NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	PREA PMR Efficacy Supplement
Application Number(s)	204168/S-10
Priority or Standard	Standard (10-month)
Submit Date(s)	May 26, 2022
Received Date(s)	May 26, 2022
PDUFA Goal Date	March 26, 2023
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	March 26, 2023
Established/Proper Name	Levomilnacipran
(Proposed) Trade Name	Fetzima
Pharmacologic Class	Serotonin norepinephrine reuptake inhibitor (SNRI)
Code name	F2695
Applicant	AbbVie Inc.
Dosage form	Extended-release capsules
Applicant proposed Dosing Regimen	Not applicable
Applicant Proposed Indication(s)/Population(s)	Not applicable
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not applicable
Recommendation on Regulatory Action	Approval. The approved age range (adults) will not be expanded; relevant pediatric information will be added to labeling
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DPMH=Division of Pediatric and Maternal Health

Glossary

5-HT	5-hydroxytryptamine (serotonin)
AE	adverse event
AR	adverse reaction
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CDRS-R	Children's Depression Rating Scale-Revised
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	double-blind
DMC	data monitoring committee
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
ER	extended release
ET	early termination
FDA	Food and Drug Administration
GCP	good clinical practice
HDF	high dose females
HDM	high dose males
HTN	hypertension
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
JAS	juvenile animal study
K-SADS-PL	Kiddie Schedule for Affective Disorders – Present and Lifetime
LLN	lower limit of normal
LS	least squares
LVM	levomilnacipran
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MRHD	maximum recommended human dose
NE	norepinephrine
NDA	new drug application
NE	norepinephrine
NOAEL	no observed adverse effect level
OC	observed case
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCS	potentially clinically significant
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	post-natal day
PP	per protocol
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Frederica formula
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCS	summary of clinical safety
SD	standard deviation
SE	standard error
SI	*Le Systeme International d/Unites* (International System of Units)
SI/B	suicidal ideation and behavior
SNRI	serotonin and norepinephrine reuptake inhibitor
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor

TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TK	toxicokinetic
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

Levomilnacipran is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) first approved on July 25, 2013, under sections 505(b)(2) and 505(u) of the Federal Food, Drug, and Cosmetic Act for the treatment of major depressive disorder (MDD). Levomilnacipran is one of the two enantiomers present in the racemate milnacipran approved by the FDA on January 14, 2009, for the management of fibromyalgia under the trade name Savella. Milnacipran was first approved in France in 1996 for the treatment of depression. Levomilnacipran is available as extended-release (ER) capsules for daily, oral administration, in 20-, 40-, 80-, and 120-mg strengths.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted two 8-week, randomized, double-blind (DB), placebo-controlled, active-reference studies in pediatric subjects with MDD. Study LVM-MD-11 was a fixed-dose study in pediatric subjects ages 12 to 17 years old and Study LVM-MD-14 was a flexible-dose study in pediatric subjects ages 7 to 17 years old. In these adequate and well-controlled studies, both levomilnacipran and the active reference (fluoxetine) failed to separate from placebo. The Applicant is not seeking an expansion of the indicated population (adults); relevant pediatric safety information will be added to labeling. Labeling will be updated to indicate that the safety and effectiveness of levomilnacipran have not been established in pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The prevalence of pediatric MDD has increased in recent years, now affecting approximately 4% of U.S. children and adolescents (Lebrun-Hartis et al., 2022). Additional effective treatments are needed. However, the clinical trials submitted in Supplement 10 did not demonstrate efficacy for levomilnacipran in pediatric MDD. Safety results were generally consistent with adult data. However, a larger number of pediatric subjects treated with levomilnacipran experienced a shift from normal blood pressure to hypertension during the double-blind (DB) study period compared with placebo. This shift also occurred more frequently in pediatric subjects than in adults who received levomilnacipran in the development program. A higher number of suicidal ideation and behavior-related adverse events (AEs) occurred with the active study drug arms compared with placebo, which appears to be consistent with the current boxed warning regarding risk of suicidal ideation and behavior in pediatric patients and young adults treated with antidepressants. Relevant safety information for pediatric patients will be included in the labeling, including additional information regarding blood pressure changes, but the indicated population will not be expanded.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The symptoms of MDD include depressed mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. In some cases, MDD can result in suicidal ideation and behavior (SI/B) and completed suicide. • According to the National Survey of Children's Health, the prevalence of pediatric MDD increased from 3.1% in 2016 to 4% in 2020 (Lebrun-Harris L et al., 2022).	MDD is a common chronic illness and the leading cause of disability worldwide. MDD in the pediatric population is less common than in adults. However, the increase in prevalence and the serious nature of symptoms make pediatric MDD a public health concern.
Current Treatment Options	• Only two antidepressants (fluoxetine and escitalopram) have been FDA-approved for treatment of MDD in pediatric patients. Several additional antidepressants have failed to demonstrate efficacy in this population.	There is a need for additional treatment options for the treatment of pediatric MDD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two pediatric short-term efficacy studies were submitted with this supplement. The primary efficacy endpoint for both studies was change from baseline to Week 8 in the Children's Depression Rating Scale-Revised (CDRS-R) total score. Neither Study LVM-MD-11 (a randomized, DB, placebo- and active-controlled, fixed-dose study in adolescents with MDD, ages 12 to 17 years) nor Study LVM-MD-14 (a randomized, DB, placebo- and active-controlled, flexible-dose study in pediatric subjects, ages 7 to 17 years) demonstrated efficacy of levomilnacipran for the treatment of pediatric MDD. The active comparator, fluoxetine, also failed to separate from placebo in these two studies.	Levomilnacipran's indicated population (adults) will not be expanded to include pediatric patients with MDD.
Risk and Risk Management	• Adverse events (AEs) that occurred in ≥2% of subjects randomized to levomilnacipran in LVM-MD-11 and at ≥ twice the frequency as in placebo-treated subjects included: nausea, tachycardia, vomiting, decreased appetite, somnolence, upper respiratory infection, heart rate increased, constipation, hyperhidrosis, sedation, palpitations, dysmenorrhea, rash, cough, influenza, and cough. The most common AEs in LVM-MD-14 (≥2% of levomilnacipran-treated subjects and twice the frequency of placebo) were: nausea, decreased appetite, tachycardia, vomiting, dizziness, and abdominal discomfort. There was significant overlap in the AEs reported in the pediatric and adult studies. In both Studies LVM-MD-11 and LVM-MD-14, a larger number of	Safety findings will be included in Section 5.3 (Elevated Blood Pressure) and Section 8.4 (Pediatric Use). Based on the data presented with this supplement, the pediatric and adult safety data are largely similar, with what appears to be a more pronounced impact on shifts from normal blood pressure to hypertension in pediatric subjects.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	subjects treated with levomilnacipran experienced a shift from normal blood pressure to hypertension during the DB study period compared with placebo. This shift also occurred more frequently in pediatric subjects than in adults exposed to levomilnacipran in the development program.	

1.4. Patient Experience Data

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

T	**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		8.1
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	8.1
		□	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

Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of individual and society-level morbidity that occurs across the lifespan and often has a chronic disease course with recurrent episodes. MDD is characterized by depressed mood and loss of interest or pleasure, as well significant weight or appetite changes, changes in sleep pattern, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide (American Psychiatric Association 2013). Persons with MDD may be unable to work, maintain relationships, and, in severe cases, may require hospitalization, or attempt or commit suicide. Although many symptoms of depression are similar between pediatric and adult presentations, mood-related symptoms may manifest in different ways at different developmental levels. In pediatric patients, depressive symptoms may occur as declining school performance, withdrawal from social activities, somatic symptoms, conduct problems, and sleep difficulties.

The 2017 National Survey on Drug Use and Health revealed that an estimated 17.3 million adults in the United States had at least one major depressive episode (MDE) that year, representing 7.1% of adults in the United States. The lifetime prevalence of MDD is estimated at 12% to 20%. Although children and adolescents have lower rates of depression compared with adults, the prevalence of MDD has increased in recent years. According to the National Survey of Children's Health, the prevalence of pediatric MDD increased from 3.1% in 2016 to 4% in 2020 (Lebrun-Harris L et al., 2022).

2.2. Analysis of Current Treatment Options

Although the Agency has approved multiple antidepressant medications for the treatment of MDD in the adult population, only two antidepressants (fluoxetine and escitalopram) have demonstrated safety and effectiveness in adequate and well-controlled studies with resultant pediatric indications in product labeling. Fluoxetine is approved for the treatment of pediatric patients ages 8 to 17 years with MDD and escitalopram is approved for patients ages 12 years and older with MDD. Clinical studies of other antidepressants have failed to demonstrate efficacy in pediatric patients despite efficacy in adults (e.g., desvenlafaxine, duloxetine, paroxetine, sertraline, venlafaxine, vilazodone, vortioxetine). Because of the differential response to treatment between adult and pediatric patients observed in clinical trials, extrapolation of efficacy is not feasible and pediatric clinical studies are required to gain a marketing indication.

See Table 1 for a summary of information regarding the antidepressants with labeled indications for pediatric MDD.

Table 1. Antidepressants with Labeled Indications for Pediatric Major Depressive Disorder

Product Name	Approval Year Adult/Pediatric	Ages of Pediatric Approval	Formulation/ Recommended Dosage	Efficacy Supporting Label	Safety Concerns in Pediatrics
Fluoxetine	1987/2003	8 to 17 years	Capsule: 10, 20, 40 mg Liquid: 20 mg/5mL Dosage: 10 to 20 mg/day (initial dose)	Two 8- to 9-week placebo-controlled clinical trials with pediatric outpatients 8 to ≤18 years with MDD	Mania/hypomania Decreased weight gain Decrease in alkaline phosphatase
Escitalopram	2002/2009	12 to 17 years	Tablets: 5, 10, 20 mg Oral solution: 1 mg/mL Dosage: 10 mg once daily with maximum recommended dose of 20 mg (titration after 3 weeks)	One 8-week flexible-dose (10 to 20 mg escitalopram), placebo-controlled outpatient study in patients 12 to 17 years with MDD Extrapolation from one 8-week, flexible-dose (citalopram 20 to 40 mg), placebo-controlled study in patients 7 to 17 years; statistically significant, but positive results were mostly in adolescent group Negative efficacy studies in the label: two flexible-dose, placebo-controlled MDD studies (one escitalopram in ages 7 to 17 years and one citalopram study in adolescents)	Most common adverse reaction: insomnia Similar safety profile to adults but higher incidence of back pain, urinary infection, vomiting, nasal congestion

Abbreviations: MDD= major depressive disorder
Source: Fluoxetine and Escitalopram U.S. Prescribing Information

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

- NDA 204168 for levomilnacipran extended-release capsules (marketed as Fetzima) was originally approved on July 25, 2013, for the treatment of major depressive disorder (MDD) in adults. The approval included three Pediatric Research Equity Act (PREA)-related postmarketing requirements (PMRs):

    - PMR 19431-1: A deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients ages 12 to 17 years. Conduct a study to obtain data on the pharmacokinetics (PK), efficacy and safety of levomilnacipran in the relevant adolescent population (ages 12 to 17 years). This must be a placebo- and active-controlled (escitalopram or fluoxetine) fixed dose study. When the appropriate number of PK samples becomes available from this adolescent study, an interim population PK analysis should be conducted to determine the dosing and regimen for the secondary efficacy and safety study in children and adolescents (ages 7 to 17 years).

    - PMR 1943-2: A deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients ages 7 to 17 years. Conduct a study to obtain data on the efficacy and safety of levomilnacipran in the relevant pediatric population (ages 7 to 17 years). This study must be a placebo- and active-controlled (fluoxetine) study. This study may be a fixed-dose study. You should submit data from population PK model using data from adults and adolescents (PMR 1943-1) to justify the dose(s) and the schedule for sparse PK sampling, at least 3 months prior to submitting the protocol.

    - PMR 1943-3: To support the use of levomilnacipran in children less than 12 years of age, you must conduct a study to assess the safety of levomilnacipran in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. You should submit the protocol for our comments prior to initiating the study. You may conduct this study concurrently with the pediatric clinical trials.

- On March 10, 2014, the Applicant provided the final draft protocol for Study LVM-TX-06/41160 RSR, titled “Toxicity Study by Oral Route (Gavage) in Juvenile Rats” and the audited draft study report for Study LVM-TX-05/40562 RSR, titled “Preliminary Toxicity Study by Oral Route (Gavage) in Juvenile Rats” was provided. The doses selected for the definitive juvenile rat study were based on the results of the preliminary study. The protocol was submitted in reference to PMR 1943-3.

- On May 8, 2014, The Applicant submitted a Proposed Pediatric Study Request (PPSR) to initiate the Agency's review and issuance of a Written Request to conduct studies to support the safety and efficacy of levomilnacipran in pediatric patients with MDD. At that time, the Applicant proposed to conduct two double-blind (DB, randomized, placebo- and active-controlled studies (LVM-MD-11 and LVM-MD-14) to evaluate the safety and efficacy of levomilnacipran and one open-label study (LVM-MD-16) to evaluate the long-term safety of levomilnacipran in the treatment of MDD in pediatric patients.

- On September 5, 2014, the Division sent the Applicant a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act, as amended by the Food and Drug Administration Amendments Act of 2007. This Written Request included the following specific study requirements for a development program in pediatric MDD: a nonclinical toxicology study; a pediatric (ages 12 to 17 years) PK, efficacy, and safety study; a pediatric (age 7 to 17 years) efficacy and safety study; and a long-term safety study for a minimum duration of 6 months of exposure to levomilnacipran in pediatric patients (ages 7 to 17 years) with MDD.

- On February 27, 2015, the Applicant responded to the Written Request, proposing a new timeframe for submitting study reports and submission of the statistical analysis plan (SAP) at a later timepoint for the first proposed study, as well as changes in wording regarding percentage of subjects completing to the nominal endpoint, gender distribution, and other minor changes.

- On August 5, 2015, the Division responded with revisions to the Written Request with extended timeframes for study submission and other changes, including the need for submission of the SAP for each study prior to study initiation. The Agency notified the Applicant that they must respond to the Written Request with agreement or non-agreement within 180 days of receipt. The revised Written Request indicated that the study reports must be submitted on or before December 17, 2022.

  The Applicant did not respond to this revision, submit any further proposed revisions to the Written Amendment, submit a long-term safety study protocol, or make an exclusivity request.

- In this supplement, the Applicant has submitted Study LVM-MD-11 to address PMR 1943-1 and Study LVM-MD-14 to address PMR 1943-2.

3.2. Summary of Presubmission/Submission Regulatory Activity

- Deferral extension requests for Studies LVM-MD-11 and LVM-MD 14 were submitted on December 16, 2015; April 3, 2017; August 15, 2017; December 19, 2018; October 25, 2019; and October 8, 2021. All but the request submitted on April 3, 2017, were granted. The April

3, 2017, deferral extension request was denied, but the Applicant responded on August 15, 2017, with further information, and the deferral extension request was granted.

- December 19, 2019: The Division requested early submission of an abbreviated clinical study report for LVM-MD-11 (PMR-1943-1) for the purpose of identifying any new major safety concerns in the study data. No new major safety signals were identified in the final abbreviated report submitted on June 5, 2020.

- February 7, 2020: Because topline results for Study LVM-MD-11 indicated no differentiation from placebo for levomilnacipran and nonsignificant differentiation from placebo for the active control, fluoxetine, the Applicant submitted a Meeting Request to discuss a proposed interim futility analysis for Study LVM-MD-14. In a Written Response communicated on April 6, 2020, the Division stated an interim futility analysis would be reasonable, but due to the flexible-dose design of the study, it would not be sensible to separate the different doses (40 mg or 80 mg) in the analysis. The SAP for the study was submitted on April 16, 2020.

- July 2020: The Applicant reported that, following a review of the results of the interim efficacy and safety data for LVM-MD-14, the Independent Data Monitoring Committee (DMC) recommended continuation Study LVM-MD-14 as planned.

- September 2021: During the pre-sNDA meeting, the Division requested that the Applicant submit full clinical study reports for both LVM-MD-11 and LVM-MD-14 for the sNDA, despite neither levomilnacipran nor active control fluoxetine separating from placebo. The Division agreed with the Applicant's proposal to request a deferral extension for LVM-MD-11 to allow for preparation of the complete study report. The Applicant and Division also agreed on required components of the sNDA submission.

- On May 26, 2022, the Applicant submitted sNDA 205168/S-10 to fulfill PMRs 1943-1 and 1943-2.

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

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were conducted during the review of this supplement.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Controls (CMC) review in Panorama (Dr. Qi, March 6, 2023). The CMC review team recommends approval of the supplement. The CMC review team recommended changes to Section 11 of the prescribing information to improve clarity and accuracy.

4.3. Clinical Microbiology

No clinical microbiology information was submitted with this supplement.

4.4. Devices and Companion Diagnostic Issues

This supplement did not include any data related to devices or companion diagnostics.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Fetzima™ (levomilnacipran, Code F2695) was approved on July 25, 2013, for the treatment of MDD in adults. Clinical evaluation of the safety and efficacy of treatment with levomilnacipran in pediatric patients (ages 7 to 17 years) was deferred as a PMR. A juvenile animal study (JAS) to support the pediatric indication was part of the PMR (PMR# 1943-3). The Applicant fulfilled PMR 1943-3 by submitting the final report of the JAS (LVM-TX-06/41160 RSR) on March 16, 2016. The findings from this study and the proposed labeling recommendations are described here.

This JAS is a combined repeat dose, neurobehavioral, and fertility study in which levomilnacipran (10, 35, and 120 mg/kg/d; low dose, mid-dose, and high dose, respectively) was administered orally by gavage to juvenile rats from post-natal day (PND) 21 to PND 90 (10 weeks). One premature death of a high dose male was observed on PND 73. Treatment-related clinical signs (hunched posture, piloerection, half-closed eyes, and ptyalism) and lower mean body weight and weight gain accompanied by lower food consumption were observed at the high dose of 120 mg/kg/d.

Consistent with the lower mean body weights, bone mineral density measurements showed lower mineral content in high dose males (HDM) and females (-10% in HDM and -9% in HDF). Even though there was an overall tendency towards a return to control values during the recovery period, lower mineral content was still observed during recovery, despite the fact that the body weights of HDM and high dose females (HDF) were comparable to controls during the recovery period. Although there was no treatment-related effect on long bone growth in males, there was a slight decrease in mean tibia length in HDF on PND 56. These findings might suggest a drug effect on bone development in animals even though one might argue it is due to the body weight effect. However, even though the effect on body weight was reversed at the end of the recovery period, the effect on bone was not reversed. It is possible that the effect on body weight was faster to return to normal but the effect on bone might take a longer time to reverse; however, a direct drug effect on bone development cannot be ruled out.

There were no treatment-related effects on neurobehavioral development, including motor activity, auditory startle reflex, and learning or memory function. Even though there was no treatment-related effect on reproductive development in males, there was a significant delay in sexual maturation for high dose females, as measured by vaginal opening (vaginal opening was approximately 4 days later than controls as well as the historical controls). It is worth noting that this delay did not affect mating or fertility. In addition, there were no treatment-related effects on body weight and body weight gain during gestation.

There were no treatment-related effects on mating and fertility, including sperm count and motility. Similarly, there were no treatment-related effects on hysterectomy data, mean gravid uterus weight, and net body weight change.

Toxicokinetic (TK) analysis showed that systemic exposure to levomilnacipran in terms of AUC_{last} increased with increasing doses in both males and females on PND 21 and PND 90. For the metabolite, F17400, the overall exposure on PND 21 and PND 90 was proportional to the parent F2695 dose. There was no accumulation of F2695 and its metabolite between PND 21 and PND 90.

Based on the lower mean body weights, decreased body weight gains and food consumption at the high dose of 120 mg/kg/d, the no observed adverse effect level (NOAEL) was the mid dose of 35 mg/mg/d for male and female juvenile rats. This dose corresponds to a mean AUC_{last} of 5965 ng*h/mL and 8707 ng*h/mL in male and female rats, respectively. The exposure values in pediatric patients at steady state are comparable to the exposures in the adult humans at the maximum recommended human dose (MRHD) of 120 mg (AUC 5200 ng*h/mL). The NOAEL dose in juvenile rats represents an-animal-to human exposure multiples of 1-fold (male rats), and 2-fold (female rats), respectively, based on AUC values.

In general, the pivotal juvenile animal study (PND 21 through PND 90, intended to cover the period of development corresponding to childhood through adolescence) was conducted appropriately using adequate doses of levomilnacipran (and in accordance with the Division's recommendations on the protocol). Based on the review of the study results, it is concluded that the study has adequately assessed the safety of levomilnacipran in juvenile rats, including general toxicity, reproductive development, and neurological/behavioral development. Therefore, relevant findings from the study will be described in Section 8.4 of the product label.

5.2. Referenced NDAs, BLAs, DMFs

Not applicable

5.2.1. Juvenile Animal Study

Preliminary or Dose Range-finding Study in juvenile rats:

Study Title: Preliminary Toxicity Study by Oral Route (Gavage) in Juvenile Rats (Sponsor Study № LVM-TX-05/40561 RSR; Laboratory Study № 40561 RSR).

The objective of this non-GLP study was to determine the maximum tolerated dose of levomilnacipran (code F2695), following daily oral administration in juvenile male and female Sprague-Dawley rats from post-natal day (PND 21) to PND 56 (5-week treatment period). Four groups of male and female (seven/group) juvenile rats were administered F2695 at dose levels of 0, 10, 35 or 120 mg/kg/d by oral gavage for 36 days. An additional three males and three

females (vehicle control- drinking water) or 18 males and 18 females (Groups 2 to 4) were added as satellite (and dosed simultaneously as the main study) for TK blood sampling (PND 21 and PND 56).

There were no treatment-related deaths in this study. Treatment-related clinical signs were limited to ptyalism (hypersalivation), mainly at the high dose of 120 mg/kg/d. Other noteworthy treatment-related findings (observed only in HDM) were lower mean body weight (-13%), decreased body weight gain, and minimal hepatocellular hypertrophy in the liver and a lower severity of splenic extramedullary hematopoiesis. There were no treatment-related findings at the mid- and low doses; therefore, the doses of 10, 35, and 120 mg/kg/d were selected by the Sponsor for the pivotal study in juvenile rats.

While the exposure of F2695 was increased by slightly more than dose proportional on PND 21 and PND 56, exposure of the metabolite F17400, was proportional to the dose of F2695 on both days. The following tables (Table 2 and Source: Excerpted directly from the Applicant's Study Report, page 28

Table 3) summarize the TK data:

Table 2 Mean Toxicokinetic Exposure Parameters for F2695

F2695 - Mean toxicokinetic exposure parameters

Sex	Male	Female	Male	Female	Male	Female
Dose-level (mg/kg/day)	10		35		120	
PND 21:						
. C_{max} (ng/mL)	530	654	2317	2446	5204	5518
. T_{max} (h)	0.5	0.5	1.0	0.5	4.0	1.0
. AUC_{last} (ng.h/mL)	1392	1259	7303	6475	36924	33720
PND 56:						
. C_{max} (ng/mL)	562	683	1206	2288	4316	7005
. T_{max} (h)	0.5	0.5	1.0	0.5	1.0	0.5
. AUC_{last} (ng.h/mL)	973	1238	3973	7972	27994	39527

On PND 21, blood samples were pooled by sampling time and per sex.
On PND 56, blood samples were taken by sampling time and per animal.

Source: Excerpted directly from the Applicant's Study Report, page 28

Table 3 Mean Toxicokinetic Exposure Parameters for Metabolite F17400

F17400- Mean toxicokinetic exposure parameters

Sex	Male	Female	Male	Female	Male	Female
Dose-level (mg/kg/day)	10		35		120	
PND 21:						
. C_{max} (ng/mL)	57.8	53.5	134	141	389	242
. T_{max} (h)	1.0	1.0	4.0	4.0	4.0	4.0
. AUC_{last} (ng.h/mL)	320	299	845	865	3051	2790
PND 56:						
. C_{max} (ng/mL)	113	116	217	209	500	299
. T_{max} (h)	1.0	1.0	1.0	1.0	4.0	8.0
. AUC_{last} (ng.h/mL)	397	344	1309	1563	4304	3875

On PND 21, blood samples were pooled by sampling time and per sex.
On PND 56, blood samples were taken by sampling time and per animal.

Source: Excerpted directly from the Applicant's Study Report, page 28

Pivotal Study in Juvenile Rats:

Study Title: Toxicity Study by Oral Route (Gavage) in Juvenile Rats

Study no.:	Sponsor Study № LVM-TX-06/41160 RSR (Laboratory Study № 41160 RSR)
Study report location:	EDR (SDN 262, 3/22/2016)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 16, 2014
GLP compliance:	OECD [(as revised in 1997, ENV/MC/CHEM (98) 17 and all subsequent OECD consensus documents)] and Directive 2004/10/EC of the European Parliament.
QA statement:	Yes
Drug, lot #, and % purity:	F2695 (levomilnacipran); Batch № 526 and 513; purity 99.9% (both batches)

Key Study Findings

- Premature death (one HDM, found dead on study Day 53)

- Hunched posture, piloerection, and half-closed eyes in HDM and HDF

- Lower mean body weight in HDM and HDF (up to -16% and -8%, respectively, compared to controls on study Days 57/67) and body weight gain in HDM and HDF associated with lower food consumption

- Significant delay in sexual maturation (vaginal opening) in HDF

- Lower bone mineral content in HDM and HDF. Slight decrease in mean tibia length in HDF

- Hepatic centrilobular hypertrophy (slight) and decreased red pulp of the spleen

- The NOAEL was 35 mg/kg/d based on lower body weight and decreased body weight gain at the high dose of 120 mg/kg/d, which corresponds to an AUC_{last} of 5965 ng*h/mL and 8707 ng*h/mL on PND 90, in males and females, respectively.

Methods

Doses:	0, 10, 35, 120 mg/kg/d
Frequency of dosing:	Once daily for 70 days (from PND 21 to PND 90, inclusive)
Route of administration:	Orally by gavage
Dose volume:	5 mL/kg/d
Formulation/Vehicle:	Solution/Drinking water treated by reversed osmosis using Elix 5 (Millipore)
Species/Strain:	Sprague-Dawley, RjHan:SD (Rats CD®)
Number/Sex/Group:	16/sex/group as Subset I and Subset II (Subsets I & II are main study animals; Subset I was primarily used for toxicology and developmental neurologic development evaluation during treatment and Subset II was primarily used for reproductive development evaluation and long bone growth. Subset II was also considered as recovery phase animals until initiation of mating), and 18/sex/test item groups (three/sex in controls) as satellite animals for TK evaluation**.**
Age at start of experiment:	PND 21
Weight at start of experiment:	44 to 60 g (males) and 42 to 60 g (females)
Study design:	This study is a combined repeat dose, neurobehavioral and fertility study in juvenile rats. On PND 20 or PND 21, the juvenile rats were separated from their dams and were housed by 3 or 4, by sex and group. Juvenile Sprague-Dawley rats were treated orally by gavage with F2695 (0, 10, 35, and 120 mg/kg/d) for 70 days (Post-Natal Day 21 through 90). General toxicology, neurobehavioral, and fertility assessments were made on all main study animals (Subset I and Subset II). TK evaluation was made (on PND 21 and PND 90) on satellite animals. During the treatment-fee period (PND 92 onwards), all Subset II animals were housed individually (i.e., 4 weeks) before pairing for reproductive function evaluation.
Deviation from study protocol:	There were several minor deviations; deviations from the protocol are provided in Appendix I, Protocol amendments. These deviations were considered not to have compromised the validity or integrity of the study.

OBSERVATION AND RESULTS

Assignment of F1 pups to treatment groups:

Based on body weights recorded on PND 20 and clinical condition, pups were allocated using a stratified body weight procedure to constitute four homogenous groups. The required number of pups within the closest weight range was used.

CLINICAL EXAMINATIONS

- **Mortality and morbidity**
  (Each animal was checked once a day prior to the start of treatment and at least twice a day during the treatment and treatment-free periods, including weekends and public holidays).

Results: One HDM of Subset I (D20396) was found dead on study Day 53 (PND 73). On PND 72, this male was found to have half-closed eyes; however, there were no changes in body weight or food consumption. At necropsy, a minimal decrease in red pulp of the spleen was observed and appears to be treatment-related. Although the Sponsor could not determine the cause death, this Reviewer considers the death as treatment-related.

There were no deaths in Subset II and satellite animals.

- **Clinical signs**
  (Observed twice daily)

Results: Treatment-related clinical signs such as piloerection, and/or half-closed eyes (perhaps toxicologically significant) were observed in most of the high dose animals of both sexes. In addition, ptyalism was observed in some of the mid- and high dose males and females. Half-closed eyes were also observed in all high dose males and females in the satellite group, although only on one occasion. There were no treatment-related clinical signs during the recovery period (PND 91- PND 149; Subset II animals).

- **Body weight and body weight changes**

(Subsets I & II; measured twice weekly before allocation to groups, on the first day of treatment, and then twice weekly during the treatment and treatment-free periods. Subset II females were also weighed on Days 0, 4, 7, 11, and 15 *post coitum*).

Results:
Mean Body weights: Treatment-related lower mean body weights in HDM and HDF (up to -16% and -8%, respectively, compared to controls on study Days 57/67; Table 4, below). The magnitude of body weight decreases in HDM may be considered adverse. The slight decreases

in body weights at the mid dose may not be of any toxicological significance. There were no effects on body weights at the low dose.

Table 4 Mean Body Weight and Mean Body Weight Change During the Treatment Period (Subsets I and II)

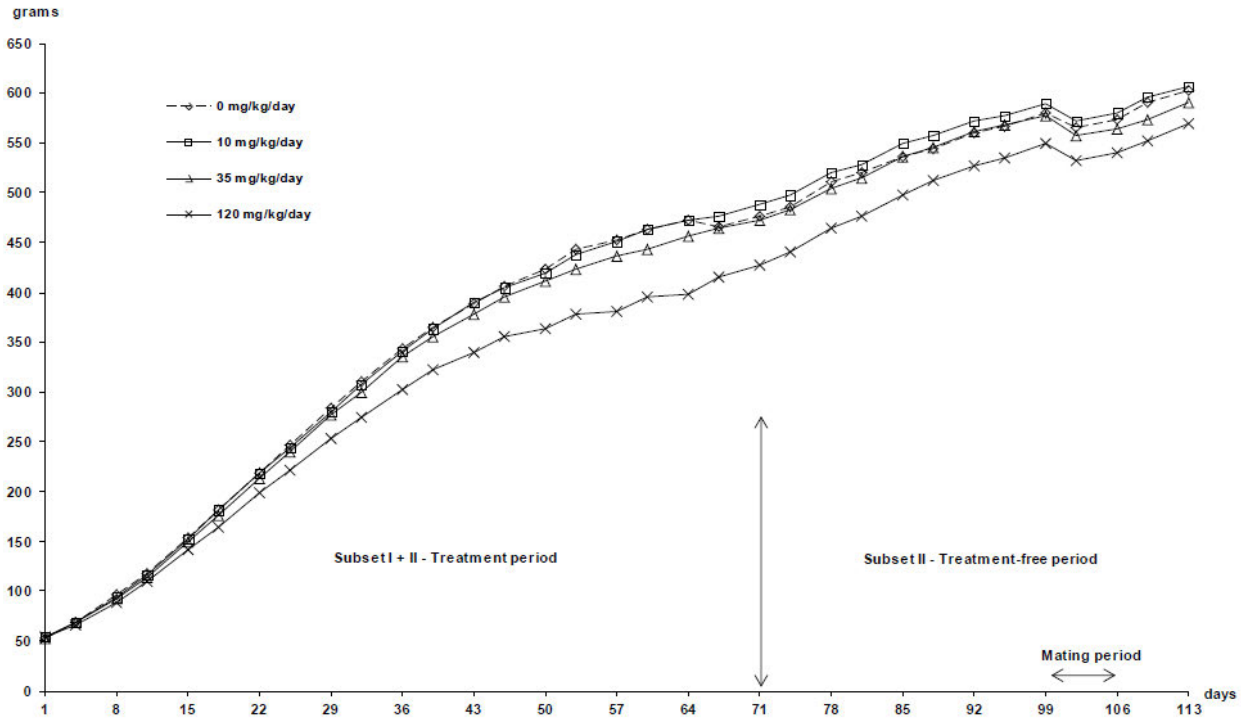
Sex	Male				Female			
Dose-level (mg/kg/day)	0	10	35	120	0	10	35	120
Number of animals	32	32	32	32/31(a)	32	32	32	32
Mean body weight (g)								
Day 1 (PND 21)	53	54 (+2)	53 (0)	54 (+2)	51	51 (0)	51 (0)	50 (-2)
Day 4	69	68 (-1)	68 (-1)	66* (-4)	65	65 (0)	63 (-3)	62* (-5)
Day 11	118	116 (-2)	114 (-3)	109** (-8)	105	104 (-1)	100* (-5)	97** (-8)
Day 18	182	181 (-1)	176 (-3)	164** (-10)	146	146 (0)	142 (-3)	139* (-5)
Day 53	443	438 (-1)	423* (-5)	378** (-15)	261	261 (0)	249 (-5)	240** (-8)
Day 57	452	451 (0)	437 (-3)	381** (-16)	266	266 (0)	254 (-5)	245** (-8)
Day 64	472	472 (0)	456 (-3)	398** (-16)	274	276 (1)	265 (-3)	254** (-7)
Day 67 (PND 90)	466	477 (+2)	465 (0)	416** (-11)	277	278 (0)	268 (-3)	257** (-7)
Mean body weight change (g)								
Days 1/4	+15	+15	+15	+12**	+13	+14	+13	+11**
Days 4/8	+27	+26	+25**	+23**	+22	+22	+20**	+20**
Days 8/11	+22	+22	+21	+20**	+18	+17	+16*	+15**
Days 15/18	+29	+29	+27**	+24**	+17	+18	+17	+17
Days 39/43	+24	+26	+23	+17	+14	+13	+10*	+9**
Days 46/50	+19	+15	+16	+8**	+10	+9	+9	+3**
Days 50/53	+18	+18	+12**	+15	+9	+9	+7	+6
Days 53/57	+9	+13	+15*	+5	+5	+5	+5	+5
Days 57/60	+11	+11	+6	+15	+4	+5	+4	+3
Days 60/64	+9	+9	+13	+2	+4	+5	+7	+6
Days 64/67	-6	+5	+9	+17**	+3	+3	+3	+4
Days 1/67	*+413*	*+423 (+2)*	*+412 (0)*	*+362** (-12)*	*+226*	*+228 (+1)*	*+217+ (-4)*	*+207** (-8)*

( ): in brackets, percentage (%) difference *vs.* controls.
/: not applicable,
(a): male D20396 dead on study Day 53, Statistical significance: *: p<0.05; **: p<0.01.

Source: Excerpted directly from the Applicant's Study Report, page 51

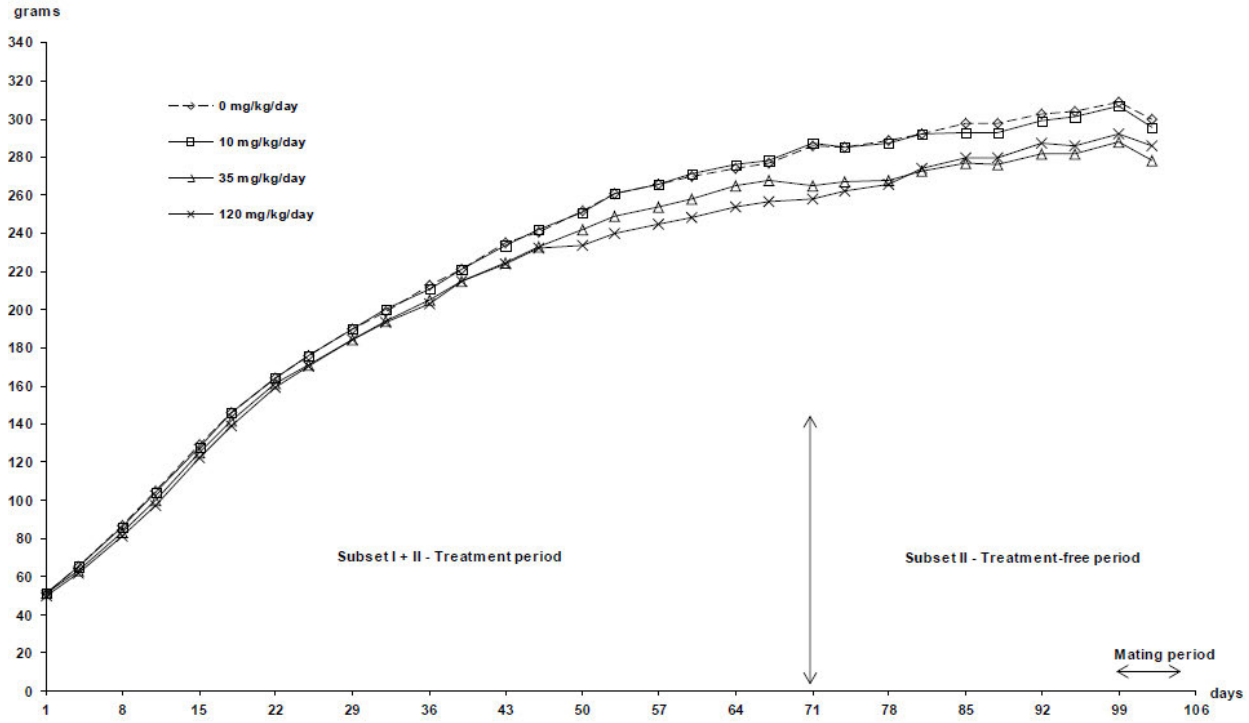
Mean body weight changes: During the treatment period, there were significant treatment-related decreases in body weight gains in HDM and HDF (-12% and -8%, respectively, compared to control; Table 4, above, and Figure 1 and Figure 2, below). Body weight changes at mid- and low dose were comparable to controls.

Figure 1 Mean Body Weight in Subset I & II Male Rats



Source: Excerpted directly from the Applicant's Study Report, page 76

Figure 2 Mean Body Weight in Subset I & II Female Rats



Source: Excerpted directly from the Applicant's Study Report, page 77

Mean body weight/body weight changes in Subset II animals (treatment-free period) are shown in Table 5, below. In Subset II, both HDM and HDF had lower mean body weights than controls at the end of the treatment period (see Day 71 body weights in HDM and HDF; -10% lower than control). However, it appears that HDM recovered slower (from study Day 88) than HDF (from study Day 74).

There were no treatment-related effects on body weight and body weight gain during the pregnancy period in Subset II animals.

Table 5 Mean Body Weight and Mean Body Weight Change During the Treatment-Free Period in Subset II Animals

Sex	Male				Female			
Dose-level (mg/kg/day)	0	10	35	120	0	10	35	120
Number of animals	16	16	16	16	16	16	16	16
Mean body weight (g)								
Day 71	477	489 (+3)	473 (-1)	428# (-10)	286	287 (0)	265 (-7)	258* (-10)
Day 74	486	498 (+2)	483 (-1)	441** (-9)	285	285 (0)	267 (-6)	262 (-8)
Day 78	511	521 (+2)	504 (-1)	464** (-9)	289	287 (-1)	268 (-7)	266 (-8)
Day 81	520	528 (+2)	515 (-1)	477** (-8)	292	292 (0)	273 (-7)	274 (-6)
Day 85	537	549 (+2)	536 (0)	498* (-7)	298	293 (-2)	277 (-7)	280 (-6)
Day 88	544	557 (+2)	545 (0)	512 (-6)	298	293 (-2)	276 (-7)	280 (-6)
Day 99	580	589 (+2)	578 (0)	550 (-5)	309	307 (-1)	288 (-7)	292 (-6)
Day 113	603	607 (+1)	591 (-2)	570 (-5)	/	/	/	/
Mean body weight change (g)								
Days 71/74	+9	+9	+10	+13	-1	-3	2	4
Days 81/85	+17	+20	+21	+22	+6	+1**	+4	+6
Days 85/88	+6	+9	+9	+14#	0	0	-1	0
Days 95/99	+13	+11	+10	+15	+5	+6	+6	+6
Days 109/113	+12	+12	+18	+18	/	/	/	/

Study Day 1 = PND 21,
(): in brackets, percentage (%) difference *vs.* controls,
/: not applicable, Statistically significant: *: p<0.05, **: p<0.01, #: p<0.001.

Source: Excerpted directly from the Applicant's Study Report, page 52

- **Food consumption**

(Subset I & II; measured twice weekly from weaning until pairing for mating and then during gestation)

Results: Treatment-related significant decreases in food consumption in HDM and HDF during the period of study Days 1 to 4 (-13% for both sexes, compared to controls) and during the period of study Days 50 to 53 (-10% and -19%, compared to controls, for males and females, respectively). There were no treatment-related variations in mean food consumption at mid- and low doses. Similarly, when compared to control, there were no significant differences in mean food consumption during the treatment-free period (Subset II), both in males and females. Likewise, mean food consumption in Subset II females during gestation were comparable to control.

- **Long bone growth**

(Subset II; long bone growth was measured weekly on 10/animals/sex/group, from PND 21 to PND 90 and on 10 females/group up to mating. The length of the tibia of each animal was accurately measured using a qualified caliper; reported to an accuracy of 0.1 mm).

Results: There were no treatment-related effects on long bone growth in male rats. However, in HDF, when compared to control, there was a slight decrease in mean tibia length on PND 56 (33.63 mm versus 35.99 mm; Table 6, below). Even though there was a reverse trend from PND 91 onwards (treatment-free period), the above decrease (-7%, compared to control) is considered treatment-related, since the effect was not completely reversed at the end of the recovery period.

Table 6 Mean Tibia Length of Subset II Females

Sex	Females				
Dose-level (mg/kg/day)	0	10	35	120	Reference Data [min.; max.]
Number of animals	10	10	10	10	
PND 21 (study Day 1)	19.35	20.13 (+4)	20.51 (+6)	20.75 (+7)	[22.98; 24.17]
PND 56 (study Day 36)	35.99	35.64 (-1)	35.01 (-3)	33.63 (-7)	[34.07; 36.30]
PND 91 (study Day 71)	41.04	40.59 (-1)	39.81 (-3)	39.54 (-4)	/
PND 119 (study Day 99)	41.91	41.53 (-1)	40.32 (-4)	39.89 (-5)	/

n = 10 first animal/sex/group.
(): in bracket, percentage (%) difference *vs.* controls.
/: no reference data.
Reference Data: (b) (4) *Study Nos. 35439 RSR* (16 females) and *36105 RSR* (16 females, treatment period: PND 7 to PND 77).

Source: Excerpted directly from the Applicant's Study Report, page 56

- **Neurologic development**

  - **Reactivity to manipulation or to different stimuli (Functional Observation Battery)**

<u>Detailed clinical examination (Subset I)</u>

Ten Subset I animals/sex/group were observed once (on PND 83 or 84), in the cage, in the hand, and in the standard arena. A variety of parameters and reflexes were assessed and graded. Auditory startle reflex was also performed on Subset II animals (10 animals/sex/group), approximately 2 weeks prior to mating.

Results: There were no treatment-related effects on any of the clinical examination parameters, except myosis. All HDM had myosis (minimal); however, the Sponsor stated that there were no

correlates at ophthalmological examination and therefore, considered to be of no toxicological significance.

Reactivity to stimuli (Subset I)

Results: There were no treatment-related effects on visual stimulus response, pupillary reflex, auditory startle reflex, and forelimb strength.

Auditory startle reflex (Subset II) on PND 107

No treatment-related effects on auditory startle reflex.

- **Motor activity**
  (Subset I; measured on the same animals tested for reactivity to manipulation or to different stimuli and on the same day using an automated infra-red sensor equipment recording individual animal activity over a 60- minute period. The following parameters were recorded: movements within the front of the cage, movements within the back of the cage, back and forth movements and vertical movements).

Results: There were no treatment-related effects on the mean number of horizontal movements and rearing in both sexes.

- **Learning and memory**
  Learning and memory tests were conducted using Cincinnati Water Maze (multiple T-maze) in all Subset I animals on PND 68 to PND 80 (treatment phase). Learning and memory tests were not assessed at the end of the treatment-free period in Subset II animals because there were no treatment-related effects on learning and memory in Subset I animals.

On the day before the first trial of the assessment, all Subset I animals were conditioned by being placed in a straight channel for one trial. The test comprised of two consecutive trials per day for 3 days (learning phase) followed (after an interval of 4 to 6 days) by three consecutive trials on 1 day (memory phase). The day following the memory phase, the animals had three consecutive trials where they were placed at the finish with the exit as the start point (reverse phase). At each trial, the following parameters were recorded:

- Result of the test (positive or negative)
- Time for positive test
- Number of wrong directions

Results: There were no treatment-related effects on learning or memory function in Subset I males and females. The number of animals failing the test, the average time taken to complete the test, and the mean number of errors occurring during the test were comparable to controls.

- **Reproductive development**

Subset II; all males were assessed each day, from PND 38 until positive, for cleavage of the balanopreputial groove (preputial separation). All females were assessed each day, from PND 28 until positive, for vaginal opening. Median times to preputial separation and vaginal opening were calculated. The body weight of each animal was recorded on the day of preputial separation or vaginal opening.

Results: There were no treatment-related effects in males on the median age at which preputial separation occurred.

A treatment-related delay in the development of vaginal opening was observed in HDF; the mean day of development of vaginal opening was approximately four days later than controls as well as historical controls (see Table 7, below). This effect does not appear to be due to decrease in body weight. However, this delay did not have an effect on mating or fertility (discussed below).

Table 7 Mean Reproductive Development Data (Subset II Females)

Sex	Female				*HCD*
Dose-level (mg/kg/day)	0	10	35	120	*[min. - max.]*
Number of animals	16	16	16	16	
Median age (days)	34.0 ± 1.1	34.0 ± 1.8	35.0 ± 2.1	38.5 ± 2.3	*[34.2 - 34.4)*
Mean body weight (g)	119.8	119.5	123.0	138.0	*[120.2 - 128.1]*

HCD: Historical Control Data (Sprague-Dawley rats, two-generation reproduction toxicity study in rats, October 2009 to July 2012), n = 74.

Source: Excerpted directly from the Applicant's Study Report, page 58

- **Ophthalmology**

(Ophthalmologic examinations were performed by a veterinary ophthalmologist on all Subsets I and II pups on PND 20/21 prior to dosing and at the end of the treatment period (on PND 85, 86 or 87). The pupils of the pups were dilated with tropicamide. After assessment of the corneal reflex, the appendages, optic media and fundus were examined by indirect ophthalmoscopy).

There were no treatment-related ophthalmology findings.

LABORATORY INVESTIGATIONS

Hematology, blood biochemistry, and urine analysis were performed for all Subset I animals at the end of the treatment period (on PND 90) and for all Subset II animals (as recovery animals)

prior to mating (on PND 120 and/or 121). The animals were fasted overnight prior to blood sampling and during urine collection.

- **Hematology**

  Results: There were no treatment-related changes in mean hematology parameters in males and females.

- **Blood biochemistry**

  Results: There were no noteworthy treatment-related changes in clinical chemistry parameters except slight increases in mean ALP in HDM and HDF on PND 90 (26% and 22%, respectively).

- **Urinalysis**

  There were no treatment-related changes in urinalysis parameters.

MATING AND FERTILITY ASSESSMENT

Mating trials were performed from PND 122 (at least 4 weeks after cessation of treatment period, sibling pairing was avoided). All mated females were sacrificed on Day 15 *post-coitum*. Females with no evidence of mating were sacrificed 16 days after the end of the pairing period. The weight of the gravid uterus was recorded for each pregnant female (with at least one fetus). The ovaries and uterus were examined to determine the number of corpora lutea, number and distribution of embryos, number and distribution of early and late resorptions, and number and distribution of implantation sites.

- **Mating assessment**

Results: There were no treatment-related effects on male or female mating indexes and on males or female fertility indexes. Mean number of days taken to mate was similar among different treatment groups.

- **Estrous cycle**

Results: There were no treatment-related effects on estrous cycle parameters. The mean number of days in estrous and the mean number of estrous cycles were comparable between control and treatment groups.

- **Hysterectomy data**

Results: There were no treatment-related effects on the mean number of corpora lutea, number of implantation sites, live embryos, dead embryos, early resorptions and pre- or post-implantation losses. One HDF (D20724) had a low number of live embryos (six live *concepti*, compared to a mean of 14.4 in controls and it appears to be the reason for the slight decrease in the mean number of live embryos in HD group). The Sponsor considered this to be incidental and not treatment-related because there were no dead embryos, and the mean post-implantation loss was lower in HD group than in controls. Similarly, the slightly higher pre-implantation losses observed in all treated groups, compared to controls (however, were not statistically significant), were considered to be incidental by the Sponsor. For example, one LDF (D20614) had seven implantation sites and 12 corpora lutea; one MDF (D20663) had 12 implantation sites and 18 corpora lutea; one HDF had 16 implantation sites and 21 corpora lutea. Since this effect was observed in only one female in each group, it was considered to be incidental and not related to treatment with the test article.

- **Mean gravid uterus and net body weight changes**

Results: There were no treatment-related effects on mean gravid uterus weight, mean carcass weight, and net body weight change.

SEMINOLOGY (Subset II)

Subset II males were sacrificed after completion of the Subset II female hysterectomies. The left epididymis was removed, weighed and sperm from the cauda was sampled for motility and morphology investigations. For testicular sperm head count, the left testis was weighed and ground and sperm heads resistant to homogenization were counted in a Neubauer chamber. Results were expressed as the number of sperm head per gram of testis and the daily sperm production rate was calculated (using a time divisor of 6.10).

Results: There were no treatment-related effects on epididymal sperm motility, epididymal sperm count, sperm cell morphology, testicular sperm head count, and testicular daily sperm production rate.

TOXICOKINETICS

Blood samples were obtained from three satellite animals/sex/drug treated group for each time-point (six time-points for drug treated groups: 0 h, 0.5 h, 1 h, 4 h, 8 h, 24 h). Control blood samples were obtained from three satellite animals/sex at one time-point (1 h after dosing). Each animal was sampled twice (once on PND 21 and once on PND 90). Blood samples were taken from the orbital sinus under light isoflurane anesthesia. Bioanalysis of F2695 and its metabolite F17400 in the plasma samples was performed using a validated LC MS/MS method.

For both F2695 and F17400, the appropriate toxicokinetic parameters were calculated on PND 21 and PND 90.

The following tables (Table 8 and Table 9) summarize the toxicokinetic evaluation of the test item (F2695) and its metabolite (F17400) in juvenile male and female rats. All animals from treated groups were exposed to F2695. There was no evidence for the presence of F2695 or F17400 in plasma samples from the control group.

Table 8 Mean Toxicokinetic Data for Male Satellite Animals

		Juvenile male rat - PND 21					
		10 mg/kgLday		35 mg/kg/day		120 mg/kg/day	
Parameter	Unit	F2695	F17400	F2695	F17400	F2695	F17400
C_0	ng/mL	0	0	0	0	0	0
C_{max}	ng/mL	553	81.5	2810	153	5357	344
T_{max}	h	0.5	1.0	1.0	4.0	4.0	4.0
T_{last}	h	8.0	8.0	8.0	8.0	24	24
AUC_{last}	h*ng/mL	1300	342	9447	897	38991	3264

		Juvenile male rat - PND 90					
		10 mg/kgLday		35 mg/kg/day		120 mg/kg/day	
Parameter	Unit	F2695	F17400	F2695	F17400	F2695	F17400
C_0	ng/mL	0	0	1.28	1.79	48.4	21.2
C_{max}	ng/mL	649	96	1778	183	6936	587
T_{max}	h	0.5	0.5	0.5	1.0	4.0	4.0
T_{last}	h	8.0	8.0	8.0	8.0	24	24
AUC_{last}	h*ng/mL	1116	377	5965	1114	49823	5406

Source: Excerpted directly from the Applicant's Study Report, page 68

Table 9 Mean Toxicokinetic Data for Female Satellite Animals

		Juvenile female rat - PND 21					
		10 mg/kgLday		35 mg/kg/day		120 mg/kg/day	
Parameter	Unit	F2695	F17400	F2695	F17400	F2695	F17400
C_0	ng/mL	0	0	0	0	0	0
C_{max}	ng/mL	616	79.6	2984	150	6226	421
T_{max}	h	0.5	1.0	0.5	4.0	4.0	4.0
T_{last}	h	8.0	8.0	8.0	8.0	24	24
AUC_{last}	h*ng/mL	1565	335	8209	869	41479	3477

		Juvenile female rat - PND 90					
		10 mg/kgLday		35 mg/kg/day		120 mg/kg/day	
Parameter	Unit	F2695	F17400	F2695	F17400	F2695	F17400
C_0	ng/mL	0	0	2.49	2	123	33.9
C_{max}	ng/mL	997	85.7	2292	149	5715	345
T_{max}	h	0.5	1.0	0.5	1.0	0.5	4.0
T_{last}	h	8.0	8.0	24	24	24	24
AUC_{last}	h*ng/mL	1669	370	8707	1349	52028	4084

Source: Excerpted directly from the Applicant's Study Report, page 69

Results: Systemic exposure to F2695 in terms of AUC_{last} increased with increasing doses in both males and females on PND 21 and PND 90. For the metabolite, F17400, the overall exposure on PND 21 and PND 90 was proportional to F2695 dose. There was no accumulation of F2695 and its metabolite between PND 21 and PND 90.

PATHOLOGY

Subset I animals: On completion of the treatment period (PND 90), after at least 14 hours fasting, surviving animals were deeply anesthetized (sodium pentobarbital, i.p.) and sacrificed by exsanguination.

Subset II animals: The females were sacrificed, without overnight fasting, by CO_2 inhalation followed by cervical dislocation on Day 15 post-coitum (when mated) or 16 days after the end of the pairing period when no positive evidence of mating was observed. On completion of the female hysterectomies, the males were sacrificed, without overnight fasting, by exsanguination after a deep anesthesia (sodium pentobarbital, i.p). Body weight of each animal (Subset I and II) was recorded before sacrifice at the end of the treatment period. The organs (in Table 36, in the Appendices, below) were weighed wet soon after dissection and the ratio of organ weight to body weight was calculated. In addition, a complete macroscopic *post-mortem* examination was performed on all study animals.

A microscopic examination was performed by the Study Pathologist (Dr. L. Longeart) on:

- All tissues in Table 36, below (from control and high-dose groups of Subset I, animals sacrificed at the end of the treatment period),
- All animals that died in Subset I,
- All macroscopic lesions in Subset I and II,
- Liver and spleen from all animals of the low- and mid- dose groups in Subset I and, from the control, low-, mid- and high-dose groups in Subset II.

Pathology peer review was performed by Dr. Celine Thuilliez at the test site. The pathology report represents a consensus between the Study Pathologist and peer review Pathologist.

Organ weights and terminal body weights

- Subset I: Terminal body weights were lower in HDM (-15%, $p \leq 0.01$) and HDF (-6%, $p \leq 0.05$). Treatment-related changes in liver and spleen weights were observed in mid- and high dose groups (Table 10, below). Although the absolute liver weight was statistically lower in HDM, the relative (relative to body weight) liver weights were slightly higher in HDM and HDF; this was correlated microscopically with centrilobular hypertrophy (see Table 11, below). The absolute and relative spleen weights were lower in a dose-related manner in both males and females. This was correlated microscopically with minimal decreased red pulp in MDM and HDM and HDF (see Table 11, below).

Table 10 Treatment-related Organ Weight Differences

	Male			Female		
Dosage (mg/kg/day):	10	35	120	10	35	120
Liver						
Absolute	-4	-2	-11*	-2	0	+2
Relative (*vs.* body weight)	-1	+4	+5	-3	+1	+9*
Spleen						
Absolute	-10	-21**	-33**	-13	-18**	-25**
Relative (*vs.* body weight)	-8	-16**	-21**	-14*	-17**	-20**

*: p≤ 0.05; **: p≤ 0.01 (either with the Dunnett or the Dunn test).
Source: Excerpted directly from the Applicant's Study Report, page 69

There were no treatment-related effects on any other organ weights; although some of the differences reached statistical significance, the differences were minimal and may be attributed to the lower terminal body weight.

- Subset II: There were no treatment-related effects on terminal body weight or organ weights, including liver and spleen weights (perhaps reflecting recovery during the treatment-free period).

❖ **Macroscopic observations**

Unscheduled death: There were no treatment-related macroscopic findings in the HDM that was found dead on PND 73 (D20396; Subset I); however, the cause of death may be treatment-related (as discussed in 'Mortality and morbidity' above).

Subsets I and II: There were no treatment-related macroscopic findings; some minor macroscopic observations in various treatment groups were considered as spontaneous changes by the Sponsor. These findings were random and showed no dose-response relationship.

❖ **Microscopic observations**:

- Unscheduled death: The only treatment-related microscopic finding in the HDM that was found dead on PND 73 (D20396; Subset I) was a minimal decrease in red pulp of the spleen.

- Subset I: Treatment-related minimal to slight centrilobular hypertrophy of the liver was observed in MDM (2/16), HDM (12/16), and HDF (12/16). In addition, treatment-related minimal decrease in splenic red pulp was observed in MDM (2/16), HDM (3/16), and HDF (2/16; see Table 10, below).

- Subset II: The treatment-related microscopic changes (such as those in Subset I animals) observed at the end of the treatment period were no longer observed in Subset II animals, indicating full recovery.

Table 11 Treatment-Related Histological Changes (including premature decedent *)

	Male				Female			
Dosage (mg/kg/day):	0	10	35	120	0	10	35	120
Liver								
Centrilobular hypertrophy								
minimal	0	0	2	3	0	0	0	4
slight	0	0	0	9	0	0	0	8
Spleen								
Decreased red pulp								
minimal	0	0	2	3	0	0	0	2

*: n = 16.

Source: Excerpted directly from the Applicant's Study Report, page 70

BONE MINERAL DENSITY

Dual-energy X-ray Absorptiometry measurements were performed within 7 days of sampling on the left femur (kept in 10% buffered formalin at RT) for all Subset I animals sacrificed at the end of the treatment period and for control and high-dose, Subset II animals sacrificed at termination (males: after all hysterectomies had performed; females: on Day 15 *p.c.*). A Discovery A QDR Series X-ray bone densitometer (Hologic, France) was used for the measurements, with application software version 12.1. Bone Mineral Content (BMC; g) and bone area (cm^2) were measured, and the Bone Mineral Density (BMD; g/cm^2) was calculated as BMC (g) divided by projected bone area (cm^2).

Measurements: The femur was scanned using regional high resolution application software with the following settings:

Scan width: 5.0 cm,
Line spacing: 0.0311 cm,
Point resolution: 0.0311 cm.

The scan length was specified in the raw data of the study. The bone was placed under 2.5 cm of saline solution in a container to mimic soft tissue and positioned on the scanner deck for measurement.

Analysis: Each scan was analyzed, and BMD was computed as follows:
Whole femur,
Distal metaphysis,
Diaphysis.
Proximal femur.

The settings of Region of Interest were kept constant for all specimens and determined in relation to the distal extremity of the bone for the distal metaphysis and diaphysis parts.

Results: Results of the bone mineral density measurements are summarized in Table 12, below. Briefly, at the end of the treatment period (Subset I), there were treatment-related lower mineral content in males and females, when compared to their respective controls. The decreases were as much as -10% in males and -9% in females for the distal metaphysis, both statistically significant. Similarly, the global mineral content was lower than control in HDM (-4%; $p \leq 0.01$) and HDF (-8%; $p \leq 0.01$). These effects are consistent with the lower mean body weight observed at the high dose. At the end of the treatment-free period (Subset II), a lower global mineral content was still observed in HDM (-4%; $p \leq 0.05$) and HDF (-4%; $p \leq 0.05$); however, there was an overall tendency towards a return to control values. At the mid- and low doses, there were no treatment-related effects on bone mineral content.

Table 12 Mean Bone Mineral Density Data

	Mean femur mineral (expressed in g/cm^2)							
Sex	Male				Female			
Dose-level (mg/kg/day)	0	10	35	120	0	10	35	120
Subsets I								
Number of animals evaluated	16	15	15	15	15	16	16	16
- global	0.24	0.24 (0)	0.24 (0)	0.23** (-4)	0.24	0.23 (-4)	0.23 (-4)	0.22** (-8)
- proximal part	0.24	0.24 (0)	0.24 (0)	0.22** (-8)	0.24	0.23 (-4)	0.23 (-4)	0.23** (-4)
- distal part (metaphysis)	0.20	0.19 (-5)	0.19 (-5)	0.18** (-10)	0.23	0.23 (0)	0.23 (0)	0.21** (-9)
- diaphysis	0.19	0.19 (0)	0.18 (-5)	0.18* (-5)	0.17	0.17 (0)	0.18 (+6)	0.17* (0)
Subsets II								
Number of animals evaluated	15	/	/	16	16	/	/	16
- global	0.28	/	/	0.27* (-4)	0.26	/	/	0.25* (-4)
- proximal part	0.27	/	/	0.26 (-4)	0.26	/	/	0.25* (-4)
- distal part (metaphysis)	0.22	/	/	0.22 (0)	0.26	/	/	0.24 (-8)
- diaphysis	0.22	/	/	0.21 (-5)	0.20	/	/	0.19* (-5)

( ): in bracket, percentage (%) difference *vs.* controls.
/: not measured.
Statistically significant: *: p<0.05, **: p<0.01.

Source: Excerpted directly from the Applicant Study Report, page 72

6 Clinical Pharmacology

6.1. Executive Summary

There were no new clinical pharmacology studies conducted to support this submission and no new labeling updates have been included in sections relevant to the clinical pharmacology. However, the Sponsor submitted the results of the pediatric studies (Study LVM-MD-11 in adolescent participants with MDD aged 12 to 17 years and Study LVM-MD-14 in pediatric participants with MDD aged 7 to 17 years). The Sponsor updated the previously developed population pharmacokinetic (PPK) model in adults with the sparse PK data collected in the pediatric studies. Given there are no updates to the label based on the PPK analysis, the PPK analyses have not been extensively reviewed. Based on the Sponsor's PPK simulations, the exposures to levomilnacipran in children 7 to <12 years old and adolescents (12 to <18 years) were relatively similar but slightly lower compared to adults.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In this efficacy supplement, the Applicant is submitting the data from Study LVM-MD-11, titled "A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Adolescent Patients with Major Depressive Disorder" and LVM-MD-14, titled "A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Pediatric Patients 7 to 17 Years with Major Depressive Disorder.

Controlled efficacy data for the 12-to-17-year-old population consist of results from Study LVM-MD-11 and LVM-MD-14 and controlled efficacy data for the 7-to-17-year-old population consist of results from LVM-MD-14. Study LVM-MD-11 was a fixed-dose study and LVM-MD-14 was a flexible-dose study. See Table 13 for a listing of clinical trials relevant to this NDA efficacy supplement.

Table 13. Listing of Clinical Trials Relevant to NDA 204168/S10

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
LVM-MD-11	02431806	Randomized, DB, placebo- and active-controlled, parallel-group, fixed-dose study	Levomilnacipran (LVM) 40 mg, LVM 80 mg, fluoxetine 20 mg, or placebo by mouth once daily	Change from baseline to Week 8 in Children's Depression Rating Scale-Revised (CDRS-R) total score	10-week duration, including 1-week screening and washout, 8-week treatment period 1-week DB taper period	Total = 547 LVM 40 mg/day = 134 LVM 80 mg/day =138 Fluoxetine 20 mg/day = 134 Placebo = 141	Subjects ages 12 to 17 years with MDD	59 sites in United States
LVM-MD-14	03569475	Randomized, DB, placebo- and active-controlled, parallel-group, flexible-dose study	Levomilnacipran 40 mg/day or 80 mg/day (optional starting at week 8), fluoxetine 20 mg/day or placebo	Change from baseline to Week 8 in Children's Depression Rating Scale-Revised (CDRS-R) total score	10-week duration, including 1-week screening and washout, 8-week treatment period	Total = 492 LVM 40 to 80 mg/day = 166 Fluoxetine	Subjects ages 7 to 17 years with MDD	47 sites in the United States

					1-week DB taper period	20 mg/day = 166 Placebo = 160		

Source: Reviewer-created from clinicaltrials.gov, accessed July 2022, and Applicant's Tabular Listing of All Clinical Studies, Study LVM-MD-11 and LVM-MD-14
Abbreviations: LVM – levomilnacipran; CDRS-R – Children's Depression Rating Scale-Revised; MDD – major depressive disorder

7.2. Review Strategy

The efficacy and safety review focused on Study LVM-MD-11 and Study LVM-MD-14. These studies are described in more detail in Section 8.1.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study LVM-MD-11

Trial Design

LVM-MD-11 was a multicenter, randomized, DB, placebo- and active-controlled (fluoxetine), parallel-group, fixed dose study in subjects ages 12 to 17 years with MDD. The study was approximately 10 weeks in duration, with a 1-week screening/washout period, an 8-week DB treatment period, and a 1-week DB taper period. The study was conducted at 59 sites in the United States.

To be eligible for inclusion in the study, subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD. Subjects were also required to have a score of at least 40 on the Children's Depression Rating Scale-Revised (CDRS-R) and a Clinical Global Impressions-Severity (CGI-S) score of at least 4 at Screening and Baseline. The Kiddie Schedule for Affective Disorders-Present and Lifetime (K-SADS-PL) was used to confirm the diagnosis of MDD and to document the subject's psychiatric history. Female subjects were required to have a negative pregnancy test at Screening. Subjects were excluded from the study based on a number of psychiatric, treatment-related, and other medical criteria. Notable exclusion criteria included any current (past 3 months) principal DSM-IV-TR-based diagnosis of an Axis I disorder other than MDD that was the primary focus of treatment, subjects with conduct disorder, and subjects with any suicide attempt within the past year, or significant risk at Screening or Baseline.

Subjects who met eligibility criteria at Baseline (Visit 2) were randomized in a DB fashion to one of four treatment groups: placebo, levomilnacipran 40 mg/day, levomilnacipran 80 mg/day, or fluoxetine 20 mg/day in a 1:1:1:1 ratio. Doses of levomilnacipran were selected based upon the PK model submitted with NDA 204168 (Study VM-MS-01, 2012).

Concomitant treatment with antidepressants, anxiolytics, antipsychotics, or anticonvulsants/mood stabilizers, or psychoactive herbal remedies were prohibited. Prohibited medications or herbal substances were discontinued and stabilized for at least 2 weeks preceding the Baseline visit. Amphetamines were allowed as treatment for attention deficit/hyperactivity disorder (ADHD) at a dose that was stable for at least 60 days before Screening. Treatment with other medications for ADHD (clonidine, atomoxetine, guanfacine) was not allowed. Zolpidem, zaleplon, eszopiclone, and melatonin were permitted up to 3 times weekly for sleep but were not permitted within the 8 hours preceding any behavioral assessments.

The study consisted of three periods (see Figure 3 for the Applicant's study design schematic):

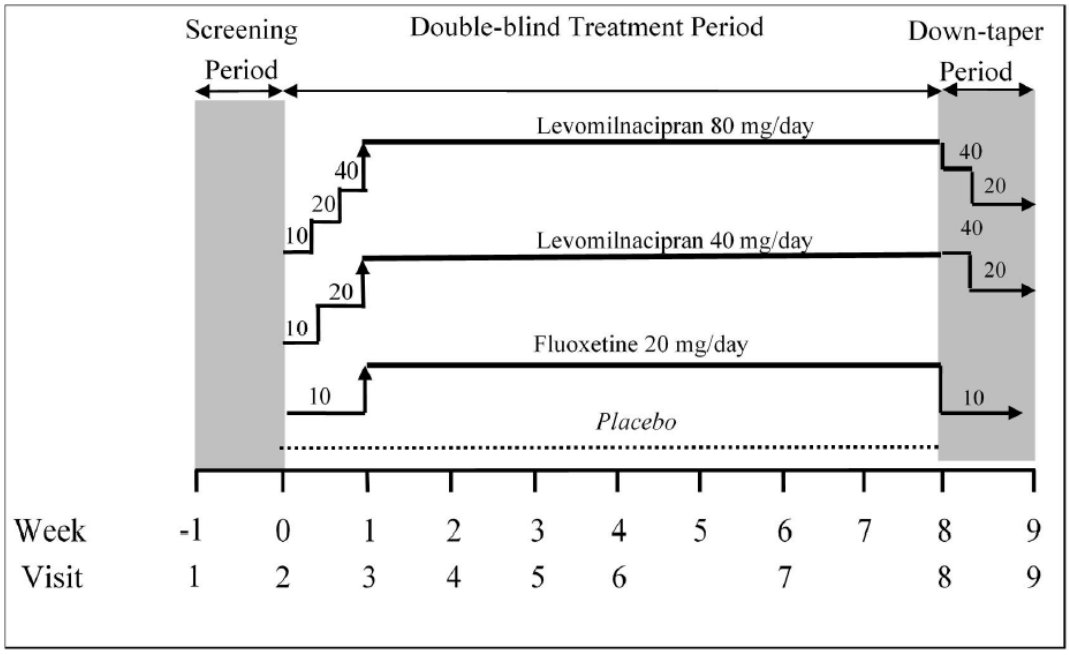
- Screening/Washout Period: 1 week
- DB Period: 8 weeks

  Doses of levomilnacipran and fluoxetine were titrated during the first 7 days of the DB period. Subjects reached the target dose of their assigned drug at the beginning of Week 2 of the period.

- DB Taper Period: 1 week

  Levomilnacipran (both the 40-mg and 80-mg groups) was administered at 40 mg on Days 1 and 2, and 20 mg on Days 3 through 7. Fluoxetine was administered at 10 mg daily on Days 1 through 7.

Figure 3. Study LVM-MD-11 Study Schematic



Source: Applicant's Clinical Study Report (CSR), page 26

Clinical Reviewer's Comment: The study design appears reasonable to evaluate the effect of levomilnacipran in pediatric MDD. The fluoxetine arm was included as an active control to assess assay sensitivity because it is a selective serotonin reuptake inhibitor (SSRI) approved for the treatment of MDD in pediatric patients ages 8 years and older.

Study Endpoints

The primary efficacy endpoint for LVM-MD-11 was the change from Baseline to Week 8 in the CDRS-R total score. The CDRS-R is a clinician-rated scale consisting of 17 items. Depression symptoms are rated on a 5-point scale from 1 to 5 for the 14 items that rate verbal observations, and a 7-point scale from 1 to 7 for the three items that rate nonverbal observations. The total score ranges from 17 ("normal") to 113 ("severe depression").

The secondary efficacy endpoint for LVM-MD-11 was the change from Baseline to Week 8 in the CGI-S score. The CGI-S is a clinician-rated scale used to rate the severity of the subject's current state of mental illness compared with an MDD patient population. The score ranges from a scale from 1 to 7, with 1 indicating "normal, not at all ill", and 7 indicating "among the most extremely ill patients."

One additional efficacy endpoint was included. The Clinical Global Impression-Improvement (CGI-I) is a clinician-rated instrument that uses the clinician's clinical opinion of the total improvement or worsening of the subject's mental illness, rated on a scale from 1 to 7, with 1 indicating "very much improved" and 7 indicating "very much worse" relative to the Baseline visit.

Safety endpoints included adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), and growth evaluations.

Pharmacokinetic modeling analysis was included in a separate report (3055-S03-000).

Clinical Reviewer's Comment: The primary efficacy endpoint of change from Baseline to Week 8 in the CDRS-R total score is reasonable and consistent with other trials of depression in pediatric subjects with MDD. The safety evaluations likewise are appropriate for the safety parameters and concerns expected from this drug, class of drug, and MDD disease state.

Statistical Analysis Plan

The efficacy analyses were based on the intention-to-treat (ITT) Population, which consisted of all randomized patients who had baseline and at least one postbaseline assessment of the CDRS-R total score.

The primary efficacy parameter was the change from Baseline to Week 8 in CDRS-R total score. The Applicant performed the primary analysis for comparing levomilnacipran 40 mg versus placebo and levomilnacipran 80 mg versus placebo for the primary efficacy parameter using an mixed models for repeated measures (MMRM) approach with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline value-by visit interaction as covariates. An unstructured covariance matrix was

used to model the covariance of within-patient scores. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. This analysis only used the observed cases of post-baseline scores without imputation of missing values.

The secondary efficacy parameter was the change from Baseline to Week 8 in CGI-S score, which would be analyzed using the MMRM approach similar to the one used for the primary efficacy parameter. To control the overall type 1 error rate for the multiple comparisons across the primary and the secondary hypotheses, the matched parallel gatekeeping procedure would be applied.

The planned sample size before the pre-specified sample size re-estimation was 520 patients (130 per treatment group). This was derived based on the MMRM model using a simulation method[1] with the following assumptions:

- An effect size of 0.36, based on a treatment difference of 4 units with a common pooled standard deviation of 11.1 for the primary efficacy parameter,
- a correlation of 0.7 between the repeated measures,
- 85% power to demonstrate the superiority of at least one of the two levomilnacipran doses to placebo,
- a dropout rate of 17% based on historical data in pediatric patients.

The Applicant performed a pre-specified blinded sample size recalculation (Feb 06, 2019) after 421 subjects (82.4%) had been randomized (347 subjects had data at both Baseline and Week 8). The Applicant used the MMRM model to estimate the pooled variance for change from Baseline in CDRS-R total score at Week 8, which included pooled study site and week as factors and baseline CDRS-R total score and baseline value-by-week interaction as covariates. Based on this MMRM model, the variance estimate for the change from Baseline in CDRS-R total score at Week 8 was 129.53, and the estimated pooled standard deviation (SD) was 11.38. Because the estimated pooled SD was larger than the assumed SD=11.1, to maintain the 85% power the Applicant increased the total sample size from 520 patients to 544 patients.

The following data sources for Study LVM-MD-11 were considered in this review:

a. Data sets
\\cdsesub1\evsprod\NDA204168\0107\m5\datasets\lvm-md-11\analysis\adam\datasets
b. Software code
\\cdsesub1\evsprod\NDA204168\0113\m5\datasets\lvm-md-11\analysis\adam\programs

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

Protocol Amendments

The original protocol, dated December 1, 2014, was amended three times.

- On July 16, 2014, the Applicant submitted the final draft protocol for LVM-MD-11.

- On March 17, 2015, following responses to FDA comments provided on October 28, 2014, and February 17, 2015 (Serial Numbers 192 and 202), the Applicant submitted the final protocol for LVM-MD-11, titled "A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Adolescent Patients with Major Depressive Disorder." No subjects were randomized under the original protocol.

- On June 10, 2015, the Applicant submitted Amendment 1 in response to the Division's March 26, 2015, request that the Applicant determine the sample size for Study LVM-MD-11 based on a treatment effect of 4 points for the primary efficacy parameter (CDRS-R total score) compared with placebo. The sample size was increased from 480 to 660 patients by changing the effect size from 0.43 (a treatment difference of 5.8 units with a common pooled standard deviation of 13.5) to 0.36 (a treatment difference of 4 units with a common pooled standard deviation of 11.1). In addition, the version of the C-SSRS was changed. There were 100 subjects randomized under this version of the protocol.

- On September 2, 2016, the Applicant submitted Amendment 2 to provide for the use of fluoxetine 10 mg capsules instead of fluoxetine 10 mg tablets because of data received on June 3, 2016, revealing that an over-encapsulated fluoxetine 10-mg tablet resupply batch failed to meet dissolution criteria. There were 413 subjects randomized under this version of the protocol.

- On June 7, 2019, the Applicant submitted Amendment 3 to reduce the sample size from 660 to 520 patients based upon statistical significance in at least one of the two dose levels. Subsequently, based on results of the pre-specified blinded interim analysis, the sample size was re-estimated to be 544 subjects. Furthermore, this amendment also proposed to remove the need to acquire samples for PK analysis, and to remove the 'nontrade' wording in relation to the formulation. This amendment was submitted subsequent to the Division granting a deferral extension request including proposed timeline revisions in addition to the PK and sample size changes listed here. There were 39 subjects randomized under this version of the protocol.

Clinical Reviewer's Comment: The amendments appear reasonable and do not appear to affect the interpretation or results of the study.

8.1.1.1. Study Results: LVM-MD-11

Compliance with Good Clinical Practices

The Applicant states this study was conducted in accordance with Good Clinical Practices (GCP).

Financial Disclosure

See Appendix 18.2 for details.

Patient Disposition

Of 807 subjects screened, 552 were randomized into the DB period and 547 subjects took at least one dose of the DB investigational product and thus were included in the safety population for LVM-MD-11. A total of 82% (448/547) of the subjects completed the DB treatment period. The withdrawal rate differed somewhat across groups, with the levomilnacipran 80 mg group having the highest proportions of withdrawals (22.5% of the total withdrawals during the DB period) and levomilnacipran 40 mg the lowest (14.2%).

The primary reasons for discontinuation during the DB period were: AEs, withdrawal of consent, and lost to follow-up. The proportions of subjects who withdrew for AEs was highest in the levomilnacipran 80 mg group (8%), identical in the levomilnacipran 40 mg and fluoxetine groups (each with 5.2%), and lowest in the placebo group (2.8%). See Table 14 for a breakdown of subject disposition and reasons for premature withdrawal from the DB study period.

Table 14. Study LVM-MD-11 Subject Disposition: Safety Population

	Placebo (n=141) N (%)	LVM 40 mg (n=134) N (%)	LVM 80 mg (n=138) N (%)	FLU 20 mg (n=134) N (%)	Total (n=547) N (%)
Completed DB Period	117 (83)	115 (85.8)	107 (77.5)	109 (81.3)	448 (81.9)
Prematurely Discontinued	24 (17)	19 (14.2)	31 (22.5)	25 (18.7)	99 (18.1)
Reason for Premature Discontinuation					
Adverse Event	4 (2.8)	7 (5.2)	11 (8)	7 (5.2)	29 (5.3)
Lack of efficacy	2 (1.4)	0 (0)	2 (1.4)	2. (1.5)	6 (1.1)
Withdrawal of Consent	10 (7.1)	7 (5.2)	5 (3.6)	5 (3.7)	27 (4.9)
Lost to Follow-Up	7 (5)	4 (3)	5 (3.6)	8 (6)	24 (4.4)

Protocol Violation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-Compliance (Study Drug)	1 (0.7)	0 (0)	3 (2.2)	1 (0.7)	5 (0.9)
Other	0 (0)	1 (0.7)	5 (3.6)	2 (1.5)	8 (1.5)
Entered and Completed DB Taper Period	111 (78.7)	109 (81.3)	104 (75.4)	107 (79.9)	431 (78.8)

Source: Applicant CSR, page 33
Abbreviations: DB = double-blind, FLU= fluoxetine, LVM = levomilnacipran

Clinical Reviewer's Comment: *Overall, the withdrawal rate for the DB period, 18.1%, was as expected for this type of study in pediatric subjects with MDD. The proportion of discontinuations ranged from 14.2% (levomilnacipran 40 mg group) to 22.5% (levomilnacipran 80 mg group), with fluoxetine (18.7%) and placebo (17%) in the middle range. As expected, there were slightly more discontinuations for AEs in the higher dose (80 mg) levomilnacipran group, suggesting a dose-response. Noncompliance with study drug discontinuations were highest in this group as well.*

The analysis populations are listed in Table 15. The randomized population refers to all subjects who were randomized to a treatment group, and the safety population consisted of all the randomized subjects who took at least one dose of the investigational product. The ITT population consisted of all subjects in the safety population with a baseline and at least one postbaseline assessment of the primary efficacy parameter.

Subjects randomized but not included in the safety population were excluded for the following reasons: lost to follow-up (two subjects, one each in placebo and levomilnacipran 40 mg), noncompliance with study drug (one subject, fluoxetine), and withdrawal of consent (two subjects, one each in levomilnacipran 40 mg and 80 mg); therefore, 547 of the 552 randomized subjects were included in the safety population. One subject included in the safety population was excluded from the ITT population because of withdrawal of consent (one subject, assigned placebo), therefore a total of 546 subjects were included in the ITT population.

Table 15. Study LVM-MD-11 Analysis Populations

Population	Placebo	LVM 40 mg	LVM 80 mg	FLU 20 mg	Total
Screened	-	-	-	-	807
Randomized	142	136	139	135	552
Safety	141	134	138	134	547
ITT	140	134	138	134	546

Abbreviations: FLU= fluoxetine, ITT= intent-to-treat, LVM= levomilnacipran

Source: Applicant CSR, page 36

Protocol Violations/Deviations

Protocol deviations were defined in accordance with the International Council for Harmonisation (ICH) guidelines and were assessed by the Applicant for their impact on analyses and data integrity or subject safety. The Applicant states the proportion of subjects who had significant protocol deviations was low (3.3%), and no deviation was considered to have affected the study outcome or interpretation of the study results or conclusions.

The Investigator of one study site (Site 054) did not conduct the study in accordance with signed statement. The Applicant conducted a sensitivity analysis excluding all data from Site 054 on the primary efficacy parameter. The same MMRM approach was applied on all observed cases of change from Baseline in CDRS-R total score except all values of Site 054.

Clinical Reviewer's Comment: I reviewed the major protocol deviations related eligibility criteria, prohibited concomitant medications, wrong IP treatment, treatment compliance, and efficacy, safety, or pharmacokinetic (PK) assessments. Over half of the deviations appeared to result from the site identified by the Applicant, as discussed above. Overall, the most significant protocol deviations primarily included issues surrounding eligibility criteria and study procedures. With one exception, most deviations occurred in only one subject. Several study subjects' Columbia-Suicide Severity Rating Scale (C-SSRS) assessments were either not reviewed in a timely manner, were not completed, or administered by untrained raters. Deviations occurred across all assigned treatment groups. I concur with the Applicant's conclusion that the protocol deviations for Study LVM-MD-11 do not impact the analysis of the study data or interpretation of the study results.

Table of Demographic Characteristics

See Table 16 for the DB Period demographic characteristics. Overall, the safety population included approximately 66% female subjects and 60.9% white subjects, with demographic characteristics balanced across the treatment arms.

Table 16. Study LVM-MD-11 Demographic Characteristics of the Primary Efficacy Analysis (ITT Set)

Demographic Parameters	Placebo (N=140) n (%)	Treatment Group (N= 272)		Fluoxetine 20 mg/day (n=134)	Total (N= 546) n (%)
		LVM 40 mg/day (N=138) n (%)	LVM 80 mg/day (N= 134) n (%)		
Sex					
Male	42 (30.0)	40 (29.9)	51 (37)	50 (37.3)	183 (33.5)
Female	98 (70.0)	94 (70.1)	87 (63)	84 (62.7)	363 (66.5)
Age					
Mean years (SD)	14.3 (1.6)	14.8 (1.6)	14.8 (1.8)	14.7 (1.7)	14.7 (1.7)
Median (years)	14	15	15	15	15
Min, max (years)	12, 17	12, 17	12, 17	12, 17	12, 17
Race					
White	81 (57.9)	81 (60.4)	83 (60.1)	88 (65.7)	333 (61.0)
Black or African American	51 (36.4)	46 (34.3)	49 (35.5)	40 (29.9)	186 (34.1)
Asian	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	4 (0.7)
American Indian or Alaska Native	1 (0.7)	0 (0)	1 (0.7)	1 (0.7)	3 (0.5)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.2)
Multiple	6 (4.3)	4 (3)	3 (2.2)	4 (3)	17 (3.1)
Missing	0 (0)	1 (0.7)	1 (0.7)	0 (0)	2 (0.4)
Ethnicity					
Hispanic or Latino	33 (23.6)	36 (26.9)	32 (23.2)	36 (26.9)	137 (25)
Not Hispanic or Latino	107 (76.4)	98 (73.1)	106 (76.8)	98 (73.1)	409 (74.9)
BMI (kg/m2)	25.9 (7.2)	27.5 (8.4)	26.5 (8)	26 (7.4)	26.5 (7.8)
Duration of MDD (years, n (%)	2.7 (2.6)	2.5 (2.5)	2.6 (2.6)	2.5 (2.5)	2.6 (2.5)
Duration, current MDD episode (months, n (%)	10.7 (16.7)	8.4 (14.2)	7.6 (9.4)	11 (16.9)	9.4 (14.6)
Age at onset (current episode) (years, n (%)	11.6 (2.9)	12.3 (2.5)	12.3 (2.7)	12.2 (2.6)	12.1 (2.7)

Source: Applicant Clinical Study Report (CSR), page 100

Clinical Reviewer's Comment: The demographic breakdown of study subjects was well balanced across treatment groups and, in general, could be considered representative of adolescents with MDD. Inclusion of subjects of Asian, American Indian, Native Hawaiian or Other Pacific Island descent was lower than in the intended clinical population. The Applicant did not include a discussion of any barriers to enrollment.

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

Overall, 31.4% of the study population had received a previous non-drug treatment for depression. The most common previous nondrug treatment for all groups was individual psychotherapy (25%).

The most common prior medication of special interest was an antidepressant. Approximately 18% of the study population had previous treatment with an SSRI, and approximately 9% had prior treatment with other antidepressants (bupropion, trazodone, duloxetine, vilazodone, mirtazapine, venlafaxine, vortioxetine). Overall, slightly fewer subjects in the placebo group (5%) had been treated with a non-SSRI antidepressant compared to the other groups (between 9 and 11%), but, otherwise, the prior treatments were well balanced across the treatment groups.

Prior use of antipsychotic and anxiolytic medications was relatively low, with fewer than 10% of subjects receiving antipsychotics and fewer than 1% receiving anxiolytics. Previous stimulant treatment ranged between 11.2% to 15.7% across the groups.

Clinical Reviewer Comment: Previous exposure to drug and nondrug treatment was similar across all treatment groups, with small differences that this reviewer does not consider likely to have impacted the results of the study. These differences in previous treatments did not appear to impact the generalizability of the study results for the population of pediatric patients with MDD.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant did not specify rescue medication use for the study. The most common psychotropic medications taken during the DB period were stimulants (overall 7.5% of the study population); stimulant use was similar between groups.

Overall, mean compliance was 97% for all treatment groups (and 97% for each group). The mean duration of treatment during the DB period in the safety population was also similar between groups, ranging between 48.6 to 52.4 days.

Clinical Reviewer Comment: Treatment compliance and concomitant medication use were similar across the treatment groups and did not raise any concerns regarding analysis or interpretation of study results.

Efficacy Results – Primary Endpoint

The primary analysis results of the primary endpoint, change from Baseline to Week 8 in CDRS-R total score, are summarized in Table 17. Neither the levomilnacipran 40 mg nor the 80 mg dose groups separated from placebo on the primary endpoint, the CDRS-R. The fluoxetine 20 mg arm, the active comparator, also failed to separate from placebo.

Table 17: Study LVM-MD-11 Primary Endpoint Results Based on Primary Analysis

	Placebo (N=132)	Levomilnacipran 40 mg/day (N=136)	Levomilnacipran 80 mg/day (N=136)	Fluoxetine 20 mg/day (N=136)
Mean CDRS-R total score at Baseline (SD)	61.3 (10.7)	61.6 (10.2)	59.9 (9.5)	61.6 (9.1)
Mean CDRS-R total score at Week 8 (SD)	39.6 (15.3)	38.1 (12.6)	37.6 (12.7)	37.5 (14.2)
LSM[1] Change from Baseline (SE)	-22.90 (1.09)	-23.28 (1.11)	-22.64 (1.12)	-24.37 (1.12)
Placebo-subtracted difference (95% CI)		-0.38 (-3.41, 2.64)	0.26 (-2.80, 3.31)	-1.47 (-4.52, 1.58)
Unadjusted P-value		0.8035	0.8681	0.3439

SD=standard deviation, SE=standard error, LSM = least squares mean, CDRS-R = Children's Depression Rating Scale-Revised, 95% CI = 95% confidence interval, unadjusted for multiplicity.
Source: Study LVM-MD-11 Clinical Study Report, Table 10, p. 51.

Data Quality and Integrity

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

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy parameter was the change from baseline to Week 8 in CGI-S score. The secondary efficacy endpoint analysis did not demonstrate a statistically significant treatment difference between levomilnacipran 40 mg/day or levomilnacipran 80 mg/day and placebo.

Dose/Dose Response

Neither the levomilnacipran 40 mg nor the 80 mg dose separated from placebo on the primary endpoint. Of note, the active control fluoxetine also failed to separate from placebo.

Durability of Response

As described above, neither the levomilnacipran 40 mg nor the 80 mg dose separated from placebo on the primary endpoint.

Persistence of Effect

As described above, neither the levomilnacipran 40 mg nor the 80 mg dose separated from placebo on the primary endpoint.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.1.2. Study LVM-MD-14

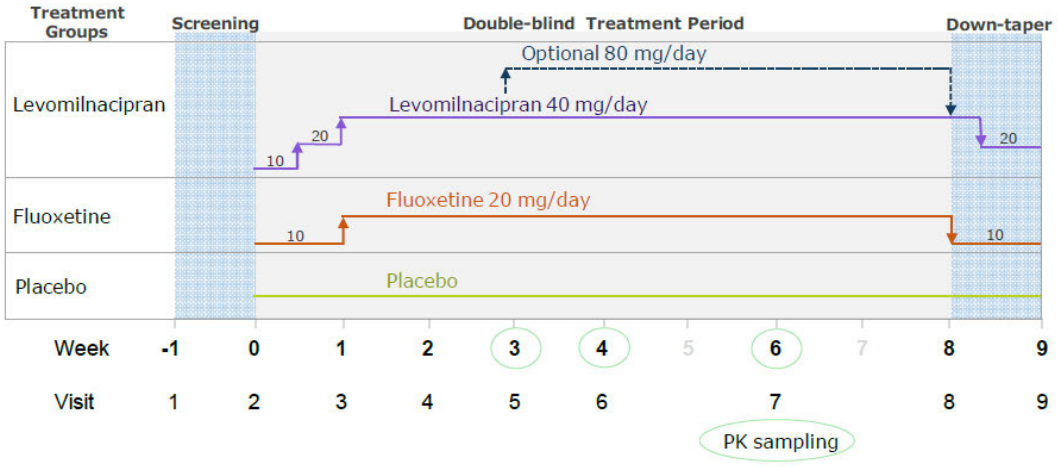
Trial Design

Study LVM-MD-14 was designed to satisfy PMR 1943-2. The study was a randomized, DB, placebo- and active-controlled (fluoxetine), multicenter, flexible-dose study evaluating the safety and efficacy of levomilnacipran for the treatment of MDD in male and female pediatric subjects aged 7 to 7 years. With the exception of dosing (flexible-dose compared to fixed-dose), and study population age (7 to 17 years compared with 12 to 17 years), this study was very similar in design to the previous study (LVM-MD-11). LVM-MD-14 was approximately 10 weeks in duration, with a 1-week screening/washout period, an 8-week DB treatment period, and a 1-week DB taper period. The study was conducted at 47 sites in the United States.

To be eligible for inclusion, subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for MDD. Subjects were also required to have a score of at least 40 on the CDRS-R and a CGI-S score of at least 4 at Screening and Baseline. The K-SADS-PL was used to confirm the diagnosis of MDD and to document the subject's psychiatric history.

See Figure 4 for the LVM-MD-14 study schematic.

Figure 4. LVM-MD-14 Study Schematic



Source: Applicant Study LVM-MD-14 protocol, page 27

Study Endpoints

The primary and secondary study endpoints were identical to Study LVM-MD-11.

Clinical Reviewer's Comment: As with Study LVM-MD-11, the endpoints are reasonable and consistent with other adequate and well-controlled trials of depression in pediatric subjects with MDD.

Statistical Analysis Plan

The efficacy analyses were based on the ITT Population, which consisted of all randomized patients who had the baseline and at least one postbaseline assessment of the CDRS-R total score.

The primary efficacy parameter was the change from Baseline to Week 8 in CDRS-R total score. The Applicant performed the primary analysis for comparing levomilnacipran 40 mg versus placebo and levomilnacipran 80 mg versus placebo for the primary efficacy parameter using an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline value-by visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. This analysis only used the observed cases of post-baseline scores without imputation of missing values.

The secondary efficacy parameter was the change from Baseline to Week 8 in CGI-S score, which would be analyzed using the MMRM approach similar to the one used for the primary efficacy parameter. To control the overall type 1 error rate for the multiple comparisons across the primary and the secondary hypotheses, the matched parallel gatekeeping procedure would be applied.

The planned sample size was 480 patients (130 per treatment group). This was derived based on the MMRM model using a simulation method with the following assumptions:

- An effect size of 0.36, based on a treatment difference of 4 units with a common pooled standard deviation of 11.1 for the primary efficacy parameter,
- a correlation of 0.7 between the repeated measures,
- 85% power to demonstrate the superiority of levomilnacipran to placebo,
- a dropout rate of 17% based on historical data in pediatric patients.

The Applicant conducted a pre-specified interim analysis to identify early signs of futility after 62% of randomized patients had either completed or discontinued the study. The futility assessment of the primary efficacy parameter (CDRS-R total score) in the ITT population was based on the conditional power. The non-binding futility criteria would be met when the conditional power for detecting a statistically significant treatment difference between the levomilnacipran treatment group (40 to 80 mg/day) and placebo at the final analysis given the interim analysis results was 0.2 (20%) or lower. However, after the futility analysis results were

reviewed by a data monitoring committee member, it was determined that this study would continue until the planned study end.

The following data sources for Study LVM-MD-14 were considered in this review:
a. Data sets
\\cdsesub1\evsprod\NDA204168\0107\m5\datasets\lvm-md-14\analysis\adam\datasets
b. Software code
\\cdsesub1\evsprod\NDA204168\0113\m5\datasets\lvm-md-14\analysis\adam\programs

Protocol Amendments

The original protocol, dated March 2, 2018, was amended twice.

- A total of 301 subjects were randomized under the original protocol.

- Amendment 1, submitted April 3, 2020, was submitted in part because the Division granted the Applicant's request to remove the PK sampling requirement for subjects aged 12 to 17 years old. The major changes in this amendment included clarification that PK samples will only be collected in subjects 7 to 11 years old and added that an interim futility analysis may be conducted when 50% of randomized subjects have either completed or discontinued the study. A total of 55 subjects were randomized under this version of the protocol.

- Amendment 2, submitted September 3, 2020, updated the protocol to provide changes necessary to adapt to the ongoing COVID-19 pandemic. The amended protocol also included updated information that the interim futility analysis was performed after 62% of randomized subjects completed or discontinued the study. A total of 145 subjects were randomized under this version of the protocol.

Clinical Reviewer Comment: The amendments appear acceptable and do not appear to affect interpretation of study results.

8.1.2.1. Study Results, LVM-MD-14

Compliance with Good Clinical Practices

The Applicant attests that the protocol was conducted in accordance with Good Clinical Practice.

Financial Disclosure

See Appendix 18.2 for details.

Subject Disposition

Of the 748 subjects screened, 501 were enrolled and randomized into the DB treatment period. A total of 492 (98.2%) subjects received study medication, and 436 (87% of those randomized) subjects completed the DB treatment period, including 146/164 (89%) assigned to placebo, 146/169 (86.4%) assigned to levomilnacipran (40 to 80 mg/day), and 144/168 (85.7%) assigned to fluoxetine 20 mg/day.

The overall withdrawal rate in the DB period was 13%, and similar across treatment groups. The most common reasons for withdrawal were "withdrawal by subject" (5.2%) and "lost to follow-up" (4%) and were relatively consistent across treatment groups. The proportion of subjects who withdrew for AEs was 1.6% overall, and lowest in the placebo group (1, 0.6%). Two subjects (1.2%) in the levomilnacipran group and five subjects (3%) in the fluoxetine group discontinued prematurely due to adverse events. Other reasons for withdrawals included early terminated per PI's discretion, early termination, and safety concerns.

Table 18. LVM-MD-14 Subject Disposition: Safety Population

	Placebo N=164 n (%)	**LVM N=169 n (%)**	**Fluoxetine N=168 n (%)**	**Total N=501 n (%)**
Completed DB Period	146 (89)	146 (86.4)	44 (85.7)	436 (87)
Prematurely Discontinued	18 (11)	23 (13.6)	24 (14.3)	65 (13)
Reasons for Premature Discontinuation				
Adverse Event	1 (0.6)	2 (1.2)	5 (3)	8 (1.6)
Lack of Efficacy	0 (0)	1 (0.6)	0 (0)	1 (0.2)
Withdrawal by Subject	7 (4.3)	10 (5.9)	9 (5.4)	26 (5.2)
Lost to Follow-Up	7 (4.3)	7 (4.1)	6 (3.6)	20 (4.0)
Protocol Deviation	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Noncompliance with Study Drug	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Other	1 (0.6)	1 (0.6)	2 (1.2)	4 (0.8)

Source: Applicant CSR, page 29
Abbreviations: DB = double-blind, LVM = levomilnacipran

Clinical Reviewer's Comment: Overall, the withdrawal rate for the DB period, 13%, was relatively low for this type of study in pediatric subjects with MDD. There were slightly more early discontinuations due to AEs in the fluoxetine group (5, 3%) compared with the levomilnacipran

(2, 1.2%) and placebo (1, 0.6%) groups.

Subjects randomized but not included in the safety population (9/501) were excluded due to lost to follow-up (two in the placebo group, and one each in the levomilnacipran and fluoxetine groups), protocol deviation (one in the levomilnacipran group), and withdrawal by subject (two in the placebo group, and one each in the levomilnacipran and fluoxetine groups). Five subjects were included in the safety population but not in the ITT Population; one placebo and two levomilnacipran subjects each were lost to follow-up, and two subjects in the levomilnacipran group were "withdrawn by subject." Therefore, 492 subjects were included in the safety population and 487 in the ITT population. See Table 19 for a breakdown of the subjects included in the LVM-MD-14 analysis populations.

Table 19. LVM-MD-14 Analysis Populations

Population	Placebo	LVM	Fluoxetine	Total
Screened	-	-	-	748
Randomized	164	169	168	501
Safety	160	166	166	492
ITT	159	162	166	487

Source: Applicant CSR, page 86
Abbreviations: LVM = levomilnacipran, ITT = intent-to-treat

COVID-19 and impact on LVM-MD-14: A total of 14 subjects (4/160 or 2.5% in the placebo group, 4/166 or 2.4% in the levomilnacipran group, and 6/166 or 3.6% in the fluoxetine group) in the safety population were impacted by COVID-19. No subjects discontinued due to COVID-19, and there was no study drug interruption. The most frequently reported impact of the COVID-19 pandemic was on study procedures, with 2.4% to 2.5% of subjects missing assessments, and 1.3% to 2.4% of subjects experiencing some remote assessments due to the pandemic. Two subjects reported treatment-emergent adverse events (TEAEs) related to COVID-19 in the safety population. Overall, the Applicant states that the subjects who reported COVID-19-related illness or non-illness related pandemic disruption did not significantly affect the enrollment and randomization of subjects into the study.

Protocol Violations/Deviations

Protocol deviations were defined as reported for Study LVM-MD-11 above. The Applicant states that none of the deviations was considered to have affected the study outcome or interpretation of the study results or conclusions.

Clinical Reviewer's Comment: *I reviewed the major protocol deviations related to informed*

consent, eligibility criteria, wrong investigational treatment or drug supply, prohibited concomitant medication, serious adverse event (SAE) reporting, and other issues. Most deviations occurred in one or two subjects and appeared to occur across all of the different treatment groups. Overall, I concur with the Applicant that these deviations would not be expected to have an impact on the study outcome or interpretation of the study results.

Table of Demographic Characteristics

See Table 20 for the DB Period demographic characteristics. Overall, the mean age of subjects was 13.5 years, and female subjects accounted for 64.6% of the total population. White (61.4%) and Black or African American (35.2%) subjects accounted for the majority of the subject population.

Clinical Reviewer's Comment: Similar to the previous study (LVM-MD-11), the demographic breakdown of study subjects was well balanced across treatment groups and, in general, could be considered representative of adolescents with MDD. The proportion of individuals identifying as Asian, American Indian/Alaskan Native, or Native Hawaiian/Other Pacific Islander was lower than in the intended clinical population. The Applicant did not include a discussion of any barriers to enrollment.

Table 20. LVM-MD-14 Demographic Characteristics of the Primary Efficacy Analysis (ITT set)

Demographic Parameters	Placebo Group (N= 159) n (%)	Active Treatment		Total (N= 487) n (%)
		LVM 40 to 80 mg/day (N= 162) n (%)	Fluoxetine 20 mg/day (N=166) n (%)	
Sex				
Male	45 (28.3)	64 (39.5)	61 (36.7)	170 (35.9)
Female	114 (71.7)	98 (60.5)	105 (63.3)	317 (65.1)
Age				
Mean years (SD)	13.6 (2.5)	13.7 (2.6)	13.3 (2.7)	13.5 (2.6)
Median (years)	14	14	14	14
Min, max (years)	7, 17	7,17	7, 17	7, 17
Race				
White	101 (63.5)	94 (58.0)	104 (62.7)	299 (61.4)
Black or African American	54 (34.0)	59 (36.4)	58 (34.9)	171 (35.1)
Asian	2 (1.3)	4 (2.5)	0 (0.0)	6 (1.2)
American Indian or Alaska Native	**1 (0.6)**	**0 (0)**	**1 (0.6)**	**2 (0.4)**
Native Hawaiian or Other Pacific Islander	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Multiple	1 (0.6)	5 (3.1)	3 (1.8)	9 (1.8)
Ethnicity				
Hispanic or Latino	45 (28.3)	40 (24.7)	40 (24.1)	125 (25.7)
Not Hispanic or Latino	114 (71.7)	122 (75.3)	126 (75.9)	362 (74.3)
BMI (kg/m2)	26.4 (8.4)	24.8 (6.9)	24.8 (7.5)	25.4 (7.6)
Duration of MDD (years, n(%)	2.5 (2.2)	2.3 (2.1)	2.5 (2)	2.4 (2.1)
Duration, current MDD episode (months, n (%)	11.9 (16.7)	10.2 (14.2)	12.3 (15)	11.5 (15.3)

Abbreviations: LVM= levomilnacipran, MDD= major depressive disorder
Source: CSR, page 92

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

Overall, 35.8% of the study population had received any previous non-drug treatment for depression. The most common previous nondrug treatment for all groups was individual psychotherapy, similar to the study population for LVM-MD-11. A total of 24.2% (n=119) subjects had previously received psychotherapy. The rates were similar across the treatment groups. Previous exposure to nondrug treatment was similar across all groups (between 35.5 and 36.3% for each group).

The most common prior medications of special interest were antidepressants. Approximately 15.9 % of the study population had previous treatment with SSRIs, and approximately 6.1% had previous treatment with other antidepressants (bupropion, trazodone, duloxetine, mirtazapine, and desvenlafaxine).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant did not specify rescue medication use for the study.

Overall, mean compliance, defined as the percentage of total number of capsules taken compared with the total number of capsules prescribed, was 98.5% for placebo, 98.4% for levomilnacipran, and 98.7% for the fluoxetine groups. The mean duration of treatment during the DB period in the safety population was 53.6 days 51.8 days, and 52.1 days, respectively.

Clinical Reviewer Comment: Similar to the previous study (LVM-MV-11), for Study LVM-MD-14, previous exposure to drug and nondrug treatment were similar across all treatment groups, with small differences that this reviewer does not consider likely to have impacted the study results.

Efficacy Results – Primary Endpoint

As in the previous study, neither levomilnacipran nor the active comparator, fluoxetine, separated from placebo on the primary efficacy endpoint, the CDRS-R, in Study LVM-MD-14. The results are shown in Table 21.

Table 21: Study LVM-MD-14 Primary Endpoint Results Based on Primary Analysis

	Placebo (N=159)	Levomilnacipran 40-80 mg/day (N=162)	Fluoxetine 20 mg/day .(N=166)
Mean CDRS-R total score at Baseline (SD)	60.8 (8.99)	60.8 (9.17)	60.9 (9.88)
Mean CDRS-R total score at Week 8 (SD)	39.7 (14.01)	38.0 (15.20)	37.6 (14.56)
LSM Change from Baseline (SE)	-21.3 (1.01)	-23.0 (1.01)	-23.1 (1.01)
Placebo-subtracted difference (95% CI)		-1.7 (-4.49, 1.04))	-1.8 (-4.59, 0.95))
Unadjusted P-value		0.2215	0.3439

SD=standard deviation, SE=standard error, LSM = least squares mean, CDRS-R = Children's Depression Rating Scale-Revised; 95% CI = 95% confidence interval, unadjusted for multiplicity.
Source: Study LVM-MD-14 Clinical Study Report, Table 10, p. 47.

Data Quality and Integrity

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

Efficacy Results – Secondary and other relevant endpoints

Neither levomilnacipran nor the active comparator, fluoxetine, separated from placebo on the secondary efficacy endpoint, the CGI-S, similarly to the results of the previous study.

Dose/Dose Response

This flexible-dose study was not designed to establish dose-response in the subject population (subjects aged 7 to 17 years with MDD). In addition, neither levomilnacipran (flexible dose, 40 to 80 mg/day) nor fluoxetine (20 mg/day) separated from placebo on the primary endpoint.

Durability of Response

As described above, levomilnacipran did not separate from placebo on the primary endpoint.

Persistence of Effect

As described above, levomilnacipran did not separate from placebo on the primary endpoint.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

As stated above, levomilnacipran did not separate from placebo in either of the two studies submitted, LVM-MD-11 and LVM-MD-14.

8.2.2. Integrated Assessment of Effectiveness

In two adequate and well-controlled studies evaluating levomilnacipran as a treatment for pediatric MDD, no statistically significant difference between levomilnacipran and placebo (or the active comparator, fluoxetine) was found in either study on the primary or secondary efficacy endpoints.

8.3. Review of Safety

8.3.1. Safety Review Approach

The safety data supporting this application are based on the Applicant's Summary of Clinical Safety (SCS), Clinical Study Reports (CSRs), and datasets from each individual study. The safety review includes an analysis of safety data from the two completed studies, LVM-MD-11 and LVM-MD-14.

As agreed in the pre-NDA meeting between the Division and the Applicant, the Applicant submitted the SCS in lieu of the Integrated Summary of Safety (ISS). The two studies were of differing designs (as referenced above), so, although the Applicant presented pooled adverse event data in the SCS, this clinical reviewer focused primarily on reviewing the safety data for each study separately. The fixed-dose study is better designed for examining a possible dose-response for safety findings.

Previous findings from the adult development program were used to compare to those in Studies LVM-MD-11 and LVM-MD-14. In the adult development program, the most common adverse reactions (occurring in ≥2% of levomilnacipran-treated subjects and a twice the rate of placebo-treated subjects) were nausea, constipation, vomiting, tachycardia, palpitations, erectile dysfunction, testicular pain, ejaculation disorder, heart rate increased, blood pressure increased, urinary hesitation, hyperhidrosis, rash, hot flush, hypotension (including dizziness postural), hypertension, and decreased appetite. In addition, blood pressure changes were also seen in the adult development program, with 10.4% of levomilnacipran-treated subjects experiencing upward shifts from normal or pre-hypertensive status to Stage I or Stage II hypertension.

8.3.2. Review of the Safety Database

Overall Exposure

Refer to Table 22 for the safety population and Table 23 for the extent of drug exposure of the completed studies LVM-MD-11 and LVM-MD-14.

Table 22. Total Completed Study Safety Population Size, LVM-MD-11 and LVM-MD-14

Study	Placebo	Levomilnacipran		Fluoxetine
		40 mg/day	80 mg/day	20 mg/day
LVM-MD-11	141	134	138	134
LM-MD-14		40 to 80 mg/day (flexible dose)		
	160	166		166

Source: Applicant CSR for LVM-MD-11, page 218, and LVM-MD-14, page 202

Table 23. Studies LVM-MD-11 and LVM-MD-14 Safety Population Extent of Drug Exposure

Study	Duration of Drug Exposure (Days)				
		Placebo	Levomilnacipran		Fluoxetine 20 mg/day
LVM-MD-11			40 mg/day	80 mg/day	
	N	141	134	138	134
	Mean	51.5 (12.8)	52.4 (11.6)	48.6 (15.5)	50.6 (13.4)
	Median	56	56	56	56
	Min, Max	1, 67	6, 65	2, 63	1, 63
LVM-MD-14			40 to 80 mg/day (flexible dose)		
	N	160	166		166
	Mean (SD)	53.6 (9.3)	51.8 (13.4)		52.1 (11.7)
	Median	56	56		56
	Range	10, 64	3, 69		4, 63

Source: Applicant CSR for LVM-MD-11, page 218, and LVM-MD-14, page 202

No long-term exposure studies were performed for pediatric subjects with MDD.

Adequacy of the safety database:

The safety population included all randomized subjects who received at least one dose of study medication. The Applicant presented each clinical study individually in the CSRs, and pooled data in the SCS.

Clinical Reviewer's Comment: Long-term exposure was addressed in the adult development program. Long-term exposure in the pediatric population is not planned, given that efficacy was not established in the short-term studies.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data were of sufficient integrity and quality for review. Office of Scientific Investigation (OSI) inspections were waived given the nature of the submission (studies where active drug did not separate from placebo) without obvious issues upon filing review.

Categorization of Adverse Events

The Applicant coded adverse events (AEs) using the lowest level term (LLT), with AEs presented using the preferred term (PT) corresponding to the LLT, according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 22 for Study LVM-MD-11 and Version 23.1 for LVM-MD 14). AEs, severity of AEs, and SAEs were appropriately defined. AE assessment included reporting by the subject being asked a nonleading question such as "How do you feel since your last visit?" at each study visit and related to results of relevant test (laboratory values, clinically relevant clinical findings, etc.). The C-SSRS was used to capture events of suicidal ideation and behavior.

Routine Clinical Tests

Blood and urine samples for clinical laboratory tests (i.e., hematology, chemistry, urinalysis) were collected. Vital signs, including blood pressure and pulse, were measured, and a standard 12-lead ECG was performed. The schedule for obtaining samples and assessing vital sign and physical parameters were identical in both studies. Refer to Table 24 below for a summary of assessments

Table 24. Routine Clinical Tests and Assessments, LVM-MD-11 and LVM-MD-14

	Screening	Baseline	DB Treatment Period	DB-Downtaper Period
Laboratory tests	X		X[a]	
Vital signs (BP, pulse, weight)		X	X[b]	
Vital signs plus height	X			X
ECGs	X		X[c]	

a.Visit 8/Early Termination (ET); b. Each weekly study visit during DB period; c. Visits 5 and 8/ET
Abbreviations: BP= blood pressure, DB= double-blind, ET= early termination, ECG= electrocardiogram
Source: Applicant LVM-MD-11 Protocol, page 5 and LVM-MD-14 Protocol page 7

Clinical Reviewer's Comment: The clinical laboratory assessments, safety assessments such as the C-SSRS, and collection schedule for labs, vital signs, and ECGs were reasonable.

8.3.4. Safety Results

Deaths

No deaths occurred in the pediatric development program.

Serious Adverse Events

In Study LVM-MD-11, six subjects (of 547 subjects, 1%) reported at least one on-therapy SAE; two (of 134 subjects, 1.5%) in the levomilnacipran 40 mg group and four (of 134 subjects, 3%) in the fluoxetine group. No SAEs were reported in the placebo or levomilnacipran 80 mg group. SAEs in the levomilnacipran 40 mg group included one overdose and one suicide attempt during the DB period and SAEs in the fluoxetine group included one suicide attempt, one suicidal ideation, one fecaloma, and one intentional overdose during the DB period. See Table 25 for details of the SAEs occurring in LVM-MD-11.

Table 25. Study LVM-MD-11: Treatment-Emergent Serious Adverse Events, Double-Blind Treatment Period

Preferred Term	Placebo N=141 n (%)	LVM 40 mg/day N=134 n (%)	LVM 80 mg/day N=138 n (%)	Fluoxetine 20 mg/day N=134 n (%)
Subjects with at least one on-treatment SAE	0 (0)	2 (1.5)	0 (0)	4 (3)
Overdose[a]	0 (0)	1 (0.7)	0 (0)	0 (0)
Suicide attempt	0 (0)	1 (0.7)	0 (0)	1 (0.7)
Fecaloma	0 (0)	0 (0)	0 (0)	1 (0.7)
Intentional[b] overdose	0 (0)	0 (0)	0 (0)	1 (0.7)
Suicidal ideation	0 (0)	0 (0)	0 (0)	1 (0.7)

a. Recreational drug overdose with no suicidal intent; b. Intentional overdose of sertraline
Source: Applicant CSR for LVM-MD-11, page 70

In Study LVM-MD-14, seven subjects (out of 492 subjects, 1.4%) reported at least one on-therapy SAE; one (of 166 subjects, 0.6%) in the levomilnacipran group, four (out of 166 subjects, 2.4%) in the fluoxetine group, and two (out of 160 subjects, 1.3%) in the placebo group. SAEs in the levomilnacipran group included major depression in one subject in the DB period. SAEs in the fluoxetine group included suicidal ideation (in two subjects), bipolar

disorder (in one subject), and self-injury (in one subject) in the DB period. SAEs in the placebo group included one reported suicide attempt in the DB treatment period and major depression in one subject during the DB taper period. See Table 26 for the breakdown of SAEs for LVM-MD-14.

Table 26. Study LVM-MD-14: Treatment-Emergent Serious Adverse Events, Double-Blind Treatment Period and Double-Blind Taper Period

Preferred Term[1]	Placebo N=160 n (%)	LVM 40 to 80 mg/day N=166 n (%)	Fluoxetine 20 mg/day N= 166 n (%)
Subjects with at least one SAE	2 (1.3)	1 (0.6)	4 (2.4)
Major depression	1 (0.6)[2]	1 (0.6)	0 (0)
Suicidal ideation	0 (0)	0 (0)	2 (1.2)
Bipolar 1 disorder	0 (0)	0 (0)	1 (0.6)
Intentional self-injury	0 (0)	0 (0)	1 (0.6
Suicide attempt	1 (0.6)	0 (0)	0 (0)

1. All SAEs reported were within the Psychiatric disorders System Organ Class
2. Occurred during double-blind taper period

Source: Applicant CSR, page 64.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study LVM-MD-11, a total of 29 (5.3%) subjects in the DB treatment period experienced AEs leading to withdrawal, with slightly higher percentages seen in the active groups; five (3.5%) in the placebo group, seven (5.2%) in the levomilnacipran 40 mg group, 11 (8%) in the levomilnacipran 80 mg group, and seven (5.2%) in the fluoxetine group. Refer to Table 27 below for a listing of the AEs leading to study discontinuation.

Table 27. LVM-MD-11 Treatment-Emergent Adverse Events Leading to Discontinuation; Double-Blind period

MedDRA PT	Placebo N= 141 n (%)	LVM 40 mg N= 134 n (%)	LVM 80 mg N= 138 n (%)	Fluoxetine 20 mg N= 134 n (%)
Subjects with at least one AE leading to discontinuation	5 (3.5)	7 (5.2)	11 (8)	7 (5.2)
Tachycardia	0 (0)	1 (0.7)	3 (2.2)	0 (0)

Vomiting	0 (0)	1 (0.7)	1 (0.7)	0 (0)
Anxiety	0 (0)	0 (0)	1 (0.7)	0 (0)
Depression	0 (0)	0 (0)	1 (0.7)	1 (0.7)
Disturbance in attention	0 (0)	0 (0)	1 (0.7)	0 (0)
Dizziness	0 (0)	0 (0)	1 (0.7)	0 (0)
Hot flush	0 (0)	0 (0)	1 (0.7)	0 (0)
Hyperhidrosis	0 (0)	0 (0)	1 (0.7)	0 (0)
Non-cardiac chest pain	0 (0)	0 (0)	1 (0.7)	0 (0)
Palpitations	0 (0)	0 (0)	1 (0.7)	0 (0)
Headache	0 (0)	2 (1.5)	0 (0)	0 (0)
Nausea	1 (0.7)	2 (1.5)	0 (0)	0 (0)
Gastroenteritis	0 (0)	1 (0.7)	0 (0)	0 (0)
Insomnia	0 (0)	1 (0.7)	0 (0)	1 (0.7)
Nightmare	0 (0)	1 (0.7)	0 (0)	0 (0)
Overdose	0 (0)	1 (0.7)	0 (0)	0 (0)
Suicide Attempt	0 (0)	1 (0.7)	0 (0)	1 (0.7)
Anger	1 (0.7)	0 (0)	0 (0)	0 (0)
ADHD	0 (0)	0 (0)	0 (0)	1 (0.7)
Constipation	0 (0)	0 (0)	0 (0)	1 (0.7)
Decreased appetite	0 (0)	0 (0)	0 (0)	1 (0.7)
Diarrhea	1 (0.7)	0 (0)	0 (0)	1 (0.7)
ECG QT Prolonged	0 (0)	0 (0)	0 (0)	1 (0.7)
ECG Abnormal	1 (0.7)	0 (0)	0 (0)	0 (0)
Hallucination, Auditory	0 (0)	0 (0)	0 (0)	1 (0.7)
Panic attack	2 (1.4)	0 (0)	0 (0)	0 (0)
Suicidal ideation	0 (0)	0 (0)	0 (0)	1 (0.7)

Source: Applicant CSR, Table 14.3.3, pages 59- 60
Abbreviations: ADHD= attention deficit/hyperactivity disorder, ECG= electrocardiogram

In Study LVM-MD-14, a total of eight (1.6%) subjects in the DB treatment period experienced adverse events leading to treatment discontinuation; one (0.6%) in the placebo group, two (1.2%) in the levomilnacipran 40 mg to 80 mg group, and five (3%) in the fluoxetine groups. As expected, discontinuations resulting from treatment-emergent adverse events were slightly higher in the active groups.

Table 28. LVM-MD-14 Treatment-Emergent Adverse Events Leading to Discontinuation; Double-Blind Period

MedDRA PT	Placebo N = 160 n (%)	LVM 40 to 80 mg N = 166 n (%)	Fluoxetine N = 166 n (%)
Participants with at least one TEAE leading to discontinuation	1 (0.6)	2 (1.2)	5 (3)
Abdominal pain, upper	0 (0)	1 (0.6)	0 (0)
Tongue discomfort	0 (0)	0 (0)	1 (0.6)
Headache	0 (0)	0 (0)	1 (0.6)
Irritability	0 (0)	1 (0.6)	0 (0)
Suicidal ideation	1 (0.6)	0 (0)	1 (0.6)
Intentional self-injury	0 (0)	0 (0)	1 (0.6)
Mania	0 (0)	0 (0)	1 (0.6)

Abbreviations: LVM= levomilnacipran, TEAE= treatment-emergent adverse event
Source: Applicant CSR for LVM-MD-14, page 296

Clinical Reviewer Comment: The proportions of discontinuations from AEs in LVM-MD-11, the fixed-dose study in 12- to 17-year-olds, was slightly higher than the proportion in LVM-MD-14, the flexible-dose study in 7- to 7-year-olds. It is possible that the flexible-dose design, with an optional increase to the higher dose of levomilnacipran 80 mg, may have prevented subjects from experiencing AEs to the extent they became intolerable. As expected, the number of discontinuations due to AEs were higher for active drug groups in both studies. The types of AEs experienced were primarily as expected for both levomilnacipran and fluoxetine, based on previous clinically available safety data, as well as for the disease state (MDD).

Significant Adverse Events

Severe, Nonserious TEAEs

In Study LVM-MD-11, the majority of TEAEs were mild or moderate. Severe TEAEs occurred at a slightly higher rate in the active treatment arms, as expected, with 12 (5.8%) subjects in the levomilnacipran 40 mg group, nine (3.9%) subjects in the levomilnacipran 80 mg group, and seven (4.7%) subjects in the fluoxetine group, compared to three (2.1%) subjects in the placebo group. The severe TEAEs in all groups included psychiatric or nervous disorders. The levomilnacipran groups had more instances of gastrointestinal disturbance (nausea, vomiting, abdominal pain) compared with the other groups. Of note, nausea and vomiting were among the most commonly reported adverse reactions in the adult development program. Abdominal pain was not reported as frequently but is listed in Section 6.1 of current labeling.

In Study LVM-MD-14, the majority of TEAEs were mild or moderate. Severe TEAEs occurred across the treatment groups similarly, with six subjects in the placebo group (4.2%), nine subjects in the levomilnacipran group (5.1%) and seven subjects in the fluoxetine group (4%) experiencing a severe TEAE. The severe TEAEs in the levomilnacipran group were primarily related to gastrointestinal issues. The severe TEAEs reported in the placebo group were generally infection-related. Severe TEAEs in the fluoxetine group included headache and other nervous system disorders.

Clinical Reviewer Comment: Severe TEAEs occurred mostly in one subject each in any of the studies. The occurrence of psychiatric or nervous system disorders across all groups was expected, as was the occurrence of gastrointestinal TEAEs among the levomilnacipran-treated groups for both studies. I identified no new safety concerns as a result of this review of severe, nonserious TEAEs.

Treatment Emergent Adverse Events

In Study LVM-MD-11, 296/547 (54.1%) of subjects experienced at least one TEAE during the DB treatment period of the study, with the proportions of subjects experiencing at least one TEAE higher in the levomilnacipran groups (81/134 or 60.4% for levomilnacipran 40 mg and 81/138 or 58.7% for the levomilnacipran 80 mg group) and fluoxetine group (70/134 or 52.2%) compared with placebo (64/141 or 45.4%). Refer to Table 29 for a breakdown of the common TEAEs occurring at least ≥2% and at least twice that of placebo or fluoxetine.

Table 29. LVM-MD-11 TEAEs Occurring in ≥2% of Levomilnacipran-Treated Subjects (and At Least Twice the Rate of Placebo- or Fluoxetine-Treated Subjects)

	Placebo N=141 n (%)	LVM 40 mg/day N=134 n (%)	LVM 80 mg/day N=138 n (%)	Fluoxetine 20 mg/day N=134 n (%)
Nausea	8 (6)	19 (14)	22 (16)	5 (4)
Tachycardia	1 (1)	13 (10)	12 (9)	5 (4)
Vomiting	3 (2)	11 (8)	11 (8)	4 (3)
Decreased appetite	2 (1)	7 (5)	9 (7)	10 (8)
Somnolence	3 (2)	6 (5)	8 (6)	2 (2)
URI	1 (1)	3 (2)	6 (4)	3 (2)
Heart Rate Increased	0 (0)	3 (2)	5 (4)	0 (0)
Constipation	2 (1)	1 (1)	4 (3)	3 (2)
Hyperhidrosis	0 (0)	1 (1)	3 (2)	2 (2)
Sedation	0 (0)	1 (1)	3 (2)	0 (0)
Palpitations	0 (0)	0 (0)	3 (2)	0 (0)
Dysmenorrhea	1 (1)	1 (1)	2 (2)	1 (1)
Rash	0 (0)	3 (2)	1 (1)	1 (1)
Cough	1 (1)	3 (2)	0 (0)	1 (1)
Influenza	2 (1)	3 (2)	0 (0)	3 (2)
UTI	0 (0)	3 (2)	0 (0)	0 (0)

Abbreviations: LVM= levomilnacipran; URI= upper respiratory infection; UTI= urinary tract infection
Source: Applicant CSR for Study LVM-MD-11; page 236

In Study LVM-MD-14, 71 (44.4%) of the subjects in the placebo group, 78 (47%) of the subjects in the levomilnacipran 40 to 80 mg group, and 81 (48.8%) of the subjects in the fluoxetine group reported at least one TEAE. The overall percentages were similar across the three groups, with the active drug groups slightly higher than the placebo group, as expected.

The most frequently occurring TEAE during the DB treatment period by PT was headache (59/492 subjects, 12%). Headache occurred at similar rates across the three treatment groups.

The TEAEs reported more frequently in the levomilnacipran groups compared to placebo (occurring in ≥2% of levomilnacipran-treated subjects and twice the frequency as in placebo-treated subjects) included: nausea, decreased appetite, tachycardia, vomiting, dizziness, and abdominal discomfort. The TEAEs more frequently reported in the levomilnacipran group compared to the fluoxetine group occurring in ≥2% of levomilnacipran-treated subjects and twice the frequency as in fluoxetine-treated subjects) were nausea, tachycardia, and vomiting. See Table 30 for a listing of commonly occurring (≥2% and greater than placebo). Note, this

differs slightly from the Applicant's listing because this reviewer rounded percentages of TEAEs to the nearest whole number. This change resulted in the addition of vomiting to the common TEAEs list.

Table 30. LVM-MD-14 TEAEs Occurring in ≥2% of Levomilnacipran-Treated Subjects (and At Least Twice the Rate of Placebo- or Fluoxetine-Treated Subjects)

	Placebo N=160 n (%)	LVM 40 to 80 mg/day N=166 n (%)	Fluoxetine 20 mg/day N=166 n (%)
Nausea	6 (4)	16 (10)	5 (3)
Decreased appetite	5 (3)	11 (7)	12 (7)
Tachycardia	0 (0)	10 (6)	2 (1)
Vomiting	3 (2)	6 (4)	3 (2)
Dizziness	2 (1)	5 (3)	8 (5)
Abdominal discomfort	0 (0)	4 (2)	0 (0)

Abbreviations: LVM = levomilnacipran
Source: Applicant CSR, page 219

Laboratory Findings

Based upon the data reported in the adult development program, few changes in laboratory parameters were expected.

For both Studies LVM-MD-11 and LVM-MD-14, mean changes from baseline to the end of the DB treatment period in hematology, chemistry, and urinalysis parameters were small and similar across treatment groups. Likewise, the incidence of potentially clinically significant (PCS) postbaseline laboratory values during the DB treatment period was low and similar across treatment groups. No concerning changes or trends were found in reviewing these data. No subject met potential Hy's Law criteria in either study.

Clinical Reviewer Comment: The results of the clinical laboratory parameters from Studies LVM-MD-11 and LVM-MD-14 do not raise new safety concerns for levomilnacipran.

Vital Signs

Overall, changes in vital signs were as expected for this drug and class of medication, as observed in studies of adult populations. Changes in blood pressure and heart rate were the most significant changes observed in vital signs across the study for subjects in the levomilnacipran arms.

Weight and Height:

Levomilnacipran may cause nausea and vomiting and decrease in appetite was noted in 3% of subjects in the adult development program, so the potential for change in weight over the two studies was of interest. Due to the short-term nature (8 weeks) of each study, change in height was not expected to be a major concern for this reviewer.

In LVM-MD-11, weight increase was the most frequently reported PCS vital sign value, with weight increase of ≥7% from baseline occurring in 11/546 (2%) of subjects overall. In the levomilnacipran 40 mg group, the most commonly reported PCS postbaseline vital sign values were weight increase ≥7% and weight decrease ≥7%, with 2/134 (1.5%) subjects reporting each. In the levomilnacipran 80 mg group, the most common potentially clinically significant vital sign was weight decrease ≥7% (5/138, 3.6%) and weight increase ≥7% (4/138, 2.9%). These were similar in nature to what was seen in the fluoxetine group, although, as expected, larger than was observed in placebo for significant weight decrease.

Overall changes in weight between baseline and the end of the DB treatment period were low, with 0 kg (2.2) for levomilnacipran 40 mg, -0.2 kg (2.3) for levomilnacipran 80 mg, 0.1 kg (2) for fluoxetine, and 0.8 kg (2) for placebo.

Of note, the TEAE of decreased appetite occurred in the levomilnacipran 40 mg and 80 mg groups, as well as the fluoxetine group, at a higher incidence than placebo. Refer to Table 29 for a breakdown of the incidence of decreased appetite across the groups.

In LVM-MD-11, due to the short duration (8 weeks) of the DB period, change in height was not expected to be a significant factor, and as expected, did not differ between the four groups for change from baseline for age- and gender-adjusted Z score.

In LVM-MD-14, mean change from baseline to Week 8 in age- and gender-adjusted Z-score for weight (in kg) for the groups were -0.4 (2) kg for the levomilnacipran group, 0.8 kg (2) kg for the placebo group, and 0 (2.6) kg for the fluoxetine group. Upon examination of the raw data, the maximum weight loss for the levomilnacipran group appeared to be 10 kg, which seemed to be an extreme outlier. Of note, the TEAE of decreased appetite occurred more frequently in the levomilnacipran-treated group and the fluoxetine-treated group compared with placebo.

As in LVM-MD-11, due to the short duration (8 weeks) of the DB period, change in height was not expected to be a significant factor, and as expected, did not differ between the four groups for LVM-MD-14.

Clinical Reviewer Comment: Changes in height and weight appeared relatively similar across the two studies. Mean changes in weight overall were small, and relatively few subjects in each group had large (e.g., >7%) changes in body weight, although more subjects in the active treatment groups had weight changes above this threshold. Because the acute studies did not

establish efficacy, additional long term safety studies that could provide more information about the trajectory of weight changes will not be conducted. Decreased appetite is a labeled adverse reaction in the adult population and was reported in the pediatric studies as well. No new safety concerns were identified as a result of reviewing the height and weight data.

Pulse:

Differences in pulse changes were expected, based on previous experience in the adult development program.

In LVM-MD-11, as described in Table 29, more subjects experienced tachycardia and heart rate increased, coded as TEAEs, in the levomilnacipran groups, compared to placebo. Mean (SD) changes in pulse from Baseline to the end of DB treatment were also higher for levomilnacipran 40 mg (7.5 mmHg, SD 12.1) and 80 mg (8.5 mmHg, SD 13.3) than for fluoxetine (-3.9 mmHg, 11.3) or placebo (-0.3 mmHg, 12).

Likewise, in LVM-MD-14, more subjects in the levomilnacipran group experienced the TEAE of tachycardia compared with fluoxetine or placebo (Table 30). Change in pulse was, as expected, greater in subjects in the levomilnacipran group (mean change 7.1 mmHg, SD 13.1), compared with 0.5 (12.1) mmHg in the placebo group and -0.8 (11.8) in the fluoxetine group.

Clinical Reviewer Comment: The changes in pulse in the pediatric development program were consistent with what was expected from the adult development data, although the percentages of subjects reporting tachycardia in the pediatric studies tended to be somewhat higher compared with adults (9% to 10% in the levomilnacipran 40 mg and 80 mg groups, respectively, in Study LVM-MD-11, compared with 6% in adults). Tachycardia also occurred in 6% of the levomilnacipran-treated subjects in Study LVM-MD-14. It was interesting to note the study with a range of younger subjects there was a lower frequency of tachycardia.

Blood Pressure:

Differences in blood pressure changes were expected for the levomilnacipran groups compared with the fluoxetine and placebo groups. The mean changes in systolic and diastolic blood pressure overall in both studies were somewhat higher for subjects treated with levomilnacipran compared with other groups. Refer to Table 31 below for detailed information on changes in diastolic blood pressure for Studies LVM-MD-14.

Table 31. Changes in Diastolic Blood Pressure in Studies LVM-MD-11 and LVM-MD-14

Study	Placebo	Levomilnacipran	Fluoxetine 20 mg
LVM-MD-11			
Mean (SD) mmHg	0.8 (8.9)	40 mg group: 4.6 (9.3) 80 mg group: 3.8 (8.6)	0.1 (8.5)
LVM-MD-14			
Mean (SD) mmHg	1.2 (8.4)	40 to 80 mg: 4.5 (9.1)	-0.1 (8)

Abbreviation: SD= standard deviation
Source: Applicant CSRs for LVM-MD-11, Table 14.3-5.3 and LVM-MD-14 Table 14.3-5.2

The most pronounced differences between groups were seen in the shifts from normal blood pressure at baseline to new onset hypertension in both Study LVM-MD-11 and Study LVM-MD-14 in the levomilnacipran-treated groups. These shifts were more pronounced than in the previous adult studies and were much more prevalent than what were reported as TEAEs in the studies.

To more precisely analyze changes in blood pressure in pediatric subjects, each systolic and diastolic blood pressure reading was transformed into systolic blood pressure percentiles and diastolic blood pressure percentiles for age, sex, and stature using the 2017 American Academy of Pediatrics hypertension (HTN) clinical practice guidelines (Flynn et al., 2017).

In Study LVM-MD-11, a higher proportion of the subjects randomized to levomilnacipran 40 mg and levomilnacipran 80 mg were defined as developing new onset hypertension, compared to subjects treated with either placebo or active comparator fluoxetine. See Table 32 below for detailed information on rates of new onset hypertension in Studies LVM-MD-11 and LVM-MD-14.

Levomilnacipran-treated subjects in Study LVM-MD-14 also experienced a higher proportion of new onset hypertension compared to subjects treated with placebo or fluoxetine. See Table 32 below for detailed information on rates of new onset hypertension.

Table 32. New Onset Hypertension in Studies LVM-MD-11 and LVM-MD-14

Study	Placebo n/N (%)	Levomilnacipran Dose: n/N (%)	Fluoxetine 20 mg n/N (%)
LVM-MD-11			
Total (12- to 17-year-old subjects)	29/140 (20.7%)	40 mg: 49/134 (36.6%) 80 mg: 39/138 (28.3%)	30/134 (22.4%)
LVM-MD-14			
7- to 11-year-old subjects	8/29 (27.6%)	40 to 80 mg: 15/35 (42.9%)	13/43 (30.2%)
12- to 17-year-old subjects	25/130 (19.2%)	40 to 80 mg: 54/127 (42.5%)	21/123 (17.1%)

Total	33/159 (20.8%)	40 to 80 mg: 69/162 (42.6%)	34/166 (20.5%)
Combined Studies			
7- to 11-year old subjects	8/29 (27.6%)	40 to 80 mg: 15/35 (42.9%)	13/43 (30.2%)
12- to 17-year old subjects	54/270 (20%)	40 to 80 mg: 142/399 (35.6%)	51/257 (19.8%)
Total combined	62/299 (20.7%)	40 to 80 mg: 157/434 (36.2%)	64/300 (21.3%)

Source: Adapted from Applicant's response to Information Request, February 17, 2023

Subjects who developed new onset hypertension were categorized to either Stage I or Stage II hypertension. Refer to Table 33 below for a pooled summary of new-onset hypertension, categorized as Stage I or Stage 2, for subjects participating in Studies LVM-MD-11 and LVM-MD-14.

Table 33. New Onset Hypertension by Stage: Pooled Results for Studies LVM-MD-11 and LVM-MD-14

	Placebo %	LVM 40 to 80 mg %	Fluoxetine 20 mg %
New-onset HTN	20.7%	36.8%	20.3%
Shift to Stage I HTN	13.4%	25.1%	14.7%
Shift to Stage II HTN	7.3%	11.7%	5.6%

Abbreviations: HTN= hypertension, LVM= levomilnacipran
Source: Adapted from Applicant's response to Information Request, February 17, 2023

Clinical Reviewer Comment: The proportion of subjects who experienced an upward shift to new onset hypertension was higher in all of the pediatric groups (including placebo; fluoxetine was not used as an active comparator in the adult development program) compared with adults in the original adult development program (approximately 10.4% in adults compared with a combined 36.2% in pediatric subjects from Studies LVM-MD-11 and LVM-MD-14).

Of particular concern were the pediatric subjects who developed blood pressure changes categorized as Stage II hypertension. Although there are no data to identify a specific level of blood pressure in childhood that leads to adverse cardiovascular outcomes in adulthood, Stage II hypertension in pediatric subjects would roughly equate to blood pressure readings of ≥140/90 mmHg in those ages at least 13 years, and either being within the ≥95th percentile + 12 mmHg or ≥ 140/90 mmHg, whichever is lower, for children ages up through 12 years old (Flynn et al., 2017). Development of sustained blood pressure readings categorized as Stage II hypertension would likely be a target for intervention.

The shifts to new onset hypertension in placebo- and fluoxetine-treated pediatric subjects were higher than expected but were still markedly lower than that of the levomilnacipran-treated groups. Subjects participating in these studies were allowed to take concomitant stimulants and other medications that may impact blood pressure, and the potential for other physical

comorbidities as well as "white-coat hypertension" cannot be ruled out, although these factors would have been present at baseline measurements as well as during the DB study period.

Because of the marked differences in shifts to Stage I and Stage II new onset hypertension seen in Studies LVM-MD-11 and LVM-MD-14, this reviewer and the Department of Pediatrics and Mental Health (DPMH) consultants recommended the addition of specific language on pediatric blood pressure changes in Section 5.3 (Warnings and Precautions, Elevated Blood Pressure) and Section 8.4 (Pediatric Use) the label.

Electrocardiograms (ECGs)

In Study LVM-MD-11, no subject in any treatment group experienced a shift from normal at baseline to abnormal at the end of the DB treatment period that was considered clinically significant. One subject in the placebo group experienced a PR interval of ≥250 msec that was considered potentially clinically significant. The proportion of subjects who experienced a non-clinically significant change in ECG parameters was small, and similar throughout the four groups (between 3.4% and 5.4%, with placebo having the highest percentage).

In Study LVM-MD-14, two subjects (2/147, 1.4%) in the levomilnacipran group experienced shifts from normal at baseline to abnormal at the end of the DB treatment period that were considered to be clinically significant. One subject experienced sinus tachycardia, and the other experienced tachycardia. No subjects in the placebo or fluoxetine groups experienced a potentially clinically significant shift in ECG parameters. No subjects in any group experienced potentially clinically significant postbaseline ECG parameters of PR, QRS, QTcB, or QTcF intervals during the DB treatment period. Likewise, more subjects in the levomlinacipran group (12/147, 8.2%), experienced a shift in ECG parameters not considered clinically significant, compared with 3/140 (2.1%) in the placebo group and 4/146 (2.7%) in the fluoxetine group.

Clinical Reviewer Comment: The ECG results from Studies LVM-MD-11 and LVM-MD-14 do not raise new safety concerns for levomilnacipran.

QT

In Study LVM-MD-11, overall, potentially clinically meaningful increases in the QT interval were uncommon. QT interval was corrected for heart rate using the Bazett formula (QTcB) and the Frederica formula (QTcF). The placebo group had the highest rate of increases >30 msec and ≤60 msec in QTcF intervals, with 6/138 (4.3%), while the levomilnacipran 40 mg group had 4/130 (3.1%), the levomilnacipran 80 mg group had 2/133 (1.5%), and the fluoxetine 20 mg group had 3/131 (2.3%). No subject experienced an increase of >60 msec in the QTcF interval.

In LVM-MD-14, potentially clinically meaningful increases in the QT interval were uncommon. QT interval was corrected for heart rate using the Bazett formula (QTcB) and the Frederica formula (QTcF). The levomilnacipran group had the highest incidence of increases >30 and ≤60

in QTcF intervals. When the QT interval was corrected for heart rate by the Fridericia formula, 4/157 (2.5%) of levomilnacipran, 3/157 (1.9%) of placebo, and 3/163 (1.8%) of fluoxetine-treated subjects experiencing an increase of >30 and ≤60 msec increase. No subject experienced an increase of >60 msec using this correction, and no subject experienced potentially clinically significant postbaseline QTcF intervals during the DB treatment period.

Clinical Reviewer Comment: The QT interval changes reported from Studies LVM-MD-11 and LVM-MD-14 do not raise new safety concerns for levomilnacipran.

Immunogenicity

No immunogenicity assessments were performed, and no immunogenicity concerns are expected with levomilnacipran.

8.3.5. Analysis of Submission-Specific Safety Issues

Suicidal Ideation and Behavior (SI/B)

Suicidal ideation and behavior (SI/B) are commonly experienced symptoms of MDD, both in pediatric and adult patients. Additionally, because of the boxed warning for antidepressants that describes an increased risk of SI/B in children, adolescents, and young adults taking antidepressants, a standardized assessment, the C-SSRS, was performed during both studies.

Table 34. Study LVM-MD-11 Columbia-Suicide Severity Rating Scale (C-SSRS) (Safety Population, Double-blind Treatment Period)

	Placebo n=141 n (%)	LMV 40 mg n=134 n (%)	LVM 80 mg n=138 n (%)	Fluoxetine n=134 n (%)
Suicidal ideation				
No suicidal ideation	102 (72.9)	90 (67.2)	104 (75.4)	93 (69.4)
Suicidal ideation	38 (27.1)	44 (32.8)	34 (24.6)	41 (30.6)
Most severe suicidal ideation				
Active ideation with specific plan and intent	0 (0)	0 (0)	0 (0)	1 (0.7)
Active ideation with some intent, without specific plan	1 (0.7)	4 (3)	7 (5.1)	6 (4.5)
Active ideation without intent	2 (1.4)	4 (3)	5 (3.6)	10 (7.5)
Non-specific active suicidal thoughts	16 (11.4)	14 (10.4)	6 (4.3)	12 (9)
Wish to be dead	19 (13.6)	22 (16.4)	16 (11.6)	12 (9)

Suicidal behavior				
No suicidal behavior	129 (92.1)	125 (93.3)	126 (91.3)	124 (92.5)
Suicidal behavior	11 (7.9)	9 (6.7)	12 (8.7)	10 (7.5)
Most severe suicidal behavior				
Completed suicide	0 (0)	0 (0)	0 (0)	0 (0)
Actual attempt	1 (0.7)	1 (0.7)	3(2.2)	3 (2.2)
Interrupted attempt	6 (4.3)	6 (4.5)	6 (4.3)	7 (5.2)
Aborted attempt	2 (1.4)	2 (1.5)	3 (2.2)	0 (0)
Preparatory acts or behavior	2 (1.4)	0 (0)	0 (0)	0 (0)

Abbreviations: LVM= levomilnacipran
Source: Applicant CSR, page 502

There were no deaths by suicide in either study. A summary of SI/B-related events is below.

In Study LVM-MD-11, one subject (0.7%) each in the placebo and levomilnacipran 40 mg groups and three subjects each (2.2%) in the levomilnacipran 80 mg and fluoxetine groups reported a suicide attempt on the C-SSRS. Not all suicide attempts noted on C-SSRS assessment forms were reported as AEs. The two suicide attempts reported as SAEs are discussed in the following paragraph.

One subject in the fluoxetine group and one subject in the levomilnacipran 40 mg group reported a SAE of suicide attempt, leading to study discontinuation in both instances. The fluoxetine-treated subject expressed suicidal ideation on Day 43 of study drug treatment and was briefly hospitalized. The event resolved three days later, on Day 46, and the subject was discharged from the hospital and withdrawn from the study. The subject in the levomilnacipran 40 mg group presented to the emergency room on Day 26 for a suicide attempt and was hospitalized. Study drug treatment was withdrawn and the subject was treated with trazodone and escitalopram. The event resolved on Day 33. In the opinion of the clinical reviewer, these SAEs may be related to the study treatment because of the duration of exposure prior to the events.

Because not all of the suicide attempts noted on C-SSRS assessment forms were reported as AEs, the other attempts in this study were not reported as TEAEs. Refer to Table 34 for a listing of attempts for each group. All attempts that were captured on the C-SSRS were examined by the clinical reviewer. The four subjects in levomilnacipran groups reporting suicide attempts on the C-SSRS are listed below:

- A 16-year-old male randomized to levomilnacipran 40 mg reported suicide attempt resulting in no physical damage per the Week 4 C-SSRS;

- A 12-year-old female randomized to levomilnacipran 80 mg reported suicide attempt resulting in no physical damage per the Week 3 C-SSRS;

- A 13-year-old female randomized to levomilnacipran 80 mg reported suicide attempt resulting in no physical damage per the Week 1 C-SSRS;

- A 14-year-old female randomized to levomilnacipran 80 mg reported suicide attempt resulting in no physical damage per the Week 1 C-SSRS.

The clinical reviewer cannot rule out the possibility of these C-SSRS responses being related to study drug.

The percentage of suicide attempts in this study was not unexpected, due to the known increased risk of SI/B in children and adolescents with MDD treated with antidepressants.

The incidence of suicidal ideation during the DB treatment was similar across groups, ranging between 25% to 33% of study subjects as reported by the C-SSRS. The incidence of suicidal behavior was also similar between groups, ranging from 7% to 9%. As the Applicant states, the incidence of subjects with suicidal ideation or suicidal behavior was lower in all groups compared with the proportion of subjects who reported a lifetime history of SI/B at screening.

Overall, in Study LVM-MD-11, the incidence of suicidal ideation and behavior across the studied parameters (per C-SSRS) during the study was similar across the treatment groups.

The results of Study LVM-MD-14 indicate similar findings related to SI/B in the study population.

Table 35: Study LVM-MD-14 Columbia-Suicide Severity Rating Scale (C-SSRS) (Safety population, Double-blind treatment Period)

	Placebo N=160 N (%)	LVM 40 to 80 mg N=166 N (%)	Fluoxetine N=166 N (%)
Suicidal ideation			
No suicidal ideation	128 (80)	140 (84.3)	147 (88.6)
Suicidal ideation	32 (20)	26 (15.7)	19 (11.4)
Most severe suicidal ideation			
Active ideation with specific plan and intent	1 (0.6)	1 (0.6)	1 (0.6)
Active ideation with some intent, without specific plan	1 (0.6)	1 (0.6)	0 (0)
Active ideation without intent	3 (1.9)	5 (3)	7 (4.2)
Non-specific active suicidal thoughts	8 (5)	4 (2.4)	2 (1.2)
Wish to be dead	19 (11.9)	15 (9)	9 (5.4)

Suicidal behavior			
No suicidal behavior	158 (98.8)	165 (99.4)	165 (99.4)
Suicidal behavior	2 (1.3)	1 (0.6)	1 (0.6)
Most severe suicidal behavior			
Completed suicide	0 (0)	0 (0)	0 (0)
Actual attempt	0 (0)	0 (0)	1 (0.6)
Interrupted attempt	0 (0)	0 (0)	0 (0)
Aborted attempt	1 (0.6)	0 (0)	0 (0)
Preparatory acts or behavior	1 (0.6)	1 (0.6)	0 (0)

Abbreviation: LVM=levomilnacipran
Source: Applicant CSR, page 428

In Study LVM-MD-14, one subject attempted suicide in the fluoxetine group (1/166, 0.6%), per the C-SSRS. This was not reported as a TEAE, due to the way AEs were reported, per the Applicant. On the Week 6 C-SSRS, this 15-year -old female subject reported making superficial cuts on both arms after being upset due to a fight with a friend. This reviewer considers that the event could potentially be related to study treatment.

Although no subjects in either the placebo group or the levomilnacipran group reported an actual suicide attempt on the C-SSRS during the DB treatment period, one subject in the placebo group reported a treatment-emergent SAE of suicide attempt during the DB treatment period (1/160, 0.6%). This 15-year-old subject reported active suicidal ideation with specific plan and intent, resulting in hospitalization and withdrawal of study drug. This event was considered an aborted suicide attempt. This event occurred approximately one week after starting study drug . Although not considered an SAE by the applicant, this reviewer considers the temporal relationship between study drug initiation and the suicidal attempt to be potentially related to the study treatment.

The incidence of suicidal ideation during the DB treatment period was numerically lowest for fluoxetine (n=19, 11%) with the levomilnacipran group at 16% (n=26 subjects) and the highest for placebo (n=32, 20%). These findings are as expected in subjects with active symptoms of MDD.

Overall, in Study LVM-MD-14, the incidence of SI/B was similar across the treatment groups, and was lower than the subjects' lifetime history of SI/B.

Clinical Reviewer Comment: Despite several of the suicide attempts captured on the C-SSRS not being included as TEAEs, the overall incidence of suicide attempts and SI/B was consistent with what is expected in pediatric MDD studies, including similar incidences of SI/B among the study drug and the active comparator. I identified no new SI/B safety concerns after reviewing the data from Studies LVM-MD-11 and LVM-MD-14. Although the frequency of SI/B was similar across groups, there are not enough data to conclude that any changes should be made to the boxed warning for increased risk of SI/B. The current labeling adequately informs healthcare professionals about potential risk of SI/B in pediatric and young adult patients taking

antidepressants.

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

Not applicable

8.3.7. Safety Analyses by Demographic Subgroups

In both Study LVM-MD-11 and LVM-MD-14, the incidence of AEs leading to withdrawal and the incidence of overall AEs were generally similar between sexes and races.

Clinical Reviewer's Comment: Given the relatively small numbers of Black, Asian, and Other races among treatment arms, it is difficult to draw any conclusions regarding race.

8.3.8. Specific Safety Studies/Clinical Trials

No new specific safety studies were submitted with this supplement.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new human carcinogenicity or tumor development studies were submitted with this supplement.

Human Reproduction and Pregnancy

In LVM-MD-14, one subject randomized to the fluoxetine group reported spontaneous abortion of pregnancy.

Pediatrics and Assessment of Effects on Growth

Levomilnacipran has been studied for up to 9 weeks of overall drug exposure in two clinical studies (8 weeks of DB treatment, followed by 1 week of DB downward taper). A total of 438 subjects aged 7 to 17 years with MDD received at least a single dose of levomilnacipran. The short-term nature of the two studies does not offer an extensive assessment of potential impact of effects on growth; however, refer to the discussion of height and weight parameters reported during the two clinical studies LVM-MD-11 and LVM-MD-14 above. No differences in change in age- and gender-adjusted height were noted.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No subjects in either study reported overdose of levomilnacipran. Two subjects in LVM-MD-11 experienced SAEs of overdose, one with a recreational drug and one with sertraline. One subject in LVM-MD-14 reported overdose on vortioxetine.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety concerns based on postmarket experience were identified by the Applicant. The current Prescribing Information, dated February 2022, lists the cardiac disorder of Takotsubo cardiomyopathy as an adverse reaction observed during post-approval use of levomilnacipran or other SNRIs.

Expectations on Safety in the Postmarket Setting

No changes to the indicated population are recommended. The labeling will be updated to reflect that the two pediatric efficacy studies resulted in adverse reaction profile similar to adults, with additional information regarding new onset hypertension that was experienced more frequently in the pediatric development program.

8.3.11. Integrated Assessment of Safety

Overall, the adverse event profile of levomilnacipran in pediatric subjects was similar to that in the adult development program, with the exception of increased incidence of new onset hypertension in pediatric subjects. Because of the changes in blood pressure, which included both development of Stage I and Stage II hypertension, additional language was included in Section 5 of the levomilnacipran labeling.

8.4. Statistical Issues

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

8.5. Conclusions and Recommendations

Study LVM-MD-11 fulfills PREA PMR 4931-1 and Study LVM-MD-14 fulfills PREA PMR 4931.2. The study results do not support the use of levomilnacipran for the treatment of MDD in pediatric patients ages 7 to 17 years. This finding will be reflected in Section 8.4 of the labeling, along with a summary of safety information. The Boxed Warning for SI/B will remain in the labeling. Because of the higher incidence of new onset hypertension in levomilnacipran-treated subjects in both studies, information about this risk in pediatric patients will be added to Section 5 of labeling.

9 Advisory Committee Meeting and Other External Consultations

Given the two negative studies, there were no questions requiring advisory committee consideration. Therefore, no advisory committee meeting was convened for this sNDA.

10 Pediatrics

Study LVM-MD-11 fulfills PREA PMR 1943-1 and Study LVM-MD-14 fulfills PREA PMR-1943-2. This sNDA included only pediatric data; Section 8.4 of labeling will be updated to indicate that safety and effectiveness of levomilnacipran have not been established in pediatric patients for the treatment of MDD. The Applicant did not request pediatric exclusivity.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant is not pursuing an expansion of the indicated population given that efficacy was not demonstrated in Studies LVM-MD-11 or LVM-MD-14. The review team recommended the following changes to the prescribing information:

Section 5.3 (Elevated Blood Pressure)
This section will be updated to describe the occurrence of new-onset hypertension observed in pediatric patients treated with levomilnacipran.

Section 8.4 (Pediatric Use)
This section was updated to include a brief description of the two pediatric clinical efficacy and safety studies as well as juvenile animal toxicity data. Because of the changes in blood pressure in the levomilnacipran-treated groups in these clinical studies, additional language will be added to Section 5 of the label. In addition, minor administrative changes were made to update language or correct minor errors.

Section 11 (Description)
The CMC review team recommended edits to the product description to improve clarity and accuracy.

12 Risk Evaluation and Mitigation Strategies (REMS)

Levomilnacipan is not currently subject to a REMS. No new safety concerns necessitating a REMS were identified during this review.

13 Postmarketing Requirements and Commitment

No new PMRs or PMCs will be issued. Study LVM-MD-11 fulfills PMR 1943-1 and Study LVM-MD-14 fulfills PMR 1943-2.

14 Division Director (Clinical) Comments

The above review reflects my input and edits. I agree with the primary review team. This application will be approved with no changes to the indication, but with the additional of pediatric information to the product label. This submission fulfills the Applicant's post-marketing requirements under PREA.

15 Appendices

15.1. References

1. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed., text rev.). https://doi.org/10.1176/appi.books.9780890425787.

2. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Danels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Giddings SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 2017;140(3):e20171904.2.

3. Lebrun-Harris LA, Ghandour RM, Kogan MD, Warren MD. Five-year Trends in U.S. Children's Health and Well-being, 2016-2020. JAMA Pediatr 2022; 176(7):e220056.

15.2. Financial Disclosure

Covered Clinical Study: LVM-MD-11

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 48		
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): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 48		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study: LVM-MD-14

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 49		
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): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 49		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Table 36 Tissue Procedure Table

Organs	Organ weights	Preservation of tissues	Microscopic examination[a]
Macroscopic lesions		X	X
Adrenals	X	X	X
Aorta		X	X
Brain (including medulla/pons cerebellar and cerebral cortex)	X	X	X
Cecum		X	X
Colon		X	X
Duodenum		X	X
Epididymides	X	X[(b)]	X[(b)]
Esophagus		X	X
Eyes with Harderian glands		X	X
Femoral bone with articulation		X	X
Gut-Associated Lymphoid Tissue (GALT)		X	X
Heart	X	X	X
Ileum		X	X
Jejunum		X	X
Kidneys	X	X	X
Larynx		X	X
Liver	X	X	X[(c)]
Lungs with bronchi		X	X
Lymph nodes (mandibular and mesenteric)		X	X
Mammary gland area		X	X
Optic nerves		X	X
Ovaries (with oviducts)	X	X	X
Pancreas		X	X
Pituitary gland		X	X
Prostate		X	X
Rectum		X	X
Salivary glands (sublingual and submandibular)		X	X
Sciatic nerve		X	X
Seminal vesicles		X	X
Skeletal muscle		X	X
Skin		X	X
Spinal cord (cervical, thoracic and lumbar)		X	X
Spleen	X	X	X[(c)]
Sternum with bone marrow		X	X
Stomach with forestomach		X	X
Testes	X	X[(b)]	X[(b)]
Thymus	X	X	X
Thyroids with parathyroids	X	X	X
Tongue		X	X
Trachea		X	X
Ureters		X	X
Urinary bladder		X	X
Uterus (horns and cervix)		X	X
Vagina		X	X

a: was performed only on control and high-dose groups, in animals sacrificed after the end of the treatment period (Subset I).

b: except left epididymis and testis which were used for seminology in Subset II animals.

c: from all animals of the low – and mid-dose groups in Subset I and, from the control, low-, mid- and high-dose groups in Subset II.

Source: Excerpted directly from Applicant's Study Report, page 37

15.1. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable

15.2. Additional Clinical Outcome Assessment Analyses

Not applicable

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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