 for assessment of AEs leading to discontinuation. Other reasons for discontinuation occurred at similar incidences between the two treatment groups.*

Protocol Deviations

One significant protocol deviation involved all study sites: due to an IRS error, during the down-taper period, subjects who received escitalopram 10 mg did not receive placebo (rather they continued to receive escitalopram 10 mg). The Applicant concluded that the efficacy analysis was not impacted because primary efficacy data was obtained at the of the end of the acute treatment phase, which preceded the down-taper phase.

Of the 275 randomized subjects, 48 (18%) had at least one protocol deviation: 17% in the escitalopram group and 18% in the placebo group. The most common protocol deviations were related to concomitant medication (9%) and investigational product dosing (8%).

Table 4: Protocol Deviations (Randomized Population)

	Placebo (N=137) n (%)	Escitalopram (N=138) n (%)	Total (N=275) n (%)
Subjects with any major protocol deviations	25 (18.2)	23 (16.7)	48 (17.5)
Concomitant medication/administration of concomitant medication	11 (8.0)	13 (9.4)	24 (8.7)
Investigational product/investigational product dosing	14 (10.2)	7 (5.1)	21 (7.6)
Investigational product/other	2 (1.5)	2 (1.4)	4 (1.5)
Inclusion or exclusion criteria	0	2 (1.4)	2 (0.7)
Randomization/other	1 (0.7)	0	1 (0.4)
Study procedure/other	0	1 (0.7)	1 (0.4)
Visit window	1 (0.7)	0	1 (0.4)

Abbreviations: N, number of subjects in the Randomized Population; n, number of subjects within a specific category.
Note: Subjects could have had a major protocol deviation in more than 1 category.
Source: SCT-MD-60 CSR, Table 7, page 65.

Clinical Reviewer's Comment*: The study-wide protocol deviation of subjects taking escitalopram 10 mg not tapering to placebo during the down-taper phase is not expected to have impacted the efficacy assessment because primary efficacy data was obtained prior to this*

deviation. However, the safety evaluation is impacted—because subjects did not undergo dose taper as planned, assessment for discontinuation symptoms could not be conducted. With respect to individual subject protocol deviations, there are no major differences of concern across treatment groups.

Demographic Characteristics

In overall study enrollment, there were higher percentages of subjects who were female, age 12 to 17 years (mean age 13 years), White, and not Hispanic. The first two characteristics mirror expected pediatric GAD demographics with preponderance in females[5] and in older adolescents.[6] Racial and ethnic characteristics of GAD are not well-established, but Black, Asian, and Hispanic minorities were underrepresented in the study relative to the general child and adolescent population of the United States.[7] Therefore, the study's findings may be of limited generalizability to these groups. There was a slight demographic imbalance between treatment groups with a greater proportion of subjects in the escitalopram group who were Hispanic compared to the placebo group (22% versus 14%, respectively). The difference was modest and in the context of overall Hispanic underrepresentation. Therefore, the imbalance is not expected to be clinically significant.

Table 5: Demographic characteristics of the primary efficacy analysis (mITT Population)

	Escitalopram (n=136)	**Placebo** (n=132)	**Total** (N=268)
Sex			
Female	93 (68%)	90 (68%)	183 (68%)
Male	43 (32%)	42 (32%)	85 (32%)
Age (years)			
Mean (SD)	12.7 (2.7)	12.4 (2.6)	12.6 (2.6)
Median	13.0	13.0	13
Min	7	7	7
Max	17	17	17
Age Group			
7 to 11 years	43 (32%)	43 (33%)	86 (32%)
12 to 17 years	93 (68%)	89 (67%)	182 (68%)

[5] Costello EJ, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. Arch Gen Psychiatry. 1996;53(12):1129-36.
[6] Walter HJ, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders. J Am Acad Child Adolesc Psychiatry. 2020;59(10):1107-24.
[7] Jones N, et al. (2021, August 12). *2020 Census Illuminates Racial and Ethnic Composition of the Country*. United States Census Bureau https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html

Race			
American Indian or Alaska Native	3 (2%)	2 (2%)	5 (2%)
Asian	2 (1%)	4 (3%)	6 (2%)
Black or African American	13 (10%)	14 (11%)	27 (10%)
Native Hawaiian or Other Pacific Islander	1 (1%)	0	1 (<1%)
Other	5 (4%)	5 (4%)	10 (4%)
White	112 (82%)	107 (81%)	219 (82%)
Ethnicity			
Hispanic or Latino	30 (22%)	19 (14%)	49 (18%)
Not Hispanic or Latino	106 (78%)	113 (86%)	219 (82%)
BMI (kg/m^2)			
Mean (SD)	21.1 (3.7)	20.7 (4.0)	20.9 (3.8)
Median	20.9	20.2	20.5
Min	14.3	14.0	14
Max	33.6	31.1	33.6
BMI z-score			
Mean (SD)	0.5 (0.9)	0.4 (0.9)	0.5 (0.9)
Median	0.7	0.5	0.6
Min	-1.9	-1.7	-1.9
Max	2.0	2.0	2.0

Source: Clinical Reviewer-generated from Study SCT-MD-60 adsl.xpt via JMP

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, baseline characteristics were generally similar between the placebo and escitalopram treatment groups; imbalances were not clinically significant. Baseline GAD severity as measured by the mean PARS severity score was similar between the two treatment groups: placebo 18.0 (SD 1.7) compared to escitalopram 18.1 (SD 1.8). This was corroborated by similar mean CGI-S scores of 4.6 (SD 0.6) in both groups. Comorbid psychiatric disorders, especially ADHD, depression, and other anxiety disorders, are common with GAD, so enrollment of subjects with these diagnoses would better represent the real-world patient population.[8] However, one challenge of trial design is balancing this generalizability with operationalized subject enrollment that allows for optimal assessment of drug effect. In Study SCT-MD-60, subjects with a current diagnosis of MDD, a lifetime diagnosis of ADHD, or a secondary DSM-5 disorder requiring pharmacologic treatment or that could confound study involvement were excluded from enrollment. However, some subjects with a prior history or current comorbid psychiatric diagnosis were enrolled.

In reported medical history, 11/237 (4%) of all subjects reported a medical history of major depression, depression, or ADHD. There were more subjects in the placebo group with this

[8] Walter HJ, et al. *Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders*. J Am Acad Child Adolesc Psychiatry. 2020;59(10):1107-24.

prior medical history compared to the escitalopram group, but differences were small and not expected to impact study findings.

- ADHD: placebo 2/136 subjects (2%) versus escitalopram 0/137
- "Depression": placebo 2/136 (2%) versus escitalopram 0/137
- Major depression: 4/136 (3%) versus escitalopram 3/137 (2%)

Based on the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI) conducted at screening, no subjects met criteria for ADHD in the past 6 months or major depression in the past 2 weeks, 17/273 (6%) of all subjects met criteria for a past major depressive episode, and 14/273 (5%) met criteria for past major depressive disorder—all at similar rates between the two treatment groups.

In reported medical history, 21/273 (8%) of all subjects reported other anxiety disorders (acrophobia, animal phobia, phobia, separation anxiety disorder, and social anxiety disorder). Rates were balanced between the two treatment groups. Based on the MINI, other concurrent anxiety disorders were present at much higher rates of 74/273 (27%) of all subjects with slightly higher rates in the escitalopram group. However, the between-group differences were small and not expected to impact study findings.

- Agoraphobia: placebo 0/136 subjects versus escitalopram 3/137 (2%)
- Separation anxiety disorder: placebo 5/136 (4%) versus escitalopram 9/137 (7%)
- Social anxiety disorder: placebo 20/136 (15%) versus escitalopram 20/137 (15%)
- Specific phobia: placebo 8/136 (6%) versus escitalopram 9/137 (7%)

In reported medical history, 52/273 (29%) of all subjects met criteria for another DSM-5 disorder and 12/273 (4%) had an inadequate response to prior psychiatric medication. Rates were balanced between the two treatment groups. In the placebo group, 10/136 subjects (7%) were currently receiving psychotherapy compared to 15/137 (11%) in the escitalopram group. Because change to psychotherapy in the preceding 6 weeks was prohibited for subject enrollment, this difference is not expected to impact study findings.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
During the 8-week acute treatment phase, mean percent compliance with placebo was 94% similar to 95% in the escitalopram group. During the 1-week down-taper treatment phase, mean percent compliance with placebo was 82% similar to 84% in the escitalopram group.

Prior Medications:
Rates of prior psychotropic medication use were generally similar between the two treatment groups:

- Stimulant: placebo 3/136 subjects (2%) compared escitalopram 0/137
- "Other psychostimulant": placebo 1/136 (1%) compared to escitalopram 0/137
- Antipsychotic: placebo 0/136 compared to escitalopram 3/137 (2%)
- Antidepressant (SSRI or SNRI): placebo 7/136 (5%) compared to escitalopram 5/137 (4%)
  - SSRI: 0/136 placebo compared to escitalopram 4/137 (3%)
- Other antidepressant: placebo 0/136 compared to escitalopram 1/137 (1%; trazodone)

Concomitant Medications:
During the acute treatment phase, 51/136 (38%) of subjects on placebo took a concomitant medication compared to 63/137 (46%) on escitalopram. During the down-taper phase, 39/136 (29%) of subjects on placebo took a concomitant medication compared to 50/137 (37%) of subjects on escitalopram. Most of these medications are not expected to impact study findings: during the acute treatment phase, the most commonly used were ibuprofen (11% of subjects), acetaminophen (8%), cetirizine (7%), salbutamol (6%), and loratadine (5%).

Relevant concomitant medication use during the acute treatment phase was generally balanced between the two treatment groups:

- Benzodiazepine-related soporifics: placebo 1/136 subjects (1%) compared to escitalopram 5/137 (4%)
- Other antidepressant (SSRI): placebo 1/136 (1%) compared to escitalopram 1/137 (1%)

Relevant concomitant medication use during the down-taper treatment phase was generally balanced between the two treatment groups:

- Other antidepressant: placebo 1/136 (1%) compared to escitalopram 2 /137 (2%)

One subject randomized to placebo was also taking escitalopram concomitantly throughout the study (no end date documented) but, as a single subject, is not expected to meaningfully impact efficacy and safety findings. Three subjects randomized to escitalopram received other SSRIs during the study: one subject was also taking fluoxetine during double-blind acute treatment and one subject each was also taking escitalopram (began on the last day of taper) or fluoxetine during down-taper treatment. These few subjects are not expected to meaningfully impact efficacy and safety findings.

Efficacy Results—Primary Endpoint

A statistically significant treatment effect for escitalopram versus placebo was observed on Week 8 for the PARS severity score; the MMRM least squares mean (LSM) change from baseline was -7.81 for the escitalopram group versus -6.38 for the placebo group for a treatment difference of -1.42 (95% CI: (−2.69, −0.15); p=0.0281; Table 6).

Table 6: Primary Analysis: Change from Baseline to Week 8 in the Pediatric Anxiety Rating Scale Severity Score (mITT Population)

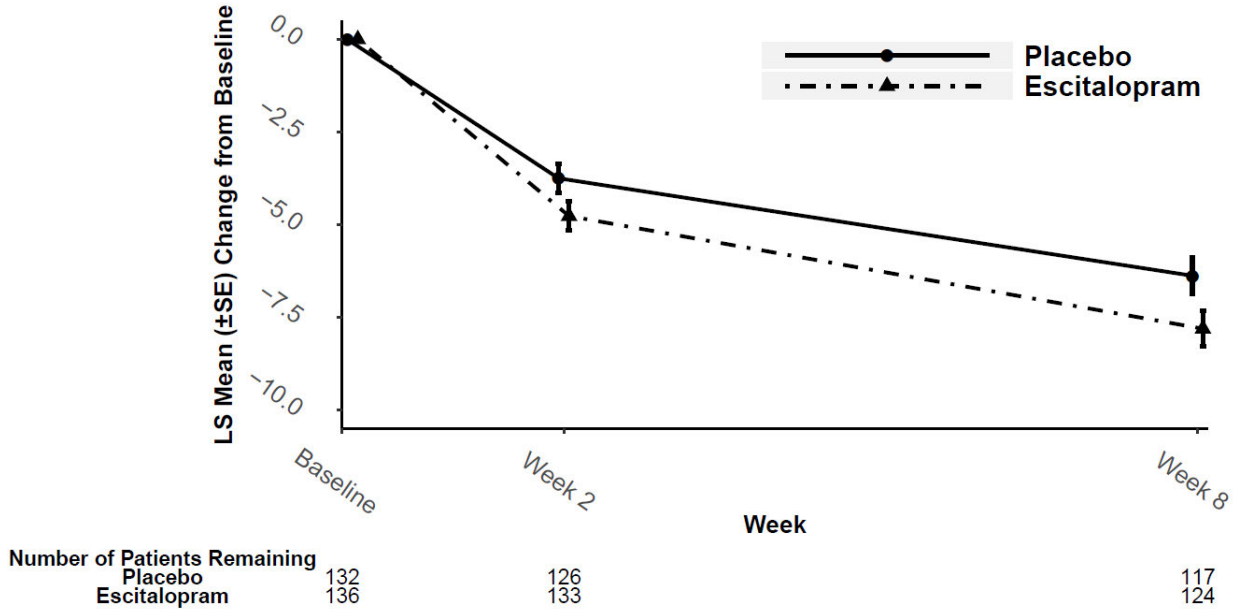
	Placebo (N=132)	Escitalopram (N=136)
Mean PARS severity score at Baseline (SD)	18.0 (1.7)	18.1 (1.8)
Mean PARS severity score at Week 8 (SD)	11.8 (5.3)	10.6 (5.2)
LSM[1] Change from Baseline (SE)	−6.38 (0.494)	−7.81 (0.484)
Placebo-subtracted difference (95% CI)		−1.42 (−2.69, −0.15)
P-value		0.0281

Abbreviations: SD=standard deviation, SE=standard error, LSM = least squares mean, PARS = Pediatric Anxiety Rating Scale, 95% CI = 95% confidence interval.
Source: Study SCT-MD-60 Clinical Study Report, Table 10, page 74, confirmed by statistical reviewer.

Figure 5 displays the LSM change from baseline in the primary efficacy measure over the 12-week treatment period. A total of 27 subjects did not have Week 8 efficacy data, and 6 of them did not have any post-baseline assessment.

Statistical Reviewer's Comment: *The statistical reviewer found that six subjects (SUBJIDs: (b) (6)) in the mITT population are not included in the primary analysis. The Applicant explained that those six subjects had only one post-baseline assessment at either Week 1 or Week 4, which were not scheduled assessment visits for efficacy. Thus, those six subjects were not included in the primary analysis although included in the mITT population. The statistical reviewer included those six subjects into the primary efficacy analysis by mapping their post-baseline assessments to the closest scheduled assessment visits (either Week 2 or Week 8) in the model; the analysis results (LSMD vs. placebo: -1.5342, 95% CI (-2.80, -0.27), p-value: 0.0178) are consistent with the primary analysis results.*

Figure 5: PARS Severity Score Change from Baseline by Visit (mITT population)



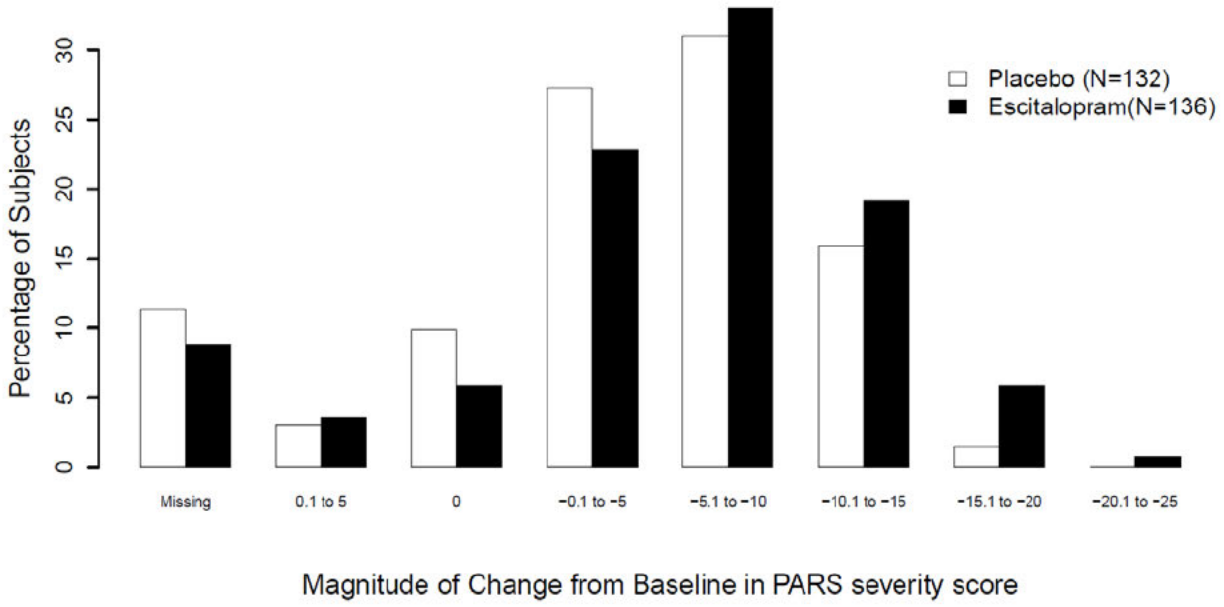
Source: Statistical Reviewer's Plot.

Statistical Reviewer's Comments: Figure 5 *suggests a separation between treatment groups at both post-baseline visits, but the numerical separation appears to be small for both visits.*

The histogram, Figure 6, displays the proportions of subjects who either improved or worsened on the primary score from baseline. The far left bars show the proportion of the subjects with missing data. Negative score represents improvement, and positive represents worsening. The Escitalopram group had a greater proportion of subjects showing improvement compared to the placebo group in most improvement intervals (interval of 5 to 25).

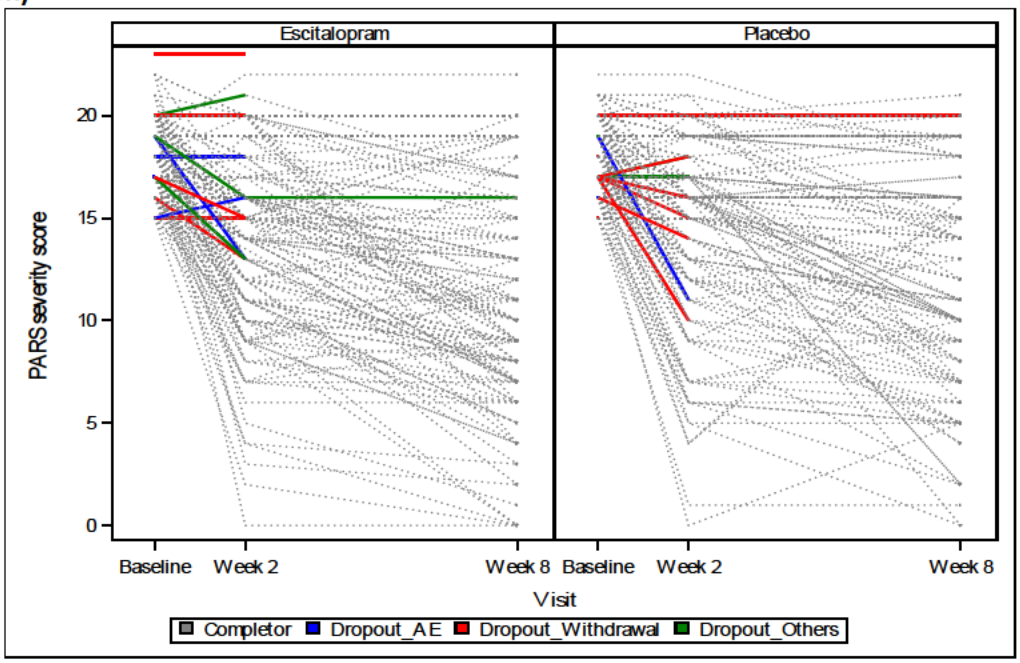
The primary statistical analysis assumes that the missing data mechanism is MAR. To explore whether this assumption appears reasonable, the statistical reviewer plotted the individual-subject observed response trajectories in PARS Severity Score by treatment group. Most of the dropouts had the similar patterns with the completers in each treatment group before they discontinued from the study (Figure 7). However, because there was only one intermittent visit, the information gathered from the dropouts' response trajectories is not very informative to explore whether most of the dropouts would continue to have similar PARS Severity Scores as those subjects who remained in the study.

Figure 6. Change from Baseline to Week 8 in PARS Severity Score (mITT Population)



Source: Statistical Reviewer's Plot.

Figure 7: Individual-subject Response Trajectories in PARS Severity Score by Treatment Groups (mITT Population)



Note: Because there was only one subject with the lack-of-efficacy discontinuation reason, the statistical reviewer included this subject in the "Others" category. Two subjects (one in placebo and one in escitalopram) discontinued from the trial after Week 2; thus, the statistical reviewer included their end-of-treatment assessments in the plot by mapping them to the visit at Week 8.
Source: Statistical Reviewer's Plot.

Sensitivity Analyses Results for Missing Data

Two sensitivity analyses were conducted for checking the MAR assumption underlying the primary efficacy MMRM analyses (mITT Population). The LOCF and a pattern mixture model using an ANCOVA analysis with the shift parameter values Δ (start at 0 and increase by 1 to 6) for the multiple imputation were performed to explore the robustness to the missing data assumption in MMRM analysis for the primary efficacy variable.

As seen in Table 7, in the LOCF analysis, the difference in LS mean (95% CI) was −1.29 (−2.58, 0.00). In the pattern-mixture model sensitivity analysis, there were no statistically significant differences between treatment groups for both shift parameters 0 and 1. The differences in LS mean (95% CI) were −1.18 (−2.46, 0.11) for shift parameter 0 and −1.19 (−2.48, 0.10) for shift parameter 1. The estimated differences in LS mean were slightly smaller than that from the MMRM-based primary analysis (-1.42, see Table 6). The standard errors were larger due to the multiple imputation implemented in the pattern-mixture model sensitivity analysis. These two factors led to large p-values.

Table 7: Change from Baseline to Week 8 in The PARS Severity Score – Sensitivity Analyses (mITT Population)

Method	Placebo (N=132)	Escitalopram (N=136)
Pattern-mixture model[a]		
Shift parameter: 0		
LS mean (SE)	−6.61 (0.493)	−7.79 (0.503)
LSMD vs placebo (95% CI)	—	−1.18 (−2.46, 0.11)
P value	—	0.0723
Shift parameter: 1		
LS mean (SE)	−6.57 (0.498)	−7.77 (0.481)
LSMD vs placebo (95% CI)	—	−1.19 (−2.48, 0.10)
p-value	—	0.0705
LOCF		
Change from baseline at Week 8		
LS mean (SE)[b]	−5.98 (0.486)	−7.27 (0.485)
LSMD vs placebo (95% CI)	—	−1.29 (−2.58, 0.00)
p-value	—	0.0498

[a]For each shift parameter value, missing values were imputed multiple times using a pattern-mixture model assuming nonfuture dependence. For each imputed data set, ANCOVA was performed. The estimates and p-values were obtained from combining all results from each individual analysis of the same shift parameter value.
[b]The estimates and P values were obtained from an ANCOVA model with treatment group and pooled study center as factors and baseline value as a covariate, where the missing values were imputed using the LOCF approach.
Abbreviations: ANCOVA=analysis of covariance; LOCF=last observation carried forward; LS=least squares; LSMD=least squares mean difference; 95% CI=95% confidence interval.
Source: Study SCT-MD-60 Clinical Study Report, Table 11, page 75, confirmed by statistical reviewer.

Statistical Reviewer's Comment: *During the IND review, we conveyed the statistical comment that LOCF was not considered as informative as the other sensitivity analyses because it is a single-imputation method, but the Applicant kept the LOCF method. Nevertheless, in this trial, the results are largely in line with the primary analysis and with the pattern-mixture model sensitivity analysis.*

The Applicant also performed a post hoc sensitivity analysis on the primary efficacy endpoint. This post hoc sensitivity analysis was similar to the pre-specified pattern-mixture model sensitivity analysis, except that the analysis used the same MMRM as for the primary analysis, rather than an ANCOVA model. For shift parameter 0, there was a statistically significant difference between treatment groups in favor of escitalopram (LSMD: −1.30 (95% CI: −2.56, −0.03); p = 0.0446). There was also a statistically significant difference between treatment groups for shift parameter 1 (LSMD vs. placebo: −1.31 (95% CI: −2.59, −0.04); p = 0.0438). There were no statistically significant differences between treatment groups for any subsequent shift parameter.

Table 8: Change from Baseline to Week 8 in the PARS Severity Score—Post Hoc Sensitivity Analysis (mITT Population)

Method	Placebo (N=132)	Escitalopram (N=136)
Pattern-mixture model[a]		
Shift parameter: 0		
LS mean (SE)	−6.48 (0.490)	−7.77 (0.493)
LSMD vs placebo (95% CI)	—	−1.30 (−2.56, −0.03)
p-value	—	0.0446
Shift parameter: 1		
LS mean (SE)	−6.44 (0.504)	−7.75 (0.483)
LSMD vs placebo (95% CI)	—	−1.31 (−2.59, −0.04)
p-value	—	0.0438
Shift parameter: 2		
LS mean (SE)	−6.44 (0.509)	−7.66 (0.490)
LSMD vs placebo (95% CI)	—	−1.21 (−2.51, 0.09)
p-value	—	0.0671
Shift parameter: 3		
LS mean (SE)	−6.42 (0.517)	−7.55 (0.487)
LSMD vs placebo (95% CI)	—	−1.14 (−2.44, 0.17)
p-value	—	0.0888

[a] For each shift parameter value, missing values were imputed multiple times using a pattern-mixture model assuming nonfuture dependence. For each imputed data set, an MMRM based on treatment group, age group strata (7-11 years vs 12-17 years), sex, pooled study center, visit, and treatment group-by-visit interaction as the fixed effects, and baseline and baseline-by-visit as covariates using an unstructured covariance matrix was performed. The estimates and *P* values were obtained from combining all results from each individual analysis of the same shift parameter value.
Abbreviations: ANCOVA=analysis of covariance; LOCF=last observation carried forward; LS=least squares; LSMD=least squares mean difference; 95% CI=95% confidence interval.
Source: Study SCT-MD-60 Clinical Study Report, Table 15, page 83, confirmed by statistical reviewer.

Statistical Reviewer's Comment: *During the pre-NDA meeting, we noticed that the Applicant's sensitivity analysis results based on pattern-mixture model appeared to be very different from the primary analysis results even when the shift parameter is 0. We expressed to the Applicant that the model employed in the sensitivity analysis should be consistent with the primary statistical model. However, the Applicant's imputation model only included treatment group and pooled study center as factors and the baseline value as a covariate, which does not retain all the covariates included in the main analysis model. Thus, the Applicant's post hoc sensitivity analysis does not ensure that the relationships between efficacy outcome and other factors are treated in a consistent way between the imputation model and the analysis model.*

Sensitivity Analyses Results for Covid Status

According to Applicant's results, most subjects (248/268) were not significantly impacted by COVID-19. A total of 80 subjects were randomized before March 17, 2020, and 188 subjects were randomized on or after the date. Respective subgroup analyses by whether subjects were significantly impacted by COVID-19 or not and by whether subjects were randomized before March 17, 2020, or not did not suggest an unusual finding. Furthermore, results of analyses by treating remote visits as missing and by adding a pandemic indicator, respectively, were in line with the primary analysis.

Statistical Reviewer's Comment: *The exploratory analyses results do not appear to be very informative. Overall, the results of the sensitivity analyses, which tried to explore the impact of the COVID-19 pandemic, do not appear to suggest that study results were affected by the public health emergency. It is noted that the analyses have several limitations and are exploratory in nature.*

Sample Size Re-estimation

The Applicant performed a pre-specified blinded sample size recalculation (March 31, 2021) after 194 subjects (75% of the planned sample size) had been randomized (172 subjects had data at both Baseline and Week 8). The Applicant used the MMRM model based on the enrolled 194 subjects to estimate the pooled variance for change from baseline in PARS severity score at Week 8, which included age group, sex, study site, and visit as factors and baseline PARS severity score and baseline value-by-visit interaction as covariates. Based on this MMRM model, the estimated pooled standard deviation (SD) was 4.97. Because the estimated pooled SD was less than the assumed SD (5.79), there is no change on the sample size of the study.

Data Quality and Integrity

The reviewers found the quality and integrity of the submitted data acceptable for the review analysis.

Efficacy Results—Secondary and other relevant endpoints

Escitalopram did not separate from placebo (statistically or numerically) on any of the secondary endpoints, including the CGI-S or CGAS score.

Dose/Dose Response

The Applicant provided the results of a graphical analysis of the relationship between the primary efficacy endpoint in SCT-MD-60, change from baseline in PARS at Week 8, and average concentration up to Week 8. There does not appear to be a dose-response relationship. See Section 6.2.2 and Figure 5.

Durability of Response

There was numerical separation from placebo at Week 2, the only post-baseline intermediate assessment of treatment effect. The clinical benefit associated with escitalopram appeared to be durable over the 8-week course of this study.

Persistence of Effect

Persistence of escitalopram treatment effect was not assessed in this study, as there were no scheduled efficacy assessments after the end of treatment.

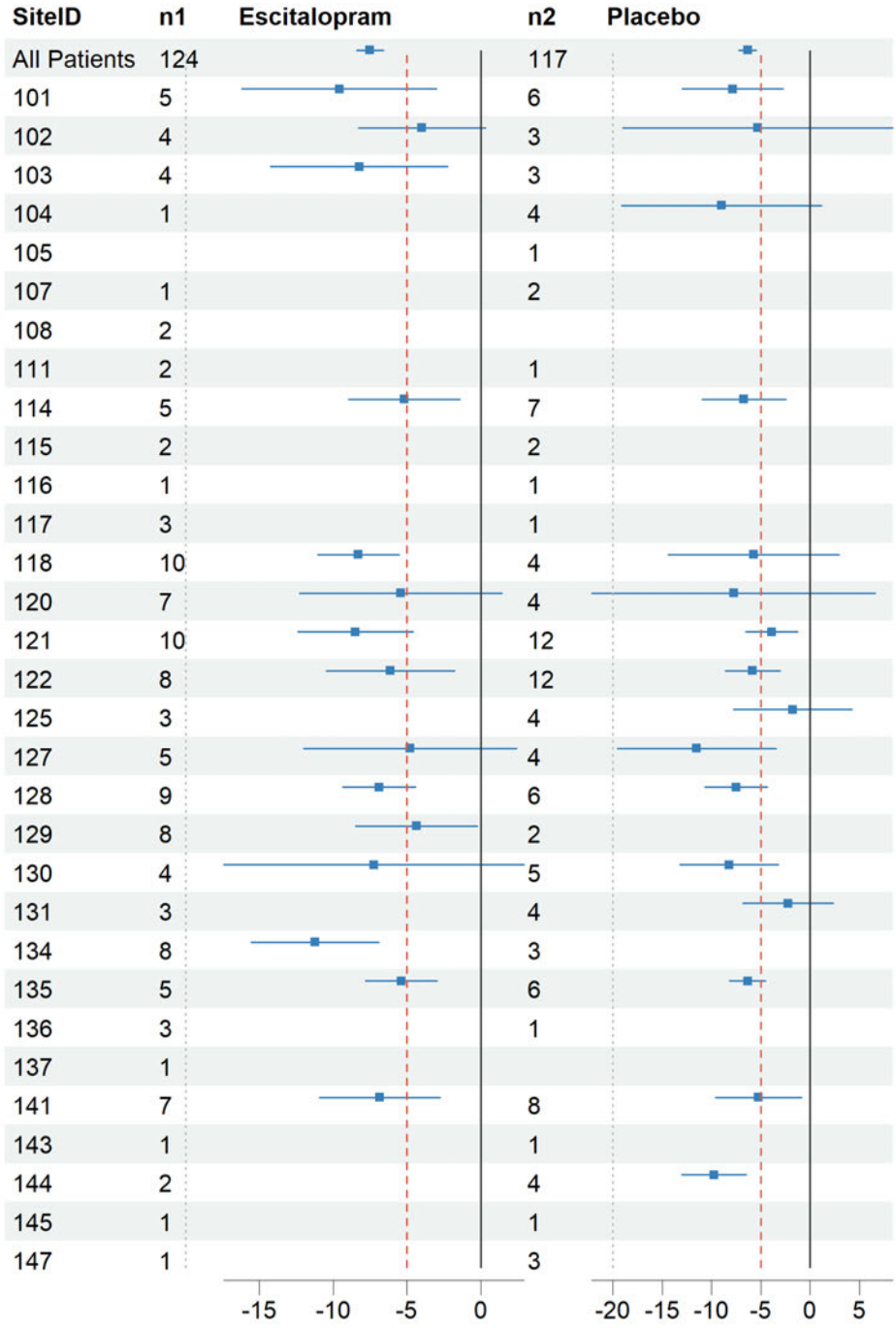
Additional Analyses Conducted on the Individual Trial

None.

Exploratory Efficacy Summary by Study Sites

Study SCT-MD-60 included a total of 35 clinical sites that screened at least one subject, and 33 sites that randomized at least one subject. The statistical reviewer explored raw means of change from baseline in the PARS severity score in escitalopram and placebo groups by study site (non-model-based calculations) in Figure 8. Most sites enrolled a small number of subjects. For all subjects (mITT population), the mean was -6.34 for placebo, and -7.51 for escitalopram, respectively.

Figure 8: Mean Change from Baseline in the PARS Severity Score by Treatment Groups at Each Study Site (mITT)

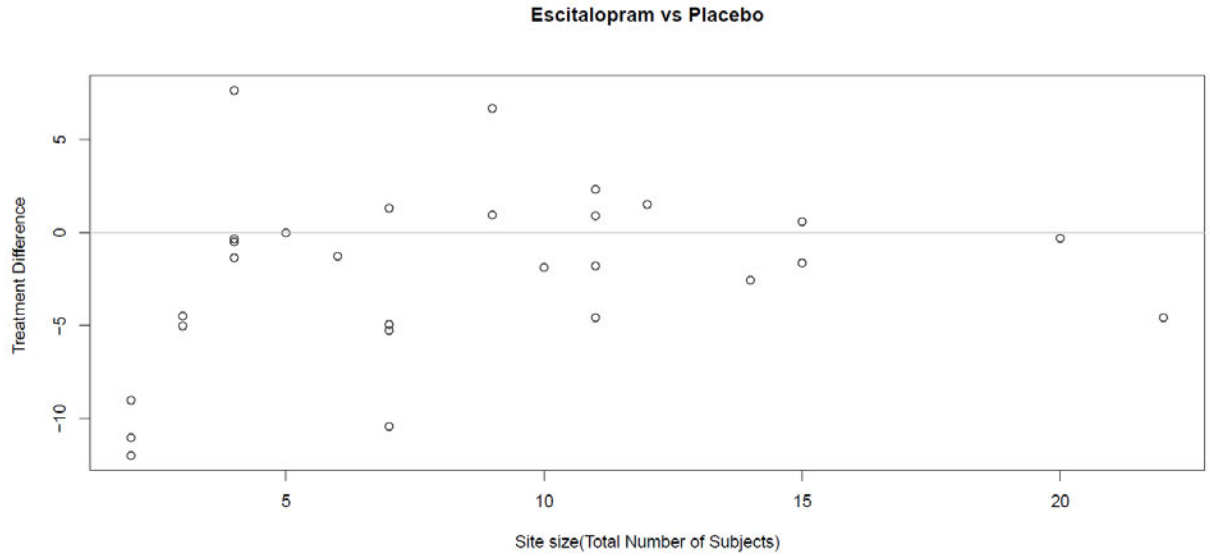


Source: Statistical Reviewer's plot.

The reviewer further explored mean treatment differences of escitalopram with placebo by study site (non-model-based calculations). Figure 9 displays the scatter plot of site treatment differences versus site sizes (number of subjects). The plot showed a trend of decreased

variability for larger site sizes. In both drug-placebo comparisons the shape of the scatter plots resembled a “horizontal cone.” No obvious outlier observations (study centers) were noted.

Figure 9: Treatment Differences of Mean Change from Baseline in the PARS Severity Score by Study Sites



Note: Sites 105, 108 and 137 are not included in the plot because those sites only included one treatment group.
Source: Statistical Reviewer’s Plot.

Subgroup Analysis

Treatment differences in mean change in PARS total score from Baseline to Week 8 were examined in subgroups of sex, race, and age. The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analyses is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory nature of the subgroup analyses in Table 9, those p-values are not presented here. The results were generally consistent across subgroups with respect to the primary analysis results except for the “all other races” subgroup, which consisted of very few subjects.

Table 9: Change from Baseline to Week 8 in the Pediatric Anxiety Rating Scale Severity Score in Subgroups—MMRM (mITT sample)

Subgroup	Treatment Group	Baseline N	Baseline Mean (SD)	Mean Change from Baseline N	Mean Change from Baseline LS Mean (SE)[a]	Treatment Difference vs. Placebo LS Mean Diff (95% CI)[1]
Sex						
Female	Escitalopram	93	18.2 (1.8)	93	-8.1 (0.6)	-1.0 (-2.60, 0.59)
	Placebo	90	18.0 (1.7)	90	-7.1 (0.6)	
Male	Escitalopram	43	17.9 (1.9)	43	-7.6 (0.8)	-2.3 (-4.67, 0.17)
	Placebo	42	18.0 (1.9)	42	-5.4 (0.9)	
Race						
White	Escitalopram	112	18.2 (1.9)	112	-7.8 (0.6)	-1.1 (-2.55, 0.35)
	Placebo	107	18.1 (1.7)	107	-6.7 (0.6)	
All other races	Escitalopram	24	17.8 (1.7)	24	-9.2 (0.8)	-4.6 (-7.51, -1.79)
	Placebo	25	17.6 (1.9)	25	-4.5 (1.0)	
Age						
7-11 years old	Escitalopram	43	18.0 (1.8)	43	-7.9 (1.0)	-1.4 (-4.09, 1.34)
	Placebo	43	18.0 (1.7)	43	-6.6 (0.9)	
12-17 years old	Escitalopram	93	18.1 (1.9)	93	-7.9 (0.6)	-1.6 (-3.09, -0.01)
	Placebo	89	18.0 (1.8)	89	-6.3 (0.6)	

[a] In each subgroup stratum, MMRM was conducted with model Terms: treatment group, age group strata (7 to 11 years vs. 12 to 17 years), sex, pooled study center, visit, treatment group-by-visit interaction, baseline, and baseline-by-visit.
Abbreviation: MMRM = Mixed Effects Model for Repeated Measures; LS = Least Squares; SE = Standard Error; SD=Standard Deviation; n = number of subjects with data; 95% CI= 95% Confidence Interval.
Source: Response to FDA Information Requests dated January 20, 2023, Tables FDA 2.1- FDA 2.3.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

Not applicable

8.2.2. Integrated Assessment of Effectiveness

The Applicant submitted a single randomized, double-blind, placebo-controlled study evaluating pediatric subjects 7 through 17 years of age with GAD. A statistically significant treatment effect was observed on a primary efficacy endpoint, the PARS, which has been previously accepted for use as a clinical endpoint for pediatric GAD. Therefore, results of Study SCT-MD-60, together with partial extrapolation from escitalopram's known efficacy in the treatment of adult GAD, form the basis of substantial evidence of effectiveness for escitalopram in the treatment of GAD in pediatric patients ages 7 to 17 years.

8.3. Review of Safety

8.3.1. Safety Review Approach

Important safety concerns associated with the use of escitalopram in adults include suicidal thoughts and behaviors in adolescents and young adults, serotonin syndrome, discontinuation syndrome, seizures, activation of mania or hypomania, hyponatremia, abnormal bleeding, interference with cognitive and motor performance, angle-closure glaucoma, use in patients with concomitant illness, and sexual dysfunction.

Adverse reaction information for pediatric patients currently included in the product label was collected in a double-blind placebo-controlled study in 576 pediatric patients 6 to 17 years of age, (286 escitalopram, 290 placebo) with MDD. The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies. However, the following adverse reactions were reported at an incidence of at least 2% in subjects taking escitalopram in MDD clinical trials and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.

This safety review examines a pediatric population 7 to 17 years of age with GAD. The clinical reviewer independently confirmed the safety analysis results using the datasets submitted by the Applicant.

The Safety Population consisted of all subjects in the randomized population who took at least one dose of study medication.

The safety review focused on the following data:

- The Study SCT-MD-60 clinical study report and 120-day safety update and submitted datasets for adverse events, laboratory measures, and vital signs are reviewed in Sections 8.3.2 to 8.3.5.

- Given that Study SCT-MD-55 was an open-label study, the review is focused on deaths, SAEs, and AE dropouts. Laboratory parameters, vital signs, and AEs of special interest were

also reviewed, but the ability to draw conclusions is limited by the uncontrolled nature of the study design.

The Applicant's submitted safety dataset is consistent with the agreed upon safety data from the pre-sNDA meeting written response dated March 09, 2022.

8.3.2. Review of the Safety Database

Overall Exposure

Four clinical studies in pediatric subjects evaluating escitalopram for the treatment of MDD were completed; treatment duration in these studies ranged from 8 weeks to 24 weeks. A total of 524 subjects received at least one dose of escitalopram in the pediatric MDD development program. This data is reflected in the approved product labeling.

One 8-week clinical efficacy and safety study in pediatric subjects evaluating escitalopram for the treatment of GAD was completed. A total of 137 subjects received at least one dose of escitalopram in the pediatric GAD development program.

A substantial proportion of subjects exposed in all age groups across both indications received the highest dose proposed for marketing.

As noted in the pre-sNDA written response, dated March 09, 2022, the Division considered this pediatric exposure dataset reasonable in informing the safety assessment in the pediatric population.

Table 10: Duration of Exposure (Overall Pediatric Safety Population)

Escitalopram Dose	Number of Pediatric Subjects Exposed to Escitalopram					
	≥1 dose	≥4 weeks	≥8 weeks	≥16 weeks	≥24 weeks	≥52 weeks
10 mg	253	278	380	86	80	0
20 mg	420	313	104	65	20	0

Source: Clinical Reviewer-generated from January 11, 2023, and February 6, 2023, Applicant responses to Division information requests.

Adequacy of the safety database

The ability to review the safety of escitalopram in the pediatric population with GAD is limited by the relatively small size of the safety population. However, based upon disease similarity, the Applicant is also relying upon the finding of safety for escitalopram in children and adolescents with MDD. Because important clinical safety differences between pediatric populations with the two diseases are not anticipated, it is reasonable to consider MDD data supportive in the escitalopram safety assessment for GAD. The duration of the treatment period in the clinical GAD efficacy Study SCT-MD-60 was 8 weeks. The treatment periods in the clinical pediatric MDD studies ranged from 8 weeks to 16 weeks in double-blind, placebo-controlled studies to 24 weeks in an open-label study. These are reasonably adequate to assess short- and long-term

safety in the pediatric population. Despite the adequacy of the overall size of the safety population and duration of exposure, the following appear to be limitations of the safety database considering dosing, patient demographics, and disease characteristics with reference to the target population in the United States:

- Flexible-dosing regimen (as opposed to a more informative fixed-dosing regimen) in the single GAD trial and most of the MDD trials
- Unblinded and uncontrolled study design of the single long-term study in pediatric subjects with MDD
- U.S. minority groups were underrepresented in Study SCT-MD-60
- Because of Study SCT-MD-60 exclusion criteria, the clinical trial population likely had fewer psychiatric comorbidities than the general pediatric GAD population in the United States.

Despite some limitations, the reviewer considers the pediatric database reasonably sufficient to assess the safety of escitalopram in the pediatric population.

8.3.3. 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. The submission is of acceptable quality. No major concerns about data integrity were noted. OSI inspection concluded inspected clinical data at the respective sites appeared reliable overall (see Section 4.1).

Categorization of Adverse Events

The clinical reviewer agreed with the Applicant's AE mapping, which used MedDRA Version 24.0. The Applicant appeared to use standard definitions and methods for AEs, including severity and seriousness coding. AEs were recorded throughout treatment and to the Week 10 follow-up assessment.

Routine Clinical Tests

The Applicant included adequate clinical assessments and tools for Study SCT-MD-60. These included an array of serum chemistry and hematology, urinalysis, vital sign, and ECG assessments (see Table 2: Schedule of Assessments):

- Hematology: hematocrit, hemoglobin, mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, platelet count, red blood cell count, white blood cell count (total count and differential)

- Chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, gamma glutamyltransferase, glucose, lactate dehydrogenase (LDH), phosphorous, potassium, sodium, total bilirubin, T3, T4, thyroid stimulating hormone, total protein, and uric acid

- Urinalysis: blood, glucose, ketones, microscopy, pH, and protein

- Other tests: HBsAg, HCVab, and HIV screening, serum and urine pregnancy test (in female subjects of child-bearing potential), urine drug screen

- Vital Signs: blood pressure, body mass index (BMI), height, pulse rate, respiratory rate, temperature, and weight

8.3.4. Safety Results

Deaths

No deaths occurred in Study SCT-MD-60.

Serious Adverse Events

Three SAEs were reported for three subjects in Study SCT-MD-60: two subjects on escitalopram (appendicitis) and one subject on placebo (kidney infection). The SAEs were unlikely drug-related and, therefore, are not considered to be new safety signals.

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, six subjects discontinued Study SCT-MD-60 due to AEs: four subjects on escitalopram (activation syndrome, intentional self-injury, nausea, and epistaxis) and two subjects on placebo (suicidal ideation and depression/fatigue). The AEs leading to discontinuation in subjects taking escitalopram are known potential drug effects and are not considered to be new safety signals.

Significant Adverse Events

There were six severe AEs in Study SCT-MD-60: four in subjects on escitalopram (appendicitis, anger, and COVID-19) and two in subjects on placebo (kidney infection and depression). The one severe AE in subjects taking escitalopram that may have been drug-related is anger and is a known potential drug effect, therefore, is not considered to be a new safety signal.

Treatment Emergent Adverse Events (TEAE) and Adverse Reactions

The AEs by preferred term table includes all AEs occurring in more than one subject in the escitalopram group. The AEs associated with escitalopram occurring in ≥2% of subjects and greater than placebo are nausea, decreased appetite, insomnia, somnolence, diarrhea, abdominal discomfort, anxiety, dizziness, nasopharyngitis, abdominal pain, anger, and irritability. Overall, the AEs that occurred in Study SCT-MD-60 are consistent with the known safety profile of escitalopram in the pediatric population and are not considered to be new safety signals.

Table 11: Study SCT-MD-60 TEAEs Occurring in >2% of Subjects on Escitalopram

Preferred Term	Escitalopram (N=137)		Placebo (N=136)	
	Number of Subjects	Proportion (%)	Number of Subjects	Proportion (%)
Nausea	18	13	7	5.1
Decreased appetite	10	7.2	4	2.9
Headache	10	7.2	10	7.3
Fatigue	7	5.1	10	7.3
Insomnia	7	5.1	2	1.5
Somnolence	7	5.1	2	1.5
Diarrhea	6	4.3	3	2.2
Abdominal discomfort	4	2.9	1	0.7
Anxiety	4	2.9	1	0.7
Dizziness	4	2.9	2	1.5
Nasopharyngitis	4	2.9	2	1.5
Abdominal pain	3	2.2	0	0
Abdominal pain upper	3	2.2	5	3.6
Anger	3	2.2	0	0
Initial insomnia	3	2.2	3	2.2
Irritability	3	2.2	1	0.7
Activation syndrome	2	1.4	0	0
Appendicitis	2	1.4	0	0
COVID-19	2	1.4	0	0
Depressed mood	2	1.4	1	0.7
Dysmenorrhea	2	1.4	0	0
Eczema	2	1.4	0	0
Epistaxis	2	1.4	1	0.7
Influenza	2	1.4	0	0
Pruritus	2	1.4	0	0
Sedation	2	1.4	2	1.5
Suicidal ideation	2	1.4	2	1.5
Tension headache	2	1.4	1	0.7

Tremor	2	1.4	0	0
Upper respiratory tract infection	2	1.4	2	1.5
Vomiting	2	1.4	1	0.7

Source: Clinical Reviewer-generated from Study SCT-MD-60 adae.xpt via MAED.

Laboratory Findings

In Study SCT-MD-60, laboratory testing was conducted at Screening and at Week 8, end-of-treatment. The following shift is noted but unlikely of clinical significance:

- Phosphorous level shift from normal to high: escitalopram 17/116 subjects (15%) compared to placebo 6/108 subjects (6%). All were <1.2x the upper limit of normal. Mean shift from baseline between the two groups were similar: escitalopram 0.01 versus placebo <0.01. There were no associated AEs reported, nor were there associated abnormal laboratory findings (e.g., calcium, creatinine, and LDH). Therefore, this finding is unlikely to be clinically significant.

Overall, laboratory results did not reveal new concerning clinical or toxicity-related issues.

Vital Signs

Vital signs were measured at Screening, Baseline, and all scheduled visits during treatment (occurring weekly or biweekly). The following growth measurements of less weight gain in subjects taking escitalopram compared to placebo are noted but do not represent a new clinically significant concern:

Table 12: Study SCT-MD-60 Growth Parameters and Related TEAEs

	Escitalopram	Placebo
Mean change in BMI z-score units (SD)	<0.01 (0.2)	0.05 (0.7)
Mean absolute change in BMI, kg/m^2 (SD)	0.1 (1.9)	0.5 (2.6)
Mean absolute change in weight, kg (SD)	0.6 (4.6)	1.5 (6.6)
Subjects with any decrease in BMI	77/134 (57%)	52/128 (41%)
Subjects with any decrease weight	61/134 (46%)	32/128 (25%)
Decreased appetite AE	10/137 (7%)	4/136 (3%)

Source: Clinical Reviewer-generated from Study SCT-MD-60 advs.xpt and adae.xpt dataset output via JMP.

Baseline BMI and BMI z-scores were similar between the two treatment groups. The growth data and reported AEs were generally more marked in the 12- to 17-year-old age cohort compared to the 7- to 11-year-old age cohort. BMI z-scores and weight z-scores less than -2-unit deviations from the mean were rare and occurred with similar prevalence between the two treatment groups. Height was not impacted, and there were no reported weight loss AEs. Therefore, the clinical significance of these growth findings is uncertain. However, there is

already a known association between SSRIs and decreased appetite and weight loss in pediatric patients. The issue is adequately described in Section 6 where appetite decreased is a listed adverse reaction and in Section 8 of the prescribing information (PI) where regular monitoring of weight and growth is recommended.

Overall, vital sign measurements in the study did not reveal new concerning clinical or toxicity-related issues.

Electrocardiograms (ECGs)

ECGs were obtained at Screening and at Week 8, end-of-treatment. Overall, ECG results in Study SCT-MD-60 did not reveal significant clinical or toxicity-related issues.

QT

There were no QTc findings in Study SCT-MD60 that would warrant changes to the current product label for escitalopram.

Immunogenicity

Not applicable

8.3.5. Analysis of Submission-Specific Safety Issues

Suicidal Ideation and Behavior

The C-SSRS was administered at Screening, Baseline, and all scheduled visits during treatment (occurring weekly or biweekly). A greater proportion of subjects on escitalopram endorsed SI/B on the C-SSRS compared to placebo: 14/137 subjects (10%) versus 4/136 (3%), respectively. For the 14 subjects on escitalopram with SI/B per the C-SSRS, seven (50%) had a history of SI/B preceding treatment initiation. For the four subjects on placebo with SI/B, three (75%) had a prior history of SI/B. Related AEs were reported infrequently and at similar rates between the two treatment groups: of the 137 subjects taking escitalopram, two (1%) reported SI AEs and one (1%) reported an intentional self-injury AE compared to 2/136 subjects (2%) taking placebo who reported SI AEs. There is already a known association between SSRIs and SI/B in pediatric patients. The issue is adequately described in a boxed warning and in Section 5 of the PI where monitoring for clinical worsening and emergence of SI/B is also recommended. The calculated number needed to harm for escitalopram based on rates of SI/B endorsed on the C-SSRS is 14, which is consistent with data included in the PI. Therefore, no changes to labeling are recommended.

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

Not applicable to the safety assessments conducted in this development program.

8.3.7. Safety Analyses by Demographic Subgroups

In Study SCT-MD-60, safety subgroup analysis was conducted for the 7-to-11-year-old age cohort compared to the 12-to-17-year-old age cohort. Treatment by age cohorts follows:

Table 13: Study SCT-MD-60 Treatment by Age Cohort

	Escitalopram (N=137)	Placebo (N=136)
7- to 11-year-old subjects	44 (32%)	45 (33%)
12- to 17-year-old subjects	93 (68%)	91 (67%)

Source: Clinical Reviewer-generated from Study SCT-MD-60 adsl.xpt dataset output via JMP.

Of the 44 subjects 7 to 11 years of age who received escitalopram, 28 (64%) received 20 mg doses. Of note, in the long-term (24-week) pediatric MDD Study MD-55, 43/118 (36%) of subjects 7 to 11 years of age received escitalopram 20 mg doses. Although data in 7- to 11-year-old subjects is limited, they are reasonably sufficient to support the safety of 20 mg doses in this pediatric age cohort.

Frequencies of reported AEs in subjects on escitalopram in the 7- to 11-year-old cohort were generally similar to the 12- to 17-year-old cohort, with a slightly higher incidence in the 12- to 17-year-old cohort (i.e., the younger pediatric age cohort did not appear more vulnerable to AEs). This finding should be interpreted with caution because of an imbalance in enrollment with nearly twice the number of subjects 12 to 17 years of age compared to 7 to 11 years of age. An exception to this is the two reports of activation syndrome AEs that occurred in the 44 subjects in the 7-to-11-year-old cohort on escitalopram (5%) compared to none in any other treatment and age cohort. Because activation syndrome is a known adverse reaction of escitalopram, particularly in younger pediatric patients, and because the number of reported AEs is small, this finding does not change the known safety profile of escitalopram; however, its occurrence in pediatric subjects with GAD will be described in Section 6 of the label.

Failure to gain appropriate weight compared to the placebo group was marked in subjects 12 to 17 years of age on escitalopram compared to subjects 7 to 11 years of age. Consistent with this, decreased appetite AEs were reported more commonly in the 12- to 17-year-old cohort compared to the 7- to 11-year-old cohort.

Table 14: Study SCT-MD-60 Decreased Appetite AEs by Age Cohort

Escitalopram				Placebo			
<12yo (n=44)	Proportion (%)	≥12yo (n=93)	Proportion (%)	<12yo (n=45)	Proportion (%)	≥12yo (n=91)	Proportion (%)
1	2%	9	10%	0	0%	4	4%

Source: Clinical Reviewer-generated from Study SCT-MD-60 adae.xpt dataset output via JMP.

8.3.8. Specific Safety Studies/Clinical Trials

Study SCT-MD-55

SCT-MD-55 was an open-label, uncontrolled, flexible-dose study of 118 subjects 7 to 11 years of age with MDD. Subjects received escitalopram 10 or 20 mg once daily over a 24-week treatment period and a 2-week down-taper period. A summary of AEs for Study SCT-MD-55 follows:

- There were no deaths.
- SAEs were reported for two out of 118 subjects (2%) and were mania and suicidal ideation.
- AEs leading to discontinuation were reported in 9 out of 118 subjects (8%) and were irritability, disturbance in attention, psychomotor hyperactivity, mania, suicidal ideation, agitation, daydreaming, dissociation, impulsive behavior, insomnia, rash (maculo-papular), and rash pruritic.
- Severe AEs were reported for 4 out of 118 subjects (3%) and were cellulitis, mania, panic attack, and suicidal ideation.

Table 15: Study SCT-MD-55 AEs Reported by ≥2% of Subjects

Preferred Term[a,b]	**Escitalopram n (%) (N = 118)**
Patients with ≥ 1 TEAE	75 (63.6)
Headache	20 (16.9)
Abdominal pain upper	13 (11.0)
Insomnia	10 (8.5)
Diarrhea	9 (7.6)
Dizziness	9 (7.6)
Nasopharyngitis	9 (7.6)
Increased appetite	7 (5.9)
Nasal congestion	7 (5.9)
Vomiting	7 (5.9)
Nausea	6 (5.1)
Contusion	5 (4.2)
Cough	5 (4.2)
Pyrexia	5 (4.2)
Somnolence	5 (4.2)
Upper respiratory tract infection	5 (4.2)
Arthralgia	4 (3.4)
Arthropod bite	4 (3.4)
Excoriation	4 (3.4)
Gastroenteritis viral	4 (3.4)
Sinus bradycardia	4 (3.4)
Abdominal pain	3 (2.5)
Aggression	3 (2.5)
Decreased appetite	3 (2.5)
Dyspepsia	3 (2.5)

Fall	3 (2.5)
Fatigue	3 (2.5)
Heart rate increased	3 (2.5)
Ligament sprain	3 (2.5)
Oropharyngeal pain	3 (2.5)
Pharyngitis streptococcal	3 (2.5)
Rash	3 (2.5)
Restlessness	3 (2.5)
Rhinitis allergic	3 (2.5)
Sinusitis	3 (2.5)
Weight increased	3 (2.5)

Note: Percentages are relative to the Safety Population.

- Version [11.1] of the *Medical Dictionary for Regulatory Activities* was used to code TEAEs.
- If a patient had more than 1 TEAE for a particular preferred term, the patient was counted once for that preferred term. Events are presented in order of decreasing frequency.

n (%) = number (percentage) of patients who had the specified TEAE; N = the number of patients in the Safety Population; TEAE = treatment-emergent adverse event.
Source: SCT-MD-55 CSR, Table 12.2.2.1-2, page 74.

There were no findings with laboratory, vital sign, and ECG investigations that were adjudicated as clinically significant.

Of the 118 subjects, 26 (22%) endorsed SI/B on the C-SSRS. Reported AEs and SI/B data are consistent with the known safety profile of escitalopram in the pediatric population. The safety findings from Study SCT-MD-55 do not indicate that there are new or unexpected safety signals and support the long-term safety of escitalopram in pediatric patients.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new human carcinogenicity studies were submitted with this application.

Human Reproduction and Pregnancy

No new information regarding human reproduction was submitted with this application.

Pediatrics and Assessment of Effects on Growth

See Section 8.3.4 for discussion of pediatric growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In Study SCT-MD-60, to evaluate for discontinuation symptoms, AEs during the 1-week drug taper period were assessed and found to be similar between the two treatment groups: escitalopram 12/137 (9%) compared to placebo 10/136 (7%). AEs reported in more than one subject were abdominal pain, headache, dizziness, decreased appetite, and SI. However, due to an IRS-related study-wide protocol deviation, this assessment for discontinuation symptoms

was significantly compromised because 35 out of 137 (26%) subjects on escitalopram were taking 10-mg doses. These subjects did not undergo dose taper as planned, rather they continued their dose instead of tapering off to placebo. However, assessment of AEs during the drug taper period is informative of subjects down-tapering from escitalopram 20 mg to 10 mg. Additionally, assessment of AEs from the end of treatment to the follow-up call 1 week later is informative of all subjects who discontinued escitalopram: escitalopram 6/137 subjects (4%) compared to placebo 8/136 (6%) reported AEs. AEs reported in more than one subject were abdominal pain, tension headache, and dizziness. Overall, evaluation for discontinuation symptoms, although limited, did not reveal new significant clinical issues. Discontinuation symptoms are known to occur with SSRIs and are adequately described in Section 5 of the escitalopram PI and change to the PI is not warranted.

No relevant overdose or abuse potential assessments were conducted. Understanding of these areas is informed by Sections 9 and 10 of the current escitalopram PI.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Escitalopram AEs identified through postmarketing experience and described in the PI follow:

Blood and Lymphatic System Disorders: anemia, agranulocytosis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia.

Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.

Ear and labyrinth disorders: vertigo Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.

Eye Disorders: angle closure glaucoma, diplopia, mydriasis, visual disturbance.

Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage.

General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise.

Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis.

Immune System Disorders: allergic reaction, anaphylaxis.

Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.

Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.

Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis.

Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor.

Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.

Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.

Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.

Reproductive System and Breast Disorders: menorrhagia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.

Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.

Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

Expectations on Safety in the Postmarket Setting

The Applicant has demonstrated acceptable safety of escitalopram in pediatric subjects with MDD and the postmarket safety profile in GAD is anticipated to be consistent with what is known for escitalopram.

8.3.11. Integrated Assessment of Safety

Although safety review based upon the current pivotal trial Study SCT-MD-60 is limited due to the flexible-dose study design, which may have obscured important safety findings, overall, the

safety assessment for escitalopram for the treatment of pediatric GAD is adequate. The safety findings from studies SCT-MD-60 and SCT-MD-55 are consistent with the known safety profile for pediatric use of escitalopram including risks for SI/B and decreased appetite with potential impact on growth—these are adequately described in current labeling. There are no new safety issues that preclude the approval of this sNDA**.**

8.4. Statistical Issues

We did not identify statistical issues that could impact the overall conclusions.

8.5. Conclusions and Recommendations

The data submitted are adequate to fulfill the PREA postmarketing requirement to evaluate the safety, efficacy, and PK of escitalopram in pediatric subjects (7 through 17 years of age) for the treatment of GAD. Information should be added to the appropriate sections of labeling to reflect the efficacy and safety findings. Efficacy of escitalopram for the treatment of pediatric GAD was demonstrated in Study SCT-MD-60. The primary efficacy analysis showed statistically significant superiority to placebo in the change from Baseline to Week 8 on the PARS. The proposed dose regimen is supported by the submitted escitalopram efficacy data and is the same indicated for pediatric MDD. The safety profile of escitalopram in the pediatric population with GAD is consistent with the known safety profile for pediatric use of escitalopram, including findings of SI/B and decreased appetite with potential impact on growth, which are adequately described in current labeling.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not refer this marketing application to an advisory committee for review. This drug is not first in its class. The clinical trial designs are similar to those for previously approved products for this indication. Evaluation of the data did not raise significant, unexpected safety or efficacy issues. Therefore, the Agency concluded that outside expertise was not necessary.

10 Pediatrics

The Pediatric Research Equity Act (PREA) was triggered with escitalopram's approval for the treatment of GAD in adults; therefore, Post Marketing Requirement (PMR) 2975-1 was issued: a deferred pediatric study to assess the safety and effectiveness of escitalopram as a treatment of GAD in pediatric patients 7 to 17 years of age; both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata. Enrollment in pivotal trial Study SCT-MD-60 demonstrated an imbalance of adolescents compared to children and female subjects compared to male subjects (both at ratios of approximately 2:1). However, these characteristics mirror expected pediatric GAD demographics. Additionally, enrollment of children 12 to 17 years of age is expected to be particularly difficult as reflected in Study SCT-MD-55, in which recruitment of subjects 7 to 11 years of age with MDD was prematurely terminated due to enrollment challenges. Therefore, Study SCT-MD-60, which assesses the safety and effectiveness of escitalopram for the treatment of pediatric GAD, is determined to be adequate for fulfilling PMR 2975-1.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

New pediatric information will be added to the prescribing information in the following sections:

1. INDICATION
- The approved population will be specified for each indication
- MDD in adults and pediatric patients 12 years and older
- GAD in adults and pediatric patients 7 years of age and older

2. DOSAGE AND ADMINISTRATION
- Dosing recommendations for GAD in pediatric patients were added: starting dose 10 mg once daily; depending on clinical response and tolerability, dose may be increased to maximum dose 20 mg once daily at an interval of no less than 2 weeks.

6. ADVERSE REACTIONS
- Updated Section 6.1 to include a brief summary of pediatric GAD data
- For clarity, the safety and effectiveness of escitalopram have not been established in pediatric patients less than 12 years of age with MDD or less than 7 years of age with GAD was added.
- Growth measurements showing less age-appropriate weight gain (absent clinically significant differences in BMI z-score, weight z-score, and height and absent weight loss AEs) in subjects taking escitalopram compared to placebo are noted but do not represent a new clinically significant concern. The clinical significance of these growth findings is uncertain, although there is already a known association between SSRIs and decreased appetite and weight loss in pediatric patients. The issue is adequately described in Section 6 where appetite decreased is a listed adverse reaction and in Section 8 of the PI where regular monitoring of weight and growth is also recommended. Therefore, no change to labeling is recommended. (See Section 8.2.4 for further details regarding growth measurements.)
- A greater proportion of subjects on escitalopram endorsed SI/B on the C-SSRS compared to placebo, but related AEs were reported infrequently and at similar rates between the two treatment groups. There is already a known association between SSRIs and SI/B in pediatric patients. The issue is adequately described in a boxed warning and in Section 5 of the PI where monitoring for clinical worsening and emergence of SI/B is also recommended. Therefore, no change to labeling is recommended. (See Section 8.2.5 for further details regarding SI/B)

8. PEDIATRIC USE
- Described the conclusion on safety and effectiveness in GAD
- Statement noting similarity of safety profile with MDD
- Juvenile animal toxicity data

Animal Data

In a juvenile animal study, male and female rats were administered escitalopram 5, 40, or 80 mg/kg/day by oral gavage from postnatal day (PND) 21 to PND 69. A delay in sexual maturation was observed in both males and females at ≥ 40 mg/kg/day with a no observed adverse effect level (NOAEL) of 5 mg/kg/day. This NOAEL was associated with plasma AUC levels less than those measured at the maximum recommended dose (MRHD) in pediatrics (20 mg). However, there was no effect on reproductive function. Increased motor activity (both ambulatory and fine movements) was observed in females prior to daily dosing at ≥ 40 mg/kg/day (3.5 times the MRHD based on AUC levels). A reversible disruption of learning and memory function was observed in males at 80 mg/kg/day with a NOAEL of 40 mg/kg/day, which was associated with an AUC level 3.5-times those measured at the MRHD in pediatrics. There was no effect on learning and memory function in treated female rats.

Note: For the sake of simplicity, the safety margins for the juvenile animal study were calculated based on the average plasma levels of both sexes in animals as the levels between sexes were comparable.

12.3 CLINICAL PHARMACOLOGY

Pediatric patients 7 to 11 years of age: Based on population PK simulations, following multiple dosing of 20 mg/day escitalopram, steady-state Cmax and AUCtau of escitalopram were increased by 93% and 86%, respectively in patients with GAD 7 to 11 years compared to adults.

Pediatric patients 12 to 17 years of age: In a single dose study of 10 mg escitalopram, AUC of escitalopram decreased by 19%, and Cmax increased by 26% in healthy pediatric subjects 12 to 17 years of age compared to adults. Following multiple dosing of 40 mg/day citalopram, escitalopram elimination half-life, steady-state Cmax and AUC were similar in patients with MDD 12 to 17 years of age compared to adult patients *[see Use in Specific Populations (8.4)]*.

14. CLINICAL STUDIES
- For clarity, that the safety and effectiveness of escitalopram have not been established in pediatric patients less than 12 years of age with MDD was added.
- Section 14.2 updated with results from Study SCT-MD-60.

12 Risk Evaluation and Mitigation Strategies (REMS)

There are multiple products in this class currently approved without a REMS. No new safety issues that would necessitate a REMS were identified during the review of this product.

13 Postmarketing Requirements and Commitment

JAS study (SCT-TX-101) is determined to be adequate for fulfilling PMR 2975-2.

Study SCT-MD-60 is determined to be adequate for fulfilling PMR 2975-1.

No additional PMRs or postmarketing commitments will be issued.

14 Division Director (Signatory) Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

15 Appendices

15.1. References

Walter HJ, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders. J Am Acad Child Adolesc Psychiatry. 2020;59(10):1107-24.

Costello EJ, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. Arch Gen Psychiatry. 1996;53(12):1129-36.

American Psychiatric Association, 2013, Diagnostic and statistical manual of mental disorders (DSM-5), Washington (DC): American Psychiatric Publishing.

Jones N, et al. (2021, August 12). 2020 Census Illuminates Racial and Ethnic Composition of the Country. United States Census Bureau https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): SCT-MD-60

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 35		
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)): N/A 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: N/A	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) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Table 16: Summary of sexual maturity data in juvenile animals treated with escitalopram

Dosage (mg/kg/day)	0 mg	5 mg	40 mg	80 mg	Historical Control
PND (days) for Vaginal Patency	33.9 ± 2.7	33.9 ± 3.1	34.7 ± 2.3	36.0 ± 2.3*	31.0-34.3
Body weight (g) at Vaginal Patency	132.4 ±13.8	137.0 ± 25.8	139.9 ± 22.9	149.2 ± 20.6	-
PND (days) of preputial separation	43.6 ± 2.6	44.1 ± 2.3	45.7 ± 2.3	45.7 ± 2.4*	41.2-45.6
Body weight (g) at separation	253.5 ± 22.1	257.6 ± 29.6	274.5 ± 44.4	271.2 ± 38.5	-

*Significantly different from the control group value p≤0.05.
Source: Created by nonclinical reviewer using the Applicant's data and historical control (HC) data.

Table 17: Summary of Path B Cincinnati Water Maze errors in males treated with escitalopram

Dose mg/kg/day	Number of Errors-Males					
During treatment period (PND 52 and 68)						
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
0	11.5 ± 8.3	1.4 ± 2.3	0.2 ± 0.6	0 ± 0	0 ± 0	0 ± 0
5	10.7± 9.1	1.9 ± 3.2	3.1 ± 4.8	0.1 ± 0.3	0.3 ± 0.8	0.1± 0.4
40	16.5 ± 9.2	4.2 ± 4.4	1.4 ± 2.2	0.8 ± 2.3	0.2 ± 0.6	0.1 ± 0.3
80	15.5± 8.8	6.7 ± 6.2*	3.4± 4.3*	1.8 ± 3.2*	0.7 ± 2.3	0.7 ± 1.6
During recovery period (PND 106 and 116)						
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
0	15.4 ± 7.8	6.6 ± 7.2	2.7 ± 3.9	1.2 ± 2.4	2.9± 6.9	1.0 ± 3.6
5	16.1± 5.1	6.3 ± 6.0	4.0 ± 5.7	1.4 ± 2.8	1.0 ± 3.2	0.3 ± 0.8
40	17.7 ± 6.7	7.7 ± 4.8	4.4 ± 5.8	0.8 ± 2.9	0.9 ± 2.5	0 ± 0
80	19.3± 9.0	8.9 ± 4.7	5.5± 6.5	1.0 ± 2.4	0.8 ± 1.8	0.1 ± 0.3

*Significantly different from the control group value p≤0.01
Source: Created by nonclinical reviewer using the Applicant's data.

Table 18: Summary of Path B Cincinnati Water Maze (Sec) Swimming Time in Males Treated with Escitalopram (Main Subset)

F1 Generation Adults - Main Subset - Path B - Males
Postnatal Days 52 to 68

Group 1 - Reference Item
Group 2 - Lexapro 5 mg/kg/day
Group 3 - Lexapro 40 mg/kg/day
Group 4 - Lexapro 80 mg/kg/day

Group	Summary Information	Trial Number 1	2	3	4	5	6
1	Mean	187.3	59.1	25.1	21.6	15.9	16.3
	SD	109.6	52.1	11.4	17.4	4.7	5.2
	N	15	15	15	15	15	15
2	Mean	140.5	60.8	57.1	19.1	19.3	17.4
	SD	88.0	70.3	65.2	7.9	19.3	9.4
	N	15	15	15	15	15	15
	% Diff (G1)	-25	3	127	-12	21	7
3	Mean	165.4	74.3	31.1	30.2	19.7	16.3
	SD	87.5	64.0	16.4	31.9	9.9	5.7
	N	15	15	15	15	15	15
	% Diff (G1)	-12	26	24	40	24	0
4	Mean	171.6	113.6	56.5	47.3	25.8	20.1
	SD	94.4	93.3	51.4	49.9	29.9	10.4
	N	15	15	15	15	15	15
	% Diff (G1)	-8	92	125	119	62	23

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Source: Provided by the Applicant from the study report (Study No. SCT-TX-101).

Table 19: Summary of Path B Cincinnati Water Maze (Sec) Swimming Time in Males Treated with Escitalopram (Recovery Subset)

F1 Generation Adults - Recovery Subset - Path B - Males
Postnatal Days 106 to 116

Group 1 - Reference Item
Group 2 - Lexapro 5 mg/kg/day
Group 3 - Lexapro 40 mg/kg/day
Group 4 - Lexapro 80 mg/kg/day

Group	Summary Information	Trial Number 1	2	3	4	5	6
1	Mean	236.7	111.6	65.2	32.9	54.8	26.8
	SD	86.0	96.5	73.9	44.2	93.5	45.6
	N	20	20	20	20	20	20
2	Mean	250.6	122.5	71.9	30.7	24.2	15.6
	SD	73.3	77.5	73.1	29.2	35.6	6.2
	N	20	20	20	20	20	20
	% Diff (G1)	6	10	10	-7	-56	-42
3	Mean	272.3	131.4	79.0	26.3	22.7	14.0
	SD	63.1	93.6	76.6	31.8	23.5	4.1
	N	20	20	20	20	20	20
	% Diff (G1)	15	18	21	-20	-59	-48
4	Mean	272.0	187.6	107.6	38.7	27.7	15.4
	SD	67.0	101.5	98.7	65.1	30.4	4.7
	N	20	20	20	20	20	19
	% Diff (G1)	15	68	65	18	-49	-42

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Source: Provided by the Applicant from the study report (Study No. SCT-TX-101).

Table 20: Summary of Toxicokinetics Parameters of Escitalopram in Rats following Oral Administration of Lexapro on PND 21 and PND 69

Summary Table 1

Summary Mean (± SE) Escitalopram Toxicokinetic Parameters in Sprague-Dawley Rat Plasma Following 5, 40, and 80 mg/kg Oral Administration of Lexapro on PND 21

Analyte	PND	Gender	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	SE C_{max} (ng/mL)	$AUC_{(0-t)}$ (hr*ng/mL)	SE $AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
Escitalopram	21	Male	5	1	32.7	3.77	80.3	11.4	NC
		Male	40	1	957	37.5	4170	320	2.21
		Male	80	2	2080	437	14400	1010	2.57
		Female	5	1	36.4	5.74	93.3	6.84	NC
		Female	40	1	1060	192	4780	562	2.57
		Female	80	1	2010	151	12200	1560	3.40

NC = Not Calculable.

Summary Table 2

Summary Mean (± SE) Escitalopram Toxicokinetic Parameters in Sprague-Dawley Rat Plasma Following 5, 40, and 80 mg/kg Oral Administration of Lexapro on PND 69

Analyte	PND	Gender	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	SE C_{max} (ng/mL)	$AUC_{(0-t)}$ (hr*ng/mL)	SE $AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)	R_{AUC}[a] (RATIO)
Escitalopram	69	Male	5	1	14.3	3.92	32.8	8.20	NC	0.408
		Male	40	1	370	32.1	1690	185	*	0.405
		Male	80	2	730	168	5630	901	3.66	0.391
		Female	5	1	31.5	11.2	84.0	23.0	1.30	0.900
		Female	40	1	561	52.5	2590	261	*	0.542
		Female	80	1	1000	104	7250	870	3.93	0.594

NC = Not Calculable.

*Result not reported because extrapolation exceeds 20%, or R-squared is less than 0.800.

[a] RAUC = PND 69 $AUC_{(0-t)}$/ PND 21 $AUC_{(0-t)}$.

Source: Provided by the Applicant from the study report (Study No. SCT-TX-101).

Table 21: Summary of Toxicokinetics Parameters of Desmethylcitalopram in Rats following Oral Administration of Lexapro on PND 21 and PND 69

Summary Table 3

Summary Mean (± SE) Desmethyl Citalopram Toxicokinetic Parameters in Sprague-Dawley Rat Plasma Following 5, 40, and 80 mg/kg Oral Administration of Lexapro on PND 21

Analyte	PND	Gender	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	SE C_{max} (ng/mL)	$AUC_{(0-t)}$ (hr*ng/mL)	SE $AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
Desmethyl Citalopram	21	Male	5	2	9.76	3.81	35.5	9.88	NC
		Male	40	4	192	15.9	1130	82.7	NC
		Male	80	8	424	40.0	6270	470	NC
		Female	5	2	11.1	1.23	30.4	3.60	NC
		Female	40	2	207	37.2	1290	96.4	NC
		Female	80	8	324	70.9	5320	805	NC

NC = Not Calculable.

Summary Table 4

Summary Mean (± SE) Desmethyl Citalopram Toxicokinetic Parameters in Sprague-Dawley Rat Plasma Following 5, 40, and 80 mg/kg Oral Administration of Lexapro on PND 69

Analyte	PND	Gender	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	SE C_{max} (ng/mL)	$AUC_{(0-t)}$ (hr*ng/mL)	SE $AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)	R_{AUC}[a] (RATIO)
Desmethyl Citalopram	69	Male	5	1	20.4	4.46	48.9	13.7	NC	1.38
		Male	40	4	512	39.8	6710	785	NC	5.92
		Male	80	8	1190	121	17600	1300	NC	2.80
		Female	5	1	15.8	4.75	56.4	13.9	1.77	1.86
		Female	40	4	299	19.3	4370	455	NC	3.40
		Female	80	8	636	59.4	10300	631	NC	1.94

NC = Not Calculable.

[a] RAUC = PND 69 $AUC_{(0-t)}$/ PND 21 $AUC_{(0-t)}$.

Source: Provided by the Applicant from the study report (Study No. SCT-TX-101).

Table 22: Summary of Toxicokinetics Parameters of Didesmethylcitalopram in Rats following Oral Administration of Lexapro on PND 21 and PND 69

Summary Table 5
Summary Mean (± SE) Didesmethyl Citalopram Toxicokinetic Parameters in Sprague-Dawley Rat Plasma Following 5, 40, and 80 mg/kg Oral Administration of Lexapro on PND 21

Analyte	PND	Gender	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	SE C_{max} (ng/mL)	$AUC_{(0-t)}$ (hr*ng/mL)	SE $AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
Didesmethyl Citalopram	21	Male	5	2	4.01	1.20	18.3	4.71	NC
		Male	40	8	30.4	3.14	430	41.3	NC
		Male	80	8	33.7	4.50	675	60.9	NC
		Female	5	2	4.09	0.883	11.6	1.70	NC
		Female	40	8	22.2	3.68	318	38.5	NC
		Female	80	8	36.3	1.81	662	66.7	NC

Summary Table 6
Summary Mean (± SE) Didesmethyl Citalopram Toxicokinetic Parameters in Sprague-Dawley Rat Plasma Following 5, 40, and 80 mg/kg Oral Administration of Lexapro on PND 69

Analyte	PND	Gender	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	SE C_{max} (ng/mL)	$AUC_{(0-t)}$ (hr*ng/mL)	SE $AUC_{(0-t)}$ (hr*ng/mL)	$T_{1/2}$ (hr)	R_{AUC}[a] (RATIO)
Didesmethyl Citalopram	69	Male	5	2	6.79	3.04	19.6	4.99	NC	1.07
		Male	40	8	89.6	14.8	1200	154	NC	2.78
		Male	80	8	178	16.4	2960	289	NC	4.38
		Female	5	2	3.90	1.48	22.5	5.01	NC	1.94
		Female	40	8	50.0	9.25	806	120	NC	2.54
		Female	80	8	109	12.9	2220	201	NC	3.35

NC = Not Calculable.
[a] RAUC = PND 69 $AUC_{(0-t)}$/ PND 21 $AUC_{(0-t)}$.

Source: Provided by the Applicant from the study report (Study No. SCT-TX-101)

15.4. Clinical Pharmacology

15.4.1. Bioanalytical Validation Report

Bioanalytical Project No.:	190276AVZD
Sponsor's Project No.	SCT-MD-60
Protocol No.:	SCT-MD-60
Protocol Title:	A Randomized, Multicenter, Double-Blind, Flexibly-dosed, Efficacy and Safety Study of Escitalopram in the Treatment of Children and Adolescents With Generalized Anxiety Disorder

Test Method Title:	Escitalopram and S-Desmethyl Citalopram in Human Lithium Heparinized Plasma over a Concentration Range of 400 to 80000 pg/mL and 100 to 20000 pg/mL, respectively using HPLC-MS/MS with Automated Extraction
Analytes:	Escitalopram and S-desmethyl citalopram
Internal Standard:	Citalopram-d_4
Calibration Ranges:	400 to 80000 pg/mL for escitalopram 100 to 20000 pg/mL for S-desmethyl citalopram
Biological Matrix:	Human lithium heparinized plasma
Assay Volume Required:	0.100 mL
Sample Extraction:	Automated liquid-liquid extraction
Type of Assay:	LC/MS/MS (API 4000)
Column:	ACE 3 C18, 30 x 4.6 mm, 3 µm
Column Temperature:	25°C
Mobile Phase A:	Methanol / Milli-Q type water with ammonium formate and formic acid
Mobile Phase B:	Methanol / Milli-Q type water
Chromatographic Mode:	Isocratic
Flow Rate:	1.000 mL/min
Chromatographic Integration / Acquisition Data System:	Analyst 1.6.3 or higher, AB Sciex
LIMS:	Watson version 7.4.1 or higher, Thermo Fisher Scientific Corporation
Quantitation Method:	Peak area ratio
Calibration Regression:	Linear
Weighting Factor:	$1/x^2$ [Peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]
Calibration equation:	$y = mx + b$
Coefficient of determination:	r^2
Analytes Retention Time:	1.11 minutes for escitalopram 1.14 minutes for S-desmethyl citalopram
IS Retention Time:	1.09 minutes
Acquisition Time:	2.00 minutes

Accuracy and Precision (Between-Run):	A: Biases: -0.65 to 4.73% CV: 1.66 to 11.86% B: Biases: 0.06 to 3.89% CV: 2.18 to 12.98%
Accuracy and Precision (Within-Run):	A: Biases: -8.71 to 17.59% CV: 0.83 to 7.89% B: Biases: -10.34 to 11.58% CV: 0.78 to 9.34%
Freeze and Thaw Stability:	4 cycles at -20°C/-80°C
Short-Term Stability of Analytes in Matrix:	24h00min at room temperature
Long-Term Stability of Analytes in Matrix:	535 days at -20°C and -80°C
Post-Preparative Stability:	167h28min at room temperature
Reinjection Reproducibility:	69h47min at room temperature

Source: Final Bioanalytical Report 190276AVZD (for Study SCT-MD-60).

15.4.2. Pharmacometric Analyses

Population PK Modeling

The Applicant submitted report rd220800-pkpd-rpt.pdf, entitled "*Population Pharmacokinetics and Exploratory Exposure Response Analysis of Escitalopram in Children and Adolescents (7-17 Years of Age) with Generalized Anxiety Disorder (GAD)*" to module 5335 of sequence 0117. The objectives of the analyses were to A) develop a population pharmacokinetics (PPK) model describing the plasma concentration of escitalopram over time and variability between and within subjects in the pediatric population 7 to 17 years of age, B) evaluate the impact of covariates on the PK of escitalopram, and C) predict individual exposure variables and do exploratory analyses of the exposure/dose/response relationship for relevant efficacy or safety variables.

The PK dataset contains 483 observations from n=116 subjects. PK data for the analyses came from Study SCT-PK-10 and study SCT-MD-60.

Table 23: Overview of the studies included in the analyses

Phase	Study ID	Study Design and Dose Regimen	N Subjects	PK Data
1	SCT-PK-10	Open label single dose study of 10 mg escitalopram oxalate tablet	11 adolescent and 12 adult healthy subjects	Total 23 full PK profiles
3	SCT-MD-60	Randomised, double-blind, placebo-controlled, multicentre, flexible dosing of 10/20 mg escitalopram QD or placebo	137 subjects with GAD treated with escitalopram and 136 on placebo 7-17 years of age	Total 4 PK samples per subject (2+2 weeks 4 and 8 of treatment)

SD = single dose, MD = multiple dose, Flexible dosing: 10 mg 2 weeks if tolerated dose escalation to 20 mg if stay on 10 mg new dose escalation tried at 4 weeks. GAD = Generalized Anxiety Disorder.
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 24.

The final PPK model includes two compartments, a sequential zero-order followed by first-order absorption process, and linear elimination. The model is parameterized in terms of apparent clearance (CL/F), apparent volume of distribution of the central compartment (V1/F), apparent volume of distribution of the peripheral compartment (V2/F), apparent intercompartmental clearance (Q/F), and duration of zero-order absorption into the depot compartment (D1). Allometric scaling is applied to volume terms with a fixed exponent of 1 and clearance terms with a fixed exponent of 0.75. The final model did not include any covariates. Between subject variability is estimated for CL/F, Vss/F, D1, and as a proportional error term. Separate proportional error is coefficients are estimated for study 10 and study 60. The parameter estimates for the final model are presented in Table 24.

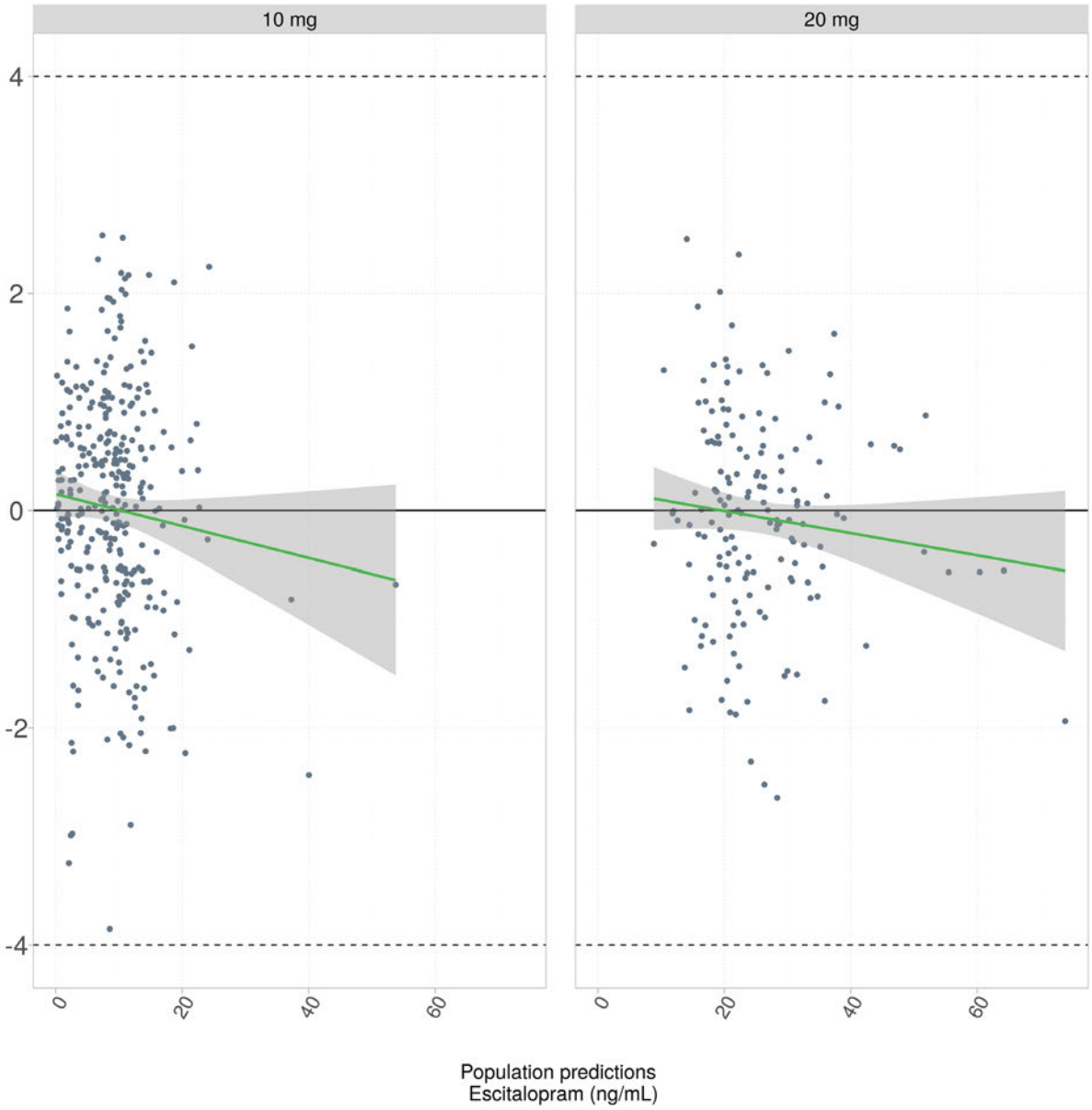
Table 24: Parameter Estimates for the Final PPK Model (run 31)

Parameter	Label	Unit	Estimate	CI95 bootstrap
θ_1	CL/F	L/h	36.3	(33.2-39.6)
θ_2	V_1/F	L	361	(192-670)
θ_5	V_2/F	L	687	(393-830)
θ_4	Q/F	L/h	133	(69.9-156)
θ_3	k_a	/h	0.439	(0.253-0.881)
θ_7	D_1	h	1.73	(1.54-2.07)
θ_8	Error Study 10	-	0.0990	(0.0771-0.124)
θ_{11}	Error Study 60	-	0.260	(0.199-0.344)
ω_1^2	IIV CL/F	VAR	0.196	(0.133-0.263)
ω_2^2	IIV V_{ss}/F	VAR	0.0260	(0.00655-0.0448)
ω_3^2	IIV D_1	VAR	0.151	(0.0496-0.339)
ω_4^2	IIV Error	VAR	0.0679	(6.79e-06-0.173)

Parameter values for the final PopPK model. ka: absorption rate. CL/F: apparent systemic clearance. V1=F: apparent central volume of distribution. V2=F: apparent peripheral volume of distribution. Q/F: apparent intercompartment clearance. w^2: variance of the IIV of parameter. D1: duration of absorption, Vss: apparent distribution volume at steady state. CI95: 95% confidence interval.
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 46.

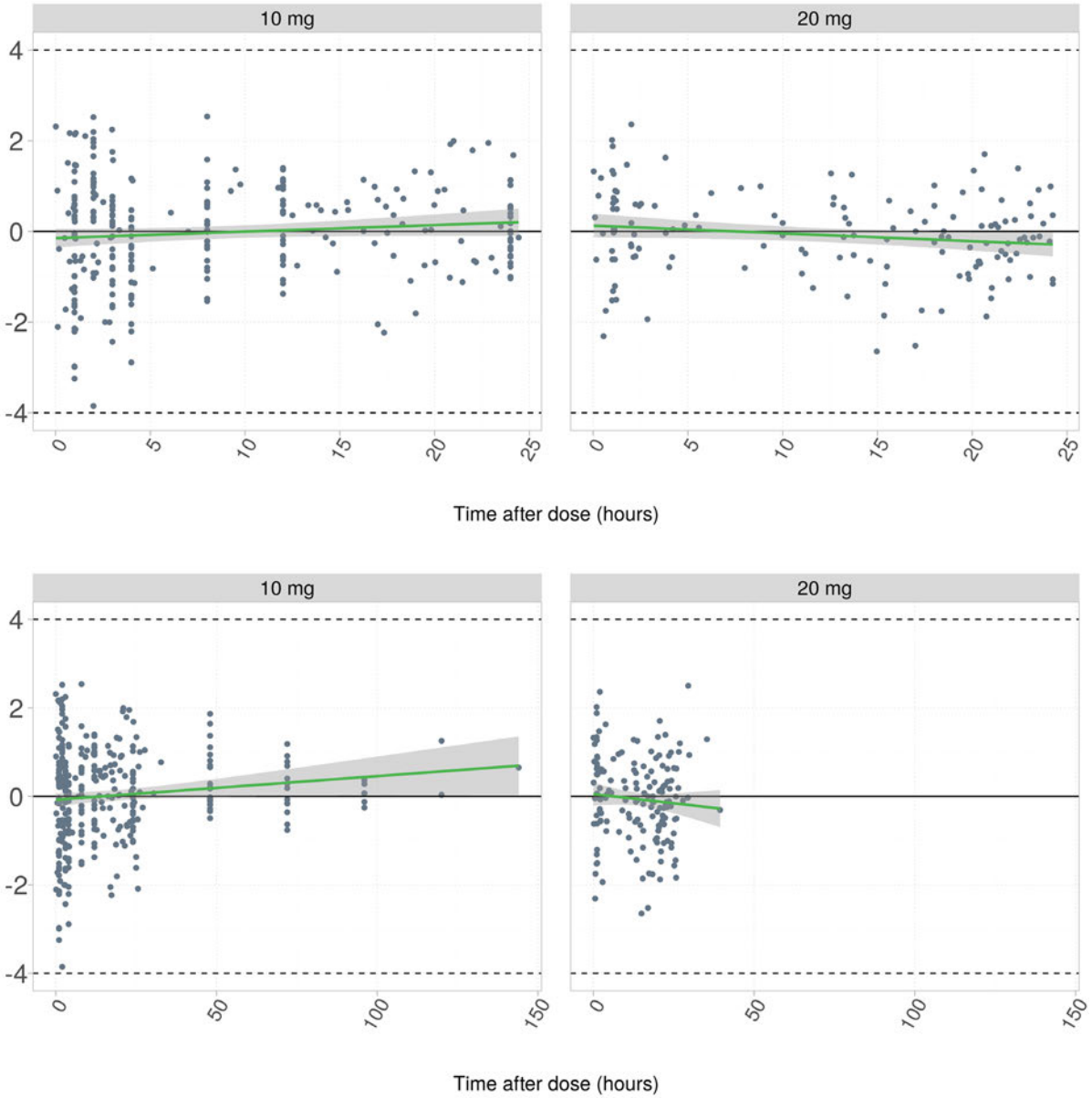
Eta shrinkage is 3.6%, 53%, and 46% for eta1 (CL/F), eta2 (Vss/F), and eta3 (D1).
The key diagnostic plots are presented below.

Figure 10: Conditional Weighted Residuals versus Predictions—Final PPK Model (Run 31)



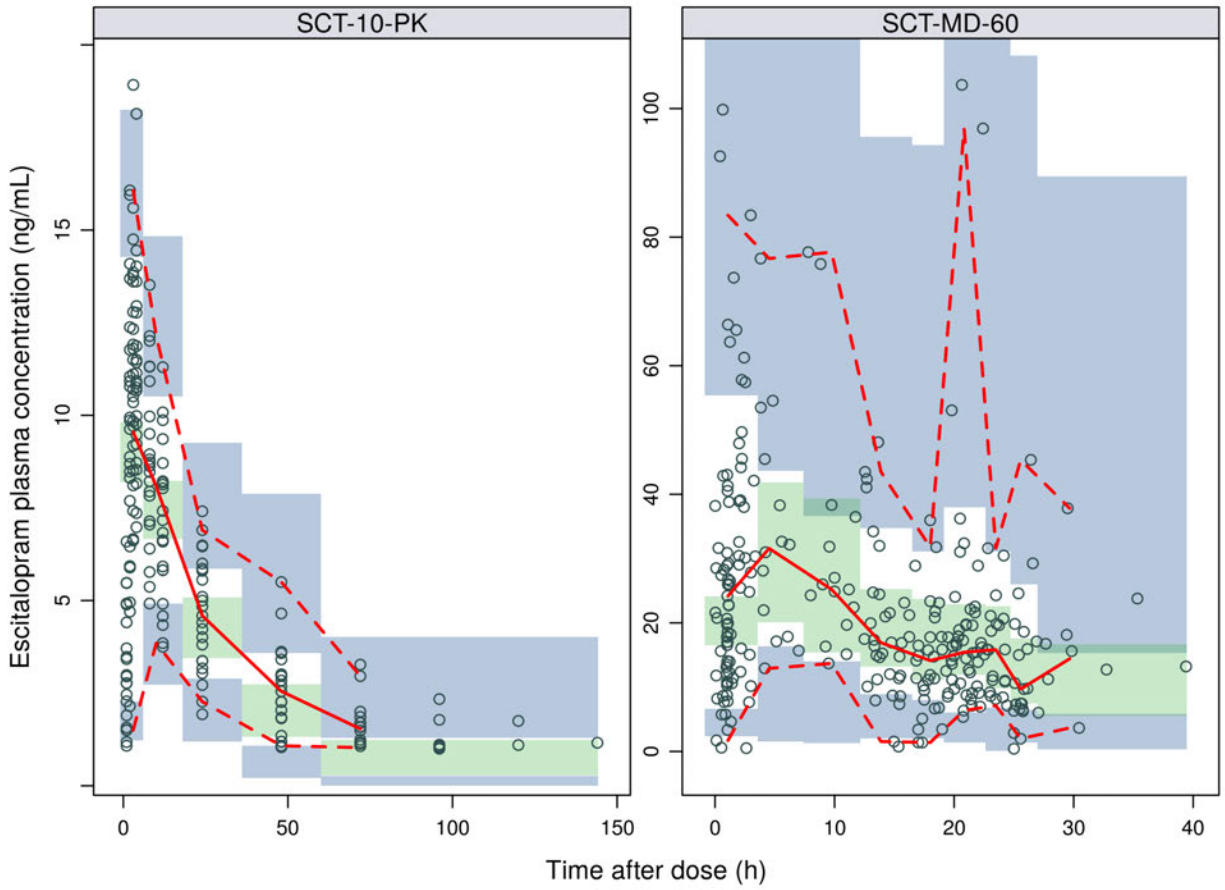
Green line: Linear smooth with 95% confidence intervals
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 49.

Figure 11: Conditional Weighted Residuals versus Time after Dose—Final PPK Model (Run 31)



Top row: Shows the estimated conditional weighted residuals vs. Time after dose, first 24 h
Bottom row: Shows the estimated conditional weighted residuals vs. Time after dose, all time points
Green line: Linear smooth with 95% confidence intervals
Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 50.

Figure 12: Visual Predictive Check by Study - Final PPK Model (Run 31)



Circles: Observations, Solid Blue Line: Median of the observed escitalopram concentrations, Dashed Lines: 2.5th and 97.5th percentiles of the observed escitalopram concentrations, Shaded Area: The shaded areas indicate the 95% CI around the median (green area), and 2.5th and 97.5th percentiles of the simulated concentrations (grey areas). Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 51.

Pharmacometric Reviewer's Comments: *The Applicant reports that eta shrinkage in ETA1 (CL/F), ETA2 (volume of distribution at steady state (Vss)) and ETA3(absorption duration) was 3.6%, 53%, and 46%, respectively. For this reason, the Applicant concluded that only CL/F random effect was considered informed enough to be plotted against covariates during model building, which is acceptable.*

There are no clear signs of bias with respect to time or concentration according to the diagnostic plots presented in
Figure 10 and Figure 11. The majority of the CWRES values are within ± 2 standard deviations in Figure 10 and Figure 11. There are no obvious concerns about the model performance based on the VPC in Figure 12.

The results of SCM procedure support the decision to exclude all screen covariates from the final PPK model. The current Lexapro label indicates that renal clearance accounts for 7% of escitalopram clearance following oral escitalopram administration. As such, it is reasonable that

renal clearance is not a covariate in the final PPK model. Though the SCM analyses do not support inclusion of concomitant medications as covariates, it should be noted that concomitant medications that induce or inhibit the metabolism of escitalopram were taken by n=2 and n=3 subjects, respectively, out of a total of n=116 subjects.

The condition number is 741.79 which does not suggest overparameterization. The bootstrap 95% confidence intervals do not contain zero for any parameters. Overall, the Applicant's model is acceptable.

Population PK Simulation

The Applicant conducted simulations using the final PPK model (run 31) to estimate the PK of children (age 7 to 11) as well as adolescents (age 12 to 17 years) versus adults. The steady-state PK of males and females aged 7 to 17 years, were simulated for a 20 mg once daily dose regimen using the median (50^{th} percentile) weights as well as the 5^{th} percentile weights of pediatric subjects at each year of age. A 70-kg adult was simulated as a reference for comparison of pediatric subjects. The simulations include between subject variability, residual variability, and parameter uncertainty from the final PPK model. The Applicant computed the AUCtau,ss, Cmax,ss, and Cmin,ss. One thousand simulations were conducted for pediatric males at each year of age with median weight, pediatric males at each year of age with 5^{th} percentile weight, pediatric females at each year of age with median weight, pediatric females at each year of age with 5^{th} percentile weight, and for the 70 kg reference subject. The results are presented as the ratio (and 95% confidence interval) of each PK metric for male and female pediatric subjects in the child and adolescent age range divided by 70 kg adult. The results of these simulations (Figure 1) and discussion of their implications on labeling can be found in the section of this review entitled, "What were the PK characteristics in adolescents (12 to 17 years) and children (7 to 11 years) compared to PK in adults?".

Exposure-Response Analyses: Efficacy

The Applicant assessed the relationship between efficacy in pediatric patients with GAD and escitalopram PK. A graphical assessment of the relationship of change from baseline on the PARS at Week 8 (the primary efficacy endpoint in Trial SCT-MD-60) with escitalopram PK was conducted. The results include a presentation of the distribution of change from baseline at Week 8 on the PARS in the placebo arm for comparison against the distribution as well as within PK quartiles. The PK metric is the average escitalopram plasma concentration up to Week 8. The results of this graphical assessment are presented in

Figure **2** in the section entitled, "Based on the exposure-response analysis, was there any relationship between exposure and efficacy or safety?". The Applicant provides the following conclusions:

> For all efficacy variables there is a trend that lower exposures correlate with preferable outcomes. One plausible reason for this could be escalation in responders vs. non-responders but the trend is present also before escalation. In short, there is not enough information to conclude from where this trend originates.
> (Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 73.)

Reviewer's comments: *In*

Figure **2** *, for adolescents, the lowest concentration quartile demonstrated a greater response (-11.5) than the three quartiles with higher Concentration (-5, -6, and -5). Also, in*

Figure **2***, for children, the second concentration quartile demonstrated a greater response (-11.5) than quartiles 1, 3, or 4 (-5, -6, and -4.5). Overall, this graphical analysis does not support the existence of an exposure-response relationship for efficacy in terms of Week 8 change from baseline on the PARS and average concentration up to Week 8. This finding may be due in part to the flexible dosing employed in Trial SCT-MD-60.*

Exposure-Response Analyses: Safety

Adverse events that the Applicant considers common were selected for exposure-safety analyses. The exposures for subjects experiencing decreased appetite, somnolence, nausea, and insomnia were plotted alongside the exposure of subjects that did not experience the AE. The results are presented in Figure 3 in the section entitled, "Based on the exposure-response analysis, was there any relationship between exposure and efficacy or safety?".

The Applicant provides the following conclusions:

> Patients treated with escitalopram and experiencing somnolence or decreased appetite had slightly higher average plasma concentrations than patients that did not experience these adverse events. No difference was observed between patients experiencing nausea or insomnia and those who did not.
> (Source: Sequence 0117, module 5335, rd220800-pkpd-rpt.pdf, page 74.)

OCP agrees with the Applicant's conclusions. Overall, the safety reviewer has concluded that there are no safety signals in this submission that preclude approval of this sNDA. See the section entitled Integrated Assessment of Safety for additional details.

15.5. Additional Clinical Outcome Assessment Analyses

Not Applicable

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