1.0 TITLE PAGE

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A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Pediatric Patients 7-17 Years With Major Depressive Disorder

LVM-MD-14

Original Protocol Date:	02 March 2018
Amendment 1:	***12 Feb 2020***
Amendment 2:	***05 Aug 2020***

Protocol Approval Form

Protocol Number: LVM-MD-14 Amendment 2

Protocol Title: A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Pediatric Patients 7-17 Years With Major Depressive Disorder

Approver:

[redacted]
[redacted], Neuroscience Development

August 4, 2020
Date

Amendment 2 Summary of Changes

The Amendment 1 protocol, dated 12 Feb 2020, has been amended to reflect the following changes:

1. During the COVID-19 pandemic, remote study visits are possible to avoid missing efficacy data but are not preferred over clinic visits.
2. Considering the coronavirus disease 2019 (COVID-19) pandemic, the benefit and risk to patients participating in this study has been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of the investigational product.
3. Updated Section 9.7.8 (Interim Analysis) to reflect that the interim futility analysis has now been performed, after 62% of randomized patients completed or discontinued the study.

Remote Study Visits:
Investigators/appropriately designated study staff will be allowed to perform selected study procedures as remote study assessments (eg, conducted via phone, video conference) if participants are unable to attend in-person due to the COVID-19 pandemic. During these remote study visits, the supplemental *Schedule of Visits and Procedures for Remote Study Visits* below should be followed and documented that the visit was conducted remotely due to COVID-19 pandemic issues.

Safety Assessments:
Safety assessments permitted to be completed remotely include assessment of adverse events and concomitant medications. The Columbia-Suicide Severity Rating Scale (C-SSRS) may be performed remotely, and any positive results will be reviewed with an Investigator-delegated clinician to ensure the participant is not at risk for suicide. Lab draws (PK, pregnancy testing and safety labs), ECG, physical exam and vital signs will need to be collected by an appropriate healthcare professional from the site or captured as a deviation if it is not possible to collect these data.

Efficacy Assessments:
Due to the nature of the participant CDRS-R assessment, the interview may be performed remotely provided that the participant has access to a videoconferencing platform where the rating clinician can visually see the participant during the discussion. The parent/caregiver CDRS-R interview may be conducted via phone or videoconferencing.

Study Medication Dispensation for Remote Study Visits:
If it is necessary to conduct any part of a visit remotely, resulting in Study Medication not being able to be dispensed to the patient at the study site, the option to have study medication delivered by courier direct-to-patient (DTP) may be possible. Approval by the Sponsor for DTP will need to be obtained from the Study Site each time DTP is utilized.

Amendment 1 Summary of Changes

The original protocol, dated 02 Mar 2018, has been amended to reflect the following changes:

1. Clarification that pharmacokinetic samples will only be collected in patients aged 7 to 11 years old.
2. Clarification that participants from Study LVM-MD-11 are excluded from participating in this study.
3. Updated exclusion item #2 to replace the term "mental retardation" with "intellectual disability" per the category in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition.
4. Added interim futility analysis for when approximately 50% of randomized patients have either completed or discontinued the study.

2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study LVM-MD-14	
Title of Study	A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Pediatric Patients 7-17 Years With Major Depressive Disorder
Study Centers	Approximately 60 study centers
Development Phase	3
Objective	To evaluate the efficacy, safety, and tolerability of levomilnacipran compared with placebo in pediatric outpatients (7-17 years) with major depressive disorder (MDD). In addition, the study is designed to obtain pharmacokinetic (PK) data to define the PK profile of levomilnacipran in the pediatric population (7-17 years of age).
Methodology	Multicenter, randomized, double-blind, placebo- and active-controlled, flexible-dose, parallel group study During the coronavirus disease 2019 (COVID-19) pandemic, remote study visits were implemented and will continue to be possible to avoid missing efficacy but are not preferred over clinic visits. The study center needs to alert the Sponsor, ahead of time when possible, that a remote procedure was performed.
Number of Patients	480 planned (160 placebo, 160 levomilnacipran, and 160 fluoxetine)
Diagnosis and Main Criteria for Inclusion	Male and female outpatients, 7 to 17 years of age (inclusive), who meet *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (DSM-5) criteria for MDD; have a score of ≥ 40 on the Children's Depression Rating Scale–Revised (CDRS-R) at Visits 1 and 2, and Clinical Global Impressions-Severity (CGI-S) score ≥ 4 at Visits 1 and 2. The Kiddie Schedule for Affective Disorders–Present and Lifetime (K-SADS–PL) will be used to confirm the diagnosis of MDD and to document the patient's psychiatric history.
Test Product, Dosage, and Mode of Administration	Encapsulated levomilnacipran extended-release (ER) 10 mg (nontrade), 20 mg, and 40 mg capsules; once-daily oral administration, at the same time each day
Duration of Study	• 10 weeks in duration: 1-week screening/washout period, followed by an 8-week double-blind treatment period and a 1-week double-blind down-taper period
Reference Therapy, Dosage, and Mode of Administration	Placebo capsules, once-daily oral administration, at the same time each day Encapsulated fluoxetine 10 mg capsules and encapsulated fluoxetine 20 mg capsules; once-daily oral administration, at the same time each day
Criteria for Evaluation	
Primary Outcome Measure	CDRS-R change from baseline at Week 8
Secondary Outcome Measure	CGI-S change from baseline at Week 8

Safety Measures	Adverse event (AE) recording, clinical laboratory tests, vital sign measurements including height and weight, electrocardiograms (ECGs), physical examinations, and Columbia–Suicide Severity Rating Scale (C-SSRS)
Pharmacokinetic Analysis	The population PK of levomilnacipran will be characterized using plasma concentration-time data. The maximum plasma drug concentration, area under the curve, time of maximum plasma concentration, half-life, apparent oral clearance and/or apparent volume of distribution for levomilnacipran ER will be estimated and a summary will be reported.
Statistical Methods	The primary efficacy parameter is the change from baseline to end of Week 8 of the double-blind treatment period in the CDRS-R total score. The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with treatment group, study center, visit, and treatment group–by-visit interaction as the fixed effects and the baseline value and baseline value–by-visit interaction as the covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. This analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values. The secondary efficacy parameter is the change from baseline to end of Week 8 of the double-blind treatment period in CGI-S. This parameter will be analyzed using an MMRM similarly to the primary efficacy parameter. All safety parameters will be analyzed descriptively. The safety analysis will be performed using the *Safety Population,* defined as all randomized patients who received at least 1 dose of the investigational product. Efficacy analyses will be performed using the *Intent-to-Treat (ITT) Population,* defined as all patients in the Safety Population who had the baseline and at least 1 postbaseline assessment of CDRS-R total score. Population PK parameters will be estimated using nonlinear mixed-effects modeling methods. The study will be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for levomilnacipran ER, with at least 80% power.

SCHEDULE OF EVALUATIONS: Study LVM-MD-14									
	Screening Period	***Double-blind Treatment Period***							***Double-blind Down-taper Period***
	Visit 1[a]	*Visit 2 (Baseline)*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Visit 8/ ET*[b]	*Visit 9/SFU*[c]
End of Study Week	–1	0	1	2	3	4	6	8	9
Informed assent (patient) and consent (parent[s])/LAR)	X								
Informed consent (caregiver)[d]	X								
Inclusion and exclusion criteria	X	X							
Determination of ability to swallow capsule	X								
Medical history	X								
Psychiatric history	X								
Medication history and nondrug psychiatric treatment history	X	X							
Concomitant medications			X	X	X	X	X	X	X
Physical examination	X[e]							X	
Clinical laboratory determinations	X[e]							X	
Serum β-hCG pregnancy test[f]	X[e]							X	
Thyroxine, TSH tests	X[e]								
Urine drug screen	X[e]								
ECG	X[e]				X			X	
Vital signs (BP, pulse, weight)		X	X	X	X	X	X		X
Vital signs (BP, pulse, weight and height[g])	X[e]							X	
K-SADS-PL[h]	X								

SCHEDULE OF EVALUATIONS: Study LVM-MD-14									
	Screening Period	***Double-blind Treatment Period***							***Double-blind Down-taper Period***
	Visit 1[a]	*Visit 2 (Baseline)*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Visit 8/ ET*[b]	*Visit 9/SFU*[c]
End of Study Week	–1	0	1	2	3	4	6	8	9
CDRS-R	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X
PK Sampling[i]					X	X	X		
AEs	X	X	X	X	X	X	X	X	X
IP dispensing		X	X	X	X	X	X	X[j]	
IP return			X	X	X	X	X	X	X[j]
IP compliance			X	X	X	X	X	X	X[j]

Note: If necessary, visits may be conducted up to 3 days before or after scheduled visits relative to the Baseline Visit (Visit 2).

a After assent and consent are obtained, the screening period may be up to 5 weeks in duration, as described in Section 9.5.5.

b Visit 8 assessments to be completed for all randomized patients who complete the study or discontinue before Week 8.

c All randomized patients must complete Visit 8/ET and, at the end of the down-taper period, return for Visit 9/SFU. Patients who do not enter the down-taper period must return for Visit 9/SFU approximately 1 week after Visit 8/ET Visit.

d If the parent(s), guardian, or legally authorized representative (LAR) is also the patient's caregiver, he/she will be asked to sign both the parent and caregiver consents.

e May be repeated at the Investigator's discretion before Visit 2.

f A pregnancy test will be obtained for female patients of childbearing potential only.

g Height will be recorded at Screening (Visit 1) and Visit 8/ET using a stadiometer.

h K-SADS-PL data will be retained as source documents at the site.

i ***PK only collected on participants aged 7-11 years.*** Sparse PK blood samples will be collected during Visit 5 (at predose and 1-4 hour postdose), Visit 6 (4-6 hours postdose), and Visit 7 (6-8 hours postdose). At Visit 5, or at any 24-hour period between Visit 5 and Visit 7, inclusive, serial blood samples will be collected from a subset of consented 7-11-year-old patients instead of sparse PK samples at the following time points: predose [20-24 hours after the most recent dose], and 2, 4, 6, 8, 10-12, and 24-hours postdose. Refer to Section 9.5.3 for additional details.

j For patients entering the double-blind down-taper period.

AE = adverse event; β-hCG = β-human chorionic gonadotropin; BP = blood pressure; CDRS-R = Children's Depression Rating Scale–Revised; CGI-I = Clinical Global Impressions–Improvement (scale); CGI-S = Clinical Global Impressions–Severity (scale); C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; IP = investigational product; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime; LAR = legally authorized representative; PK = pharmacokinetic; SFU = Safety Follow-up; TSH = thyroid stimulating hormone

2.1 SCHEDULE OF EVALUATIONS THAT MAY BE PERFORMED REMOTELY

	Double-blind Treatment Period							
	Visit 2 (Baseline)	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Visit 8/ ET[b]*	*Visit 9/ SFU[c]*
End of Study Week	0	1	2	3	4	6	8	9
Inclusion and exclusion criteria	X							
Medication history and nondrug psychiatric treatment history	X							
Concomitant medications[a]		X	X	X	X	X	X	X
Physical examination[a]							X	
Clinical laboratory determinations[a]							X	
Serum β-hCG pregnancy test[a]							X	
ECG[a]				X			X	
Vital signs (BP, pulse, weight)[a]	X	X	X	X	X	X		X
Vital signs (BP, pulse, weight and height)[a]							X	
CDRS-R[a]	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	
CGI-I		X	X	X	X	X	X	
C-SSRS[a]	X	X	X	X	X	X	X	X
PK Sampling[a]				X	X	X		
AEs[a]		X	X	X	X	X	X	X
IP dispensing[a]	X	X	X	X	X	X	X	
IP return[a]		X	X	X	X	X	X	X
IP compliance[a]		X	X	X	X	X	X	X

Note: If necessary, visits may be conducted up to 3 days before or after scheduled visits relative to the Baseline Visit (Visit 2).

a Remote assessments must be performed by an appropriate, qualified health care professional from the site. Patient data which are collected via phone, videoconference, or telehealth video should remain consistent with either methods for each patient. For remote visits, study drug may be sent to patients via preferred courier or curbside pickup.

b Visit 8 assessments to be completed for all randomized patients who complete the study or discontinue before Week 8.

c All randomized patients must complete Visit 8/ET and, at the end of the down-taper period, return for Visit 9/SFU. Patients who do not enter the down-taper period must return for Visit 9/SFU approximately 1 week after Visit 8/ET Visit.

AE = adverse event; β-hCG = β-human chorionic gonadotropin; BP = blood pressure; CDRS-R = Children's Depression Rating Scale–Revised; CGI-I = Clinical Global Impressions–Improvement (scale); CGI-S = Clinical Global Impressions–Severity (scale); C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; IP = investigational product; PK = pharmacokinetic; SFU = Safety Follow-up

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4.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HTP	5-hydroxytryptophan
AGN	Allergan
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BP	blood pressure
CDRS-R	Children's Depression Rating Scale-Revised
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DHEA	dehydroepiandrosterone
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition
DTP	direct-to-patient
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
ER	extended release
ET	early termination
FDA	Food and Drug Administration
FR	Federal Register

GCP	good clinical practice
GLMM	generalized linear mixed model
β-hCG	β-human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent to treat
IWRS	interactive Web response system
K-SADS-PL	Kiddie Schedule for Affective Disorders–Present and Lifetime
LAR	legally authorized representative
LOCF	last observation carried forward
MDD	major depressive disorder
MMRM	mixed-effects model for repeated measures
NDA	New Drug Application
NE	norepinephrine
PCS	potentially clinically significant
PID	patient identification
PK	pharmacokinetic, pharmacokinetics
PVC	premature ventricular contraction
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{1/2}$)
QTcF	QT interval corrected for heart rate using the Frederica formula ($QTcF = QT/[RR]^{1/3}$)
RSM	Regional Site Manager

SAE	serious adverse event
SFU	safety follow-up
SNRI	serotonin and norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States
Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Allergan (AGN [the Sponsor]) along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with the US CFR, Title 21, Part 56.

Outside the United States
This study will be carried out in full compliance with the guidelines of the independent ethics committee (IEC) and government agencies of each respective country as well as the European Union Clinical Trial Directive (Directive 2001/20/EC), where applicable. Before the study begins, the study center will require approval from an IEC and government agency. During the study, AGN or authorized representative will provide timely and accurate reports to the IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IEC of SAEs or other significant safety findings. The study protocol, ICF, information sheet advertisements, and amendments (if any) will be approved by the IEC at the study center in conformance with CFR, Title 21, Part 56, the European Union Clinical Trial Directive (Directive 2001/20/EC), and local regulations.

5.2 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the US CFR.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, the Sponsor will engage with study site personnel in efforts to ensure the safety of patients, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage patient continuity of care. This may include alternative methods for assessments (eg, phone contacts or virtual site visits), and shipping investigational product and/or supplies direct to patients to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify the Sponsor if any urgent safety measures are taken to protect the patients against any immediate hazard.

5.3 PATIENT INFORMATION AND INFORMED CONSENT

After being given an explanation of the study and before participating in any study procedures, each patient, if developmentally appropriate, must provide written assent, and his or her parent(s), legal guardian(s), or legally authorized representative (LAR) (hereafter referred to as parent/guardian/LAR) must provide voluntary and written informed consent in compliance with 21 CFR, Parts 50 and 312 and give HIPAA authorization (or an equivalent of HIPAA authorization in non-US countries).

The signed documents will be placed in the Investigator's study files. A unique patient identification (PID) number will be assigned.

5.3.1 Patient Assent Form

To participate in the study, the patient will read, assent understanding of, sign the assent form, and be made aware they can withdraw from the study at any time. Patients who are unable to read the assent form will have the statements read to them. If the patient cannot sign the form, a witness will be allowed to provide written verification of oral assent. A copy of the signed assent will be given to the patient's parent/guardian/LAR.

5.3.2 Parent, Legal Guardian, and Legally Authorized Representative Informed Consent

Written informed consent will be obtained from the patient's parent/guardian/LAR before the patient participates in any study-related procedure. To provide consent for the patient's participation in the study, the patient's parent/guardian/LAR will read, assent to an understanding of, and sign an instrument of informed consent or other locally applicable regulations and authorization form after having had an opportunity to discuss the forms with the Investigator before signing. The parent/guardian/LAR will be made aware that the patient may withdraw from the study at any time and will receive a copy of the signed ICF. Patients who reach the age of majority (ie, 18 years of age in most jurisdictions) during the course of the study, are required to be re-consented.

5.3.3 Caregiver Consent

A caregiver is a person identified as able and willing to provide safety and efficacy information about the patient and oversee the administration of investigational product, and may be a different individual than the parent/guardian/LAR. The caregiver must commit to accompanying the patient to each study visit. To be eligible for the study, the caregiver, whether or not he or she is the parent/guardian/LAR, must read and sign the caregiver consent and meet the relevant inclusion/exclusion criteria. If the parent/guardian/LAR is the caregiver, he or she will be asked to sign both the parent/legal guardian permission (ICF) and the caregiver consent. If a caregiver is replaced during the study, each caregiver must provide separate ICF/caregiver consents and will be given a signed copy of his/her caregiver consent.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 60 study centers.

The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator's Statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator at each site must meet his or her obligations to the patients, ethics committee, AGN, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to staff qualified by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of their capabilities and performance is consistent with the study investigational plan. The Investigator at each site will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB/IEC, and completing the electronic case report forms (eCRFs). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

7.0 INTRODUCTION

Major depressive disorder (MDD) is a common and serious illness in children and adolescents. Epidemiological studies and clinical samples estimate the prevalence of MDD as approximately 1%-2% of prepubertal children, and between 3% and 8% of adolescents (Zalsman 2006). By the ages of 10 to 15, girls appear to be more likely to experience depression than boys (Angold 1998).

MDD is commonly associated with feelings of worthlessness, low self-esteem, and thoughts of suicide and its psychosocial burden in the formative years can compromise the developmental process. Patients also experience difficulties with concentration and motivation, impairing functioning in this critical period. Each year as many as 20% of adolescents have suicidal ideation and 9% attempt suicide (Grunbaum JA 2002). Suicide is a leading cause of death in adolescents and is a major public health concern (CDC 2014). A major risk factor for suicide in adolescents is major depression.

MDD in children and adolescents can be chronic and recurrent. The mean length of pediatric depressive episodes is approximately 7 months, and in the course of a first episode, up to 40% of patients appear to recover without specific treatment. However, patients who do not recover appear to be at high risk of chronic depression, and those who do recover have high rates of recurrence and dysthymia (Zalsman 2006).

As a pharmacological treatment, the use of selective serotonin reuptake inhibitors (SSRIs) for children and adults increased approximately 7-fold during the 1990s. Fluoxetine (Prozac®), an SSRI, is approved by the FDA for the treatment of MDD in children and adolescents 8 years and older. Escitalopram (Lexapro®), another SSRI, is approved for the treatment of MDD in patients aged 12 and over. Currently, no serotonin and norepinephrine reuptake inhibitors (SNRIs) have been approved for the treatment of MDD in children or adolescents.

Levomilnacipran is an SNRI approved for the treatment of MDD in adults in the United States. The pharmacologic mechanism of the antidepressant activity of levomilnacipran and other SNRIs (ie, duloxetine, venlafaxine, and desvenlafaxine) is thought to be mediated through inhibition of norepinephrine (NE) and 5-hydroxytryptamine (serotonin) (5-HT) reuptake in the central nervous system. Although all SNRIs (as a class) block 5-HT and NE reuptake, currently marketed SNRIs (duloxetine, venlafaxine, and desvenlafaxine) are more potent inhibitors of 5-HT reuptake than of NE reuptake (Deecher 2006; Vaishnavi 2004). Levomilnacipran exhibits a distinct *in vitro* profile, exhibiting more potent inhibition of NE reuptake than 5-HT reuptake (Auclair 2013). This greater potency at the NE transporter may confer additional improvements specifically in those domains associated with noradrenergic neurotransmission; for example: alertness, energy, attention, and anhedonia (Montgomery and Briley, 2011).

The efficacy of levomilnacipran as measured by the Montgomery-Åsberg Depression Rating Scale total score was established in 3 pivotal studies of adult patients with MDD. Levomilnacipran also demonstrated superiority over placebo as measured by improvement in the Sheehan Disability Scale functional impairment total score. These studies, which were conducted in the United States and Canada, were placebo-controlled; no active comparator was included. Two of the studies were fixed-dose studies (LVM-MD-01: placebo, levomilnacipran 40 mg/day, 80 mg/day, and 120 mg/day; and LVM-MD-10: placebo, levomilnacipran 40 and 80 mg/day) and 1 study was flexible-dose (LVM-MD-03: placebo, levomilnacipran 40 mg/day to 120 mg/day).

In summary, MDD is a condition common in children and adolescents and is a major public health concern. Current approved treatment options for this condition are limited to the 2 aforementioned SSRI products. Since the modulation of energy, vigilance, and arousal can be directly linked to the noradrenergic system, it has been suggested that antidepressants with a prominent noradrenergic component, such as levomilnacipran, may be particularly effective in addressing functional impairment, decreased concentration, lassitude, mental and physical slowing, and decreased self-care (Citrome 2013). Brain serotonin and norepinephrine systems continue to mature through childhood and adolescence, however, and these maturational effects may generate age-related differences in patients' responses to pharmacotherapy. Thus, it is important that further investigation of SNRI treatment options such as levomilnacipran be evaluated systematically for the treatment of MDD in children and adolescents, so that an SNRI's efficacy and safety profile can be characterized in this population.

The current study of levomilnacipran extended release (ER) in pediatric patients (7-17 years old) with MDD will be conducted as required under the Pediatric Research Equity Act and as agreed upon with the FDA as a part of Postmarketing Requirement studies.

8.0 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy, safety, and tolerability of levomilnacipran compared with placebo in pediatric outpatients (7-17 years) with MDD.

In addition, the study is designed to obtain pharmacokinetic (PK) data to define the PK profile of levomilnacipran in the pediatric population (7-17 years of age).

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

Study LVM-MD-14 will be a multicenter, randomized, double-blind, placebo- and active-controlled, flexible-dose, parallel group study in pediatric patients, ages 7-17 years. The study will be approximately 10 weeks in duration:

- 1-week screening/washout period
- 8-week double-blind treatment period
- 1-week double-blind down-taper period

The screening/washout period will be generally 1 week (± 3 days) prior to Visit 2 (Baseline), but may be extended up to a total of 5 weeks to accommodate prior medication washout or to repeat assessments. Patients will not receive any investigational product during the screening period.

Patients who meet the eligibility criteria at Visit 2 (Baseline) will be randomized to 1 of 3 treatment groups: placebo, levomilnacipran, or fluoxetine. See Section 9.4.5 for details regarding dose selection and timing.

All randomized patients who complete the 8-week double-blind treatment period and patients who prematurely discontinue from the study before completing 8 weeks of double-blind treatment should enter the 1-week, double-blind down-taper period unless it is considered not clinically appropriate by the Investigator.

All randomized patients must complete Visit 8/Early Termination (ET) Visit and, at the end of the down-taper period, return for Visit 9/Safety Follow-up (SFU) Visit. Patients who do not enter the down-taper period must return for Visit 9/SFU Visit approximately 1 week after Visit 8/ET Visit.

Approximately 480 patients (160 per treatment group) are planned to be randomized in the study.

Figure 9-1 provides a schematic of the study design.

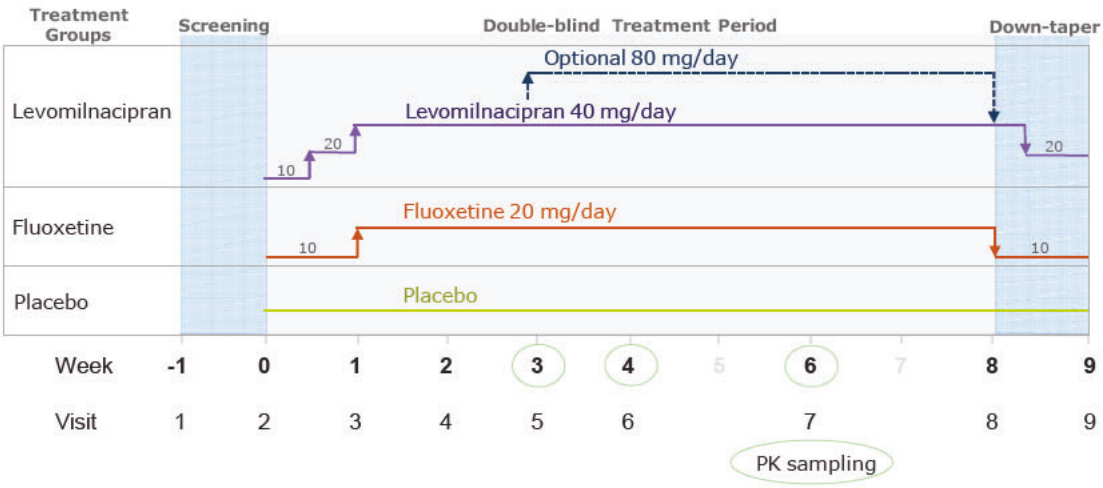
The coronavirus disease 2019 (COVID-19) pandemic developed after this study began, and this protocol has been amended to account for study procedures that may need to be modified in association with adhering to local guidelines or regulations or site flexibility to complete study-required procedures.

During the COVID-19 pandemic, remote study visits, in which data are collected via phone or videoconference, were and will continue to be possible when needed. To accommodate changes that sites may need to implement during the pandemic, Section 2.0 outlines the conduct of study assessments during on-site clinic visits, which is the preferred method of conducting the study, while study assessments for remote visits are included in Section 2.1. Sites will need to inform the Sponsor of the need for a remote visit in advance whenever possible.

In the event that it is required to perform procedures remotely, every effort should be made to perform the remote assessment in a manner as similar as possible to the on-site assessment. Patient data collected via phone or video conferencing should remain consistent with either method for each patient.

Detailed descriptions of each study visit are provided in Section 9.5.5.

Figure 9-1. Study Design



Levomilnacipran treatment group: During the double-blind treatment period, patients will take levomilnacipran 10 mg/day on Days 1-3, 20 mg/day on Days 4-7, and 40 mg/day during Weeks 2 through 8. Based on therapeutic response and tolerability, an additional dose increase to 80 mg/day is permitted at Week 3. During the down-taper period, patients will take levomilnacipran 40 mg/day for 2 days, and then levomilnacipran 20 mg/day for 5 days.
Fluoxetine (active comparator) treatment group: During the double-blind treatment period, patients will take fluoxetine 10 mg/day on Days 1-7, and then 20 mg/day during Weeks 2 through Week 8. During the down-taper period, patients will take fluoxetine 10 mg/day for 7 days.

9.1.1 COVID-19 Specific Process

To promote patient safety and ensure the completion of study-required procedures during the COVID-19 pandemic, the following processes will be implemented.

The patient must not have signs/symptoms associated with COVID-19 infection or known exposure to a confirmed case of COVID-19 infection during 14 days prior to Screening. Patients who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:

- Symptomatic patients: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (eg, cough, shortness of breath)

- Asymptomatic patients: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: patients who develop symptoms will follow guidance above for symptomatic patients)

Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Visit conduct options will allow remote visits as outlined below:

- Option 1: In-clinic visits

This is the preferred option. All study visits are performed as in clinic visits with all assessments outlined in the Schedule of Assessments in Section 2.0.

- Option 2: Remote visits (except screening)

This option is only to be used if local guidance, regulations, or the needs of the patient prevent the site or the patient from completing on-site visit procedures. Screening visits must take place as an in-clinic visit with all assessments outlined in the schedule of assessments in Section 2.0. All other visit procedures (V2-V8) can be completed remotely with the assessments outlined in Section 2.1. The study center needs to alert the Sponsor, ahead of time when possible, that a remote procedure was performed.

For remote visits, there is an option to have study drug delivered by preferred courier. Approval from the Sponsor study team must be obtained from the study center each time the preferred courier service is utilized.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This placebo- and active-controlled, flexible-dose design with an 8-week double-blind treatment period was chosen based on prior studies that established the efficacy and safety of levomilnacipran in adult patients with MDD. In this study, Investigators must use a valid and reliable diagnostic method for recruiting and enrolling children and adolescents meeting *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (DSM-5; American Psychiatric Association 2013) criteria for MDD.

A placebo arm is included for comparison since placebo-controlled superiority trials have been shown to be conducive to higher quality studies and to provide more reliable outcomes than non-inferiority comparisons to a previously approved drug (Feifel 2008; Laughren 2001; Gispen-de Wied 2012). In addition, placebo in place of the (limited) standard therapy should not cause irreversible health problems or extreme suffering (depression is recognized by the FDA as a condition in which there is substantial improvement and variability in placebo groups; see FDA Guidance for Industry: E10, May 2001).

Fluoxetine was selected as an active comparator for assay sensitivity in the present study because it is an SSRI approved by the FDA for the treatment of MDD in children and adolescents 8 years and older.

In the current study, safety and efficacy assessments are included in every visit to determine adequacy of response, safety, and tolerability for all patients.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

Patients must provide assent to participate and their parent/guardian/LAR and caregiver (even if the same as the parent/guardian/LAR) must provide written informed consent prior to the conduct of any study-specific procedures (see also Section 5.3).

To be eligible to participate in the study, patients must meet the following criteria:

1. Male or female outpatients 7 to 17 years of age, inclusive, at Visit 1
2. Patients must meet DSM-5 criteria for MDD, confirmed by K-SADS-PL
3. Patients must have a score ≥ 40 on the Children's Depression Rating Scale-Revised (CDRS-R) at Visits 1 and 2
4. Patients must have a Clinical Global Impressions-Severity (CGI-S) score ≥ 4 at Visits 1 and 2
5. Patients must have a caregiver who can and is willing to consent to be responsible for safety monitoring of the patient, provide information about the patient's condition, oversee the administration of investigational product, and accompany the patient to all study visits (see Section 5.3)
6. Patients must have normal physical examination findings, vital sign values, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal results that are judged not clinically significant by the Investigator
7. Female patients of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result at Visit 1
8. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection or known exposure to a confirmed case of COVID-19 infection during 14 days prior to Screening.

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria at Visit 1 (Screening) or Visit 2 (Baseline) will not be eligible to participate in the study**:**

Psychiatric Criteria

1. DSM-5–based diagnosis of an axis I disorder other than MDD that is the primary focus of treatment. Patients with conduct disorder will not be allowed to participate.

Patients with comorbid diagnoses of learning disorders, attention deficit disorder (with or without hyperactivity), communication disorders, separation anxiety disorder, dysthymic disorder, oppositional defiant disorder, and anxiety disorders will be allowed to participate in the study as long as these conditions are not the primary focus of any treatment and they comply with concomitant medication limitations as listed in Appendix III

2. Prior diagnosis of ***intellectual disability*** or amnestic or other cognitive disorders based on DSM-5 criteria

3. Imminent risk of injuring self or others or causing damage to property as judged by the Investigator

4. Suicide risk as determined by meeting either of the following criteria:
   - Any suicide attempt within the past year
   - Significant risk at Visit 1 (Screening) or Visit 2 (Baseline), as judged by the Investigator based on the psychiatric interview or information collected in the Columbia-Suicide Severity Rating Scale (C-SSRS)

Treatment-Related Criteria

5. History of allergy, intolerance, or hypersensitivity to levomilnacipran, milnacipran, fluoxetine, or any other SSRI or SNRI or known hypersensitivity to the investigational products' non-medicinal ingredients including gelatin and cellulose

6. Patients requiring prohibited concomitant medication or herbal supplements that could not be discontinued or switched to an allowable alternative medication and stabilized for at least 2 weeks preceding Visit 2 (Baseline)

7. Patients taking any psychoactive drug or psychoactive herbal remedy within 5 half-lives before Baseline (Visit 2), (St. John's wort, ginkgo biloba, kava kava, SAMe, valerian root, dehydroepiandrosterone (DHEA), tyrosine, tryptophan and 5-hydroxytryptophan (5-HTP), antidepressants, anxiolytics, monoamine oxidase inhibitors, antipsychotics, or anticonvulsants/mood stabilizers, carbamazepine, or others). Patients who have ever been treated with a depot antipsychotic must also be excluded

8. Patients who have initiated or terminated psychotherapy or behavior therapy within 1 month before Visit 1 (Screening), or who plan to initiate or change such therapies during the course of the study

Other Medical criteria

9. A clinically significant disease state that, in the investigator's opinion, might indicate that the patient is unsuitable for the study

10. A history or evidence of malignancy, unless the condition has been stable for > 3 years for a malignancy other than excised basal cell carcinoma; excised basal cell carcinoma must have been stable for ≥ 1 year

11. Any cardiovascular disease or condition that is clinically significant, unstable, or decompensated. Additionally, patients with any of the following conditions are excluded from participation in the study:
    a. Second-degree (if Mobitz II) or third-degree atrioventricular block
    b. Premature ventricular contraction (PVC) associated with clinical symptoms and/or any complex PVCs (ie, PVCs that are frequent [> 30/hour] or ≥ 2 beats if multifocal or show bigeminy, trigeminy, quadrigeminy, couplets, triplets [salvos], or R-on-T phenomenon)
    c. Atrial fibrillation or flutter that is symptomatic or associated with uncontrolled heart rate or hemodynamic instability, requiring anticoagulation, or is of recent (< 12 months) or unknown onset
    d. Any systolic and/or diastolic blood pressure (BP) and/or manually measured pulse rate and/or QTc interval (Frederica corrected) that is symptomatic or clinically significant per the opinion of the Investigator

12. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 3 months before Visit 1 (Screening)

13. Any condition that would be expected to affect drug absorption (eg, gastric bypass surgery)

14. History of seizure disorder (except simple childhood febrile seizures before age 5), unexplained syncope or black-out episodes, stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes the patient toward a risk for seizure

15. Liver enzyme tests (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) > 2 times the upper limit of normal (ULN)

16. History of conditions that might worsen with SSRI or SNRI treatment (eg, syndrome of inappropriate antidiuretic hormone secretion)

17. History of drug or alcohol abuse or dependence within the past year

18. Positive result from the blood alcohol test or the urine drug screen (UDS) for prohibited substance, with the following exceptions:

    a. Positive blood alcohol test may be allowed if there is a negative repeat test before Visit 2 (Baseline)

    b. Amphetamines can be allowed if prescribed for treatment of attention deficit disorder at a dose that is stable for at least 60 days before Visit 1 (Screening). If not stable for at least 60 days before Visit 1 (Screening), the patient should be discontinued. However, the patient can be rescreened on a later date

    c. Patients who have a positive UDS for other prohibited substances (barbiturates, benzodiazepines, opiates, cannabinoids, cocaine, methadone, phencyclidine, or other prohibited concomitant medications) may be allowed to enroll if (1) the substance use is discontinued, and (2) this is documented by a negative UDS before Visit 2 (Baseline). If the repeat UDS cannot be performed within 21 days of the initial UDS, the patient should be discontinued. The patient can be rescreened on a later date if use is discontinued and must have a negative UDS

19. Pregnant, breastfeeding, and/or planning to become pregnant and/or breastfeed during the study or within 30 days following the end of study participation

20. For female patients of childbearing potential who are sexually active:

    Not practicing a reliable method of contraception that will continue for the duration of the study and within 30 days following the end of study participation. Reliable contraception is defined as:

    a. surgical sterilization

    b. oral contraceptives (consisting of an estrogen-progestin combination or progestin alone)

    c. transdermally delivered contraceptives (eg, Ortho-Evra), depot injections (eg, Depo-Provera)

    d. vaginal contraceptive ring (eg, NuvaRing), contraceptive implants (eg, Implanon, Norplant II/Jadelle)

    e. an intrauterine device

    f. diaphragm plus condom (the only acceptable double-barrier method)

    g. Other forms of contraceptives (pharmacological and/or non-pharmacological) are not accepted

Use of hormonal contraceptives by females of childbearing potential must have been stable for at least 1 month before Visit 1 and must follow that product's package insert instructions concerning additional protection at times when doses might be missed. The following are examples of contraception methods that are not acceptable: rhythm, withdrawal, single-barrier methods (eg, contraceptive sponge, female condom or male condom alone or with spermicide, diaphragm alone or with spermicide), the sole planned reliance on emergency contraceptives (eg, Plan B). Patients who are abstinent must agree to use one of the acceptable forms of contraception should they become sexually active.

21. For sexually active male patients:

    Not agreeing to use contraception as detailed below during the treatment period and for at least 30 days after the last dose of investigational product.

    A male condom plus partner use of a contraceptive method with a failure rate of < 1% per year when having penile-vaginal intercourse with a female partner of childbearing potential

Other Criteria

22. Patients who are unable to swallow capsules

23. Participation in Study LVM-MD-11.

24. Treatment with any investigational product within 3 months (or at least 5 half-lives, whichever is longer) of Visit 1. Treatment with any investigational product other than those provided by AGN during study participation will be a protocol violation, and the patient will be terminated from this study

25. Employee or immediate relative of an employee of AGN, any of its affiliates or partners, or of the study center

26. Patients or patients whose parent/guardian/LAR and/or caregivers are unable to speak and understand English (or their native language if this can be accommodated by the site and is approved by the Sponsor) sufficiently to understand the nature of the study, to provide informed assent/consent, or to allow the completion of all study assessments

27. Unable or unlikely to comply with the study protocol or are unsuitable for any other reason, as judged by the Investigator

9.3.3 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who gave voluntary assent and/or whose parent/guardian/LAR and/or caregiver signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study. Patients can be prematurely discontinued from the study for any of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Withdrawal by subject
- Adverse event (AE)
- Lack of efficacy
- Protocol deviation
- Non-compliance with study drug
- Lost to follow-up
- Study terminated by Sponsor
- Site terminated by Sponsor
- Other

All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at ET (see Section 9.5.5.6 for details on assessments performed at Visit 8/ET). Patients who discontinued from the study and did not return to the site for final assessments must be requested in writing to do so and to return any unused investigational product. A copy of the letter, together with the source documentation, will be kept by the Investigator. The reasons for premature discontinuation from the study will be recorded on the Study Disposition Pages of the eCRF.

All randomized patients must complete Visit 8/ET Visit and return for Visit 9/SFU at the end of the down-taper period. Patients who do not enter the down-taper period must return for Visit 9/SFU approximately 1 week after Visit 8/ET Visit.

9.3.4 Patient Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

9.3.5 Demographic Considerations

Efforts will be made to have reasonable representation with respect to gender, race, and ethnicity, reflecting the proportions in the disease population. AGN will monitor enrollment and may instruct the sites accordingly.

9.4 TREATMENTS

Patients meeting the eligibility criteria at Visit 2 (Baseline) will be randomized in a double-blind fashion to 1 of 3 treatment groups: placebo, levomilnacipran, or fluoxetine.

9.4.1 Treatments Administered

At Visit 1 (Screening) and after consent/assent is obtained, patients will be given a placebo capsule to swallow to confirm their ability to swallow investigational product.

Investigational product in the form of over-encapsulated capsules will be packaged in blister cards and provided by AGN. Patients will be supplied with blinded investigational product and will be instructed to take 2 capsules orally each morning (see Section 9.4.5 for details). Confirmation that dosing scheme (including titration and down-taper) and dosing instructions were discussed with the patient and caregiver, and that dosing instructions were provided will be recorded in the source documents.

9.4.2 Identity of Investigational Products

Investigational product will be supplied by AGN as capsules containing placebo or nontrade levomilnacipran 10 mg capsules, trade levomilnacipran 20 mg capsules, trade levomilnacipran 40 mg capsules, fluoxetine 10 mg capsules, or fluoxetine 20 mg capsules packaged in blister cards.

The blister cards will contain sufficient numbers of doses for the interval of days between scheduled visits plus additional doses to accommodate visit scheduling.

The blister cards will be labeled with the protocol number, storage information, warning language (viz, “Caution: New Drug—Limited by Federal Law to Investigational Use”), and instructions to take as directed. The Investigator will write the date, visit number, study week, and PID number on the label.

All investigational product will be provided and shipped to the study centers by AGN and must be stored in an appropriate secure area (eg, a locked cabinet in a locked room) at room temperature (25°C or 77°F, with a permitted range of 15°C-30°C or 59°F-86°F), and must be protected from light, heat, and moisture.

The Investigator is responsible for recording the receipt and use of all investigational product supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused investigational product must be returned; and, whenever investigational product are returned, unit counts must be performed. All investigational product must be accounted for. At the end of the study, all unused investigational product and empty investigational product packages must be returned to the Sponsor at the address provided in the Study Reference Binder.

9.4.3 Method of Assigning Patients to Treatment Groups

After the patient, parent/guardian/LAR, and caregiver provide assent and sign the ICF at Visit 1 (Screening), study personnel will register the patient in the interactive Web response system (IWRS), and the system will assign the patient a sequential PID number. The first patient entered into the system at each site will be assigned the first number in the sequence by the system. This PID number will be used to identify the patient throughout the study (ie, at all study phases).

The study center must contact the IWRS at Baseline (Visit 2) and all subsequent study visits in order to obtain the instructions on kit number for the investigational product to be dispensed to the patient at that visit.

A detailed description of IWRS procedures is contained in the IWRS Site User Guide that should be stored in the Study Reference Binder.

9.4.4 Selection of Dosages in the Study

Doses of levomilnacipran in pediatric patients (7-17 years of age) were selected based on modeling of available PK data submitted with NDA 204,168 from the adult healthy volunteers and patients with MDD, as well as adolescent patients (12-17 years of age, LVM-MD-11, 2017) with MDD. Based on the results of modeling a common dosing scheme for both age groups of 7-11 and 12-17 years is appropriate. While the adolescent age group, 12-17 years of age, demonstrates similar plasma concentrations as adults administered the same dose of 80 mg/day, for the younger age group, 7-11 years of age, data indicate that equivalent concentrations are achieved with approximately a 33% dose reduction. Thus, 80 mg/day is expected to show exposure similar to exposures seen for the adult population administered 120 mg/day.

Based on the above findings, levomilnacipran 40 mg/day, with an optional increase to 80 mg/day based on therapeutic response and tolerability, is appropriate for the pediatric patient age range (7-17 years of age). The corresponding plasma concentrations of these doses in pediatric patients are expected to remain within the plasma concentrations associated with the approved therapeutic dose range for adults.

9.4.5 Selection and Timing of Dose for Each Patient

All investigational products should be taken orally as a single dose, once-daily at the same time each day. After consent/assent is obtained, patients undergoing screening will be required to swallow a placebo capsule to confirm their ability to swallow the investigational product, as part of their eligibility assessment.

Patients who meet all eligibility criteria at Visit 1 (Screening) and who continue to meet all the eligibility criteria for participation in the study will be assigned a randomization number at Visit 2 (Baseline) and dispensed the corresponding blister card containing capsules of double-blind investigational product for Week 1. Patients will begin dosing with double-blind capsules on the next day. Patients will be instructed to take 2 capsules orally as a single dose, once daily at approximately the same time each day (morning dosing recommended), with or without food.

Dosing may be switched from the morning to another time of day if a patient prefers or if tolerability issues arise. However, any switch must allow at least 20 hours between 2 consecutive doses.

9.4.5.1 Screening Period

At Visit 1 (Screening) after consent/assent is obtained, a placebo capsule will be administered for the purpose of eligibility determination. Patients will be given a placebo capsule to swallow. If a patient is unable to swallow the placebo capsule, the patient will be ineligible for study participation.

9.4.5.2 Double-blind Treatment Period

The titration schedule is as follows:

- Levomilnacipran: Days 1-3, 10 mg/day; Days 4-7, 20 mg/day; Week 2 through Week 8, 40 mg/day; Based on therapeutic response and tolerability, an additional dose increase to 80 mg/day is permitted at Week 3.

- Fluoxetine 20 mg/day (active comparator): Week 1, 10 mg/day; Week 2 through Week 8, 20 mg/day

Patients will be assigned a randomization number at Visit 2 (Baseline) and dispensed the corresponding blister card containing capsules of double-blind investigational product for Week 1. Patients will begin dosing with double-blind capsules on the next morning. Patients will be instructed to take 2 capsules from each column (1 each from Row A and Row B) as a single dose daily each morning with or without food. The double-blind dosing regimen is presented in Table 9-1.

Table 9-1. Double-blind Dosing Regimen

Treatment Group	***Row***	***Week***					
		1		***2***	***3-8***	***Down-Taper 9/ET***	
		Days 1-3	*Days 4-7*	*Days 1-7*	*Days 1-7*	*Days 1-2*	*Days 3-7*
Levomilnacipran 40 mg - 80 mg	A	LVM 10 mg	LVM 20 mg	LVM 40 mg	LVM 40 mg	LVM 40 mg	LVM 20 mg
	B	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	A	Optional dose escalation to 80 mg as determined by treating physician			LVM 40 mg	LVM 40 mg	LVM 20 mg
	B				LVM 40 mg	Placebo	Placebo
Fluoxetine 20 mg	A	Fluoxetine 10 mg	Fluoxetine 10 mg	Fluoxetine 20 mg	Fluoxetine 20 mg	Fluoxetine 10 mg	Fluoxetine 10 mg
	B	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Placebo	A	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	B	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

ET = Early termination; LVM = levomilnacipran.

Patients will be instructed to return the blister card with any remaining investigational product, and to return it even if it is empty, preferably at the next study visit. Additional investigational product will be dispensed as per the schedule shown in Section 2.0.

If a patient experiences an AE, the investigational product may be stopped for up to a maximum of 4 consecutive days. The date and reason for missed doses must be recorded on the appropriate page of the eCRF. If appropriate, as deemed by the investigator, patient may resume medication at 40 mg/day or reduce to 40 mg/day (if taking 80 mg/day). Those unable to tolerate 40 mg/day should be discontinued from the study.

9.4.5.3 Double-Blind Down-Taper Period

All randomized patients who complete the 8-week double-blind treatment period and patients who prematurely discontinue from the study before completing 8 weeks of double-blind treatment should enter the 1-week, double-blind down-taper period unless it is considered not clinically appropriate by the Investigator. The double-blind down-titration regimen is as follows:

- Levomilnacipran 40 mg/day and 80 mg/day: Days 1-2, 40 mg/day; Days 3-7, 20 mg/day
- Fluoxetine 20 mg/day: Days 1-7, 10 mg/day

9.4.6 Blinding

A list of patient randomization codes will be generated by Statistical Programming at AGN and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

9.4.7 Unblinding

The IWRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the investigator, it is in the patient's best interest to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition. In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

9.4.8 Prior and Concomitant Therapy

A list of concomitant medications that are allowed and not allowed for either episodic or chronic use is provided in Appendix III. Medication history (psychotropic medication history during the previous 5 years and all other medications during the past 12 months) will be recorded at Visit 1 (Screening) in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

9.4.9 Monitoring Treatment Compliance

Investigational product compliance during any treatment period will be closely monitored by counting the number of capsules dispensed and returned. Before new investigational product is dispensed at each visit, every effort will be made to collect all unused investigational product. Patients who do not take investigational product for 5 or more consecutive days, or consistently demonstrate poor compliance (< 80% or > 120% in 2 consecutive visit intervals, measured by capsule count) should be considered for study discontinuation. Investigators should consult with the Study Physician before discontinuing a patient due to poor compliance.

9.4.10 Treatment After Discontinuation

Patients whose MDD symptoms worsen or are determined by the Investigator to be inadequately controlled before completing the double-blind treatment period are allowed to discontinue investigational product and start appropriate treatment at the Investigator's discretion. This new treatment will not be provided by AGN. Patients who initiate a new treatment for MDD must be discontinued from the study.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy Assessments

The efficacy assessments will include the CDRS-R, CGI-S, and Clinician Global Impressions-Improvement (CGI-I). Efficacy assessments are not to be administered if the patient is not accompanied by his/her consented caregiver. The K-SADS-PL and all efficacy assessments will be conducted by experienced clinicians meeting training requirements and qualifications standards established by AGN and rater training vendor.

9.5.1.1 Primary Efficacy Assessment

The CDRS-R (Appendix V; Poznanski and Mokros 1996) is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6-17 years and contains 17 ordinally-scaled items that evaluate the presence and severity of symptoms commonly associated with childhood depression. The CDRS-R total score ranges from 17 to 113.

The CDRS-R will be administered separately to the patient and to the caregiver. For each item, the clinician administering the interviews will select the rating that provides the best description of the patient and will then determine the total score.

9.5.1.2 Secondary Efficacy Assessment

The CGI-S (Appendix VI; Guy 1976) is a clinician-rated scale used to rate the severity of the patient's current state of mental illness compared with an MDD patient population. The patient will be rated on a scale from 1 to 7, with 1 indicating a "normal, not at all ill" and 7 indicating "among the most extremely ill patients."

9.5.1.3 Additional Efficacy Assessment

The CGI-I is a clinician-rated instrument (Appendix VII). Based on the Investigator's clinical opinion, the total improvement or worsening of the patient's mental illness is rated on a scale from 1 to 7, with 1 being very much improved and 7 being very much worse, relative to Visit 2 (Baseline), regardless of whether the Investigator considers the worsening to be related to investigational product.

9.5.2 Safety Assessments

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits. Scheduled safety assessments are not to be administered if the patient is not accompanied by his/her consented caregiver.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of data collection for this study, any untoward event that was reported from the time the patient signed the ICF until 30 days after the last dose of treatment is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or other study center personnel
- All diseases that occur after signing ICF, including any change in severity or frequency of preexisting disease
- Laboratory values that are deemed to be clinically significant by the Investigator
- Physical exam findings, including vital sign measurements, that are deemed to be clinically significant by the Investigator

Please note that medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

9.5.2.2 Causality Assessment

For each AE, the Investigator must provide an assessment of causal relationship to the investigational product. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility that the investigational product caused the event?

Yes: There is evidence to suggest a causal relationship between the investigational product and AE, ie:

- There is a reasonable temporal relationship between the investigational product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the investigational product and AE, ie:

- There is no reasonable temporal relationship between the investigational product and the event, or
- The patient did not take the investigational product, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or
- The event is commonly occurring in the (study) population independent of investigational product exposure

9.5.2.3 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4). Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

9.5.2.4 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of investigational product dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.5.2.5 Reporting Adverse Events and Serious Adverse Events

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, “How do you feel since your last visit?” Study center personnel will record all pertinent information in the patient’s eCRF.

In addition, any SAEs reported by the patient (or patient representative) or otherwise identified by the Investigator after the study period (ie, after 30 days post last dose) should be documented and reported.

All AEs must be recorded on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to the investigational product.

For every AE, the Investigator must:

- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and causal relationship
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

In addition, patients and caregivers are to be reminded, as described in the ICF and in accordance with Section 9.5.2.1, to notify site personnel of any AEs occurring during the 30-day poststudy period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. AEs are also to be recorded in the eCRF if at least one of the following conditions is met: 1) the event meets the criteria for an SAE (see Sections 9.5.2.4 and 9.5.2.6), and/or 2) the event is judged by the Investigator to be potentially causally related to investigational product.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the investigational product. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

9.5.2.6 Immediate Reporting of Serious Adverse Events and Events of Special Interest

AGN is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, AGN must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to Global Drug Safety on the SAE Form for Clinical Trials. The Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE Form for Clinical Trials to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed within 24 hours of knowledge of the event at the study center.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. **AGN may contact the study center to solicit additional information or follow up on the event.**

Fax the SAE Form for Clinical Trials to AGN:

SAE fax number:
Primary: 1-714-796-9504
Back-up: 1-714-246-5295

9.5.2.7 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the patient signs the ICF until 30 days after the last dose of investigational product. Within 24 hours of learning of a pregnancy, the study center personnel must report the event to Global Drug Safety on the Clinical Trial Pregnancy Form and fax it to the SAE/Pregnancy fax number stated in Section 9.5.2.6, even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in Section 9.5.2.6 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Form.

9.5.2.8 Potential Hy's Law Cases

Potential Hy's law criteria are:

- ALT or AST ≥ 3 × ULN *AND*
- Total bilirubin ≥ 2 × ULN *AND*
- Alkaline phosphatase < 2 × ULN

Study center personnel must report every patient who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time he or she signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of investigational product (if the final visit does not occur).

A laboratory alert for potential Hy's laws cases will be in place and the laboratory must notify Investigators and AGN immediately when the above criteria have been met. A potential Hy's law case must be faxed to AGN on an AE of Special Interest Form as soon as possible (within 24 hours of learning of the potential Hy's law case) to the SAE/Pregnancy fax number stated in Section 9.5.2.6, even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Physician and in accordance with the FDA "Guidance for Industry: Drug Induced Liver Injury- Pre-Marketing Clinical Evaluation" July 2009.

9.5.2.9 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected as detailed in the Schedule of Evaluations (Section 2.0). During Screening, the Investigator will assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory; patients with abnormalities judged to be clinically significant will be excluded from the study.

Patients will be instructed to fast overnight (for at least 8 hours) before coming in for their appointments when clinical laboratory blood tests are to be drawn. If non-fasting, an attempt should be made to draw blood at least 4 hours after a meal.

A UDS will be conducted for all patients at Visit 1 (Screening). A negative UDS for prohibited substances (illegal drugs or prohibited concomitant medications [see Appendix III and Exclusion Criterion #18]) is required before Visit 2 (Baseline) for the patient to continue in the study. Amphetamines can be allowed if prescribed for treatment of attention deficit disorder at a dose that is stable for at least 60 days before Visit 1 (Screening). If not stable for at least 60 days before Visit 1 (Screening), the patient should be discontinued. However, the patient can be rescreened on a later date.

Patients who have a positive UDS at Visit 1 (Screening) for other prohibited substances (barbiturates, benzodiazepines, opiates, cannabinoids, cocaine, methadone, phencyclidine, or other prohibited concomitant medications) may be allowed to enroll if (1) there is no suspicion of drug abuse per the Investigator judgment, (2) the use is discontinued and (3) this is documented by a negative UDS before Visit 2 (Baseline). If the repeat test cannot be performed within 21 days, the patient should be discontinued from the study. The patient can be rescreened on a later date and must have a negative UDS to be considered for inclusion in the study.

Alcohol consumption is prohibited during the study. A UDS or blood alcohol test may be performed at any time during the study at the discretion of the Investigator. A patient with a positive blood alcohol test or a positive UDS for any prohibited substances at any postrandomization visit may be allowed to continue in the study if approved by the Investigator and by the Study Physician.

Females of childbearing potential will be required to have a serum β-hCG pregnancy test at Visit 1 (Screening) and Visit 8/ET. Positive pregnancy test results at Visit 1 will exclude female patients from participating in the study. At every study visit, Investigators should inquire about the use of acceptable methods of contraception in females of childbearing potential who are, or become, sexually active, and perform a urine pregnancy test if there is any question of non-compliance with contraception. If the urine pregnancy test is negative, a serum β-hCG pregnancy test must be performed to rule out pregnancy. Any positive pregnancy test results during the study will result in patient termination from the study.

The following clinical laboratory levels will be measured:

Hematology:	Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry:	Sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, bilirubin (total; direct; indirect), AST, ALT, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides
Urinalysis:	Specific gravity, pH, protein, glucose, ketones, nitrite, bilirubin, and blood
Thyroid:	Free thyroxine and thyroid stimulating hormone (TSH) tests at Visit 1 (Screening)
Hepatitis screening:	Hepatitis-C virus antibody, hepatitis-B surface antigen, and hepatitis-B core antibody total will be tested. Reflex hepatitis-B core antibody IgM will be performed for all hepatitis-B core antibody total positive or reactive results. Hepatitis screening will be conducted at Visit 1 (Screening)
UDS:	Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine. UDS will be performed for all patients at Visit 1 (Screening). UDS may be repeated during the study at the Investigator's discretion
Blood alcohol level:	Blood alcohol level will be conducted at Visit 1 (Screening). May be performed at random during the study upon request of the Investigator
Serum β-hCG:	Female patients of childbearing potential only. Will be performed at Visit 1 (Screening) and for randomized patients at Visit 8/ET. Urine pregnancy tests may be performed at the discretion of the Investigator at any visit during the double-blind treatment period; if negative, perform a serum β-hCG test to rule out pregnancy.

Other laboratory assessments may be repeated at any visit if there was an abnormal finding at the most recent, previous evaluation or if additional information is clinically necessary to appropriately evaluate the patient's current condition, follow up and/or manage an AE. Fasting for at least 8 hours is recommended before unscheduled visits to assess serum chemistry.

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

9.5.2.10 Vital Signs

Vital sign measurements, seated radial pulse rate, seated systolic and diastolic BP, and body weight, will be documented at every visit. Pulse and BP readings will be taken twice after the patient has been sitting for at least 5 minutes. The second measurement will be entered in the eCRF. A BP cuff of appropriate size for the patient should be used. The same arm and BP cuff should be used for all BP and radial pulse measurements throughout the study.

BP may be measured manually or by machine, but the same method of measurement should be used for a patient throughout the study. Radial pulse rate should be measured manually. All BP and radial pulse measurements will be recorded in the patient's source documents.

Patients should be instructed not to wear clothing with tight sleeves when they come to have their BP measured. Additionally, they should be kept as calm and undisturbed as possible while BP and pulse measurements are taken (ie, there should be no talking while the BP is being measured).

Height will be measured as accurately as possible using a stadiometer while the patient is standing with no shoes on and recorded at Visit 1 (Screening) and Visit 8/ET. Patients should wear their usual indoor clothing, but take off their jacket and shoes during weight measurements. For each patient, body weight and height should be determined using the same equipment during the study after confirming proper calibration.

9.5.2.11 Electrocardiograms

A 12-lead ECG will be performed at Visit 1 (Screening), Visit 5 (Week 3), and at Visit 8 (Week 8/ET). The paper speed will be standard 25 mm/sec. ECGs will be electronically transmitted for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded for the following parameters in lead II or lead III: PR interval, QRS duration, and uncorrected QT interval. QTcF (Frederica corrected QT interval) and QTcB (Bazett corrected QT interval) will be calculated.

The overall interpretation and determination of the clinical relevance of ECG findings using the central laboratory ECG interpretation report will be the responsibility of the Investigator and will be recorded in the patient's eCRF.

9.5.2.12 Other Safety Assessments

9.5.2.12.1 Physical Examination

A complete physical examination will be performed at Visit 1 (Screening) and at Visit 8 (Week 8/ET) by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

9.5.2.12.2 Columbia–Suicide Severity Rating Scale

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The paper version of the C-SSRS will be completed at all study visits. At Visit 1 (Screening), the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior (Appendix VIII). At all other visits, the C-SSRS will be completed for ideation and behavior since the previous visit (Appendix IX). The C-SSRS will be evaluated and signed at each visit by a qualified staff member (ie, the Investigator or designee that has extensive professional training and experience in assessing mental illness), before the patient leaves the study center.

The patient should not be released from the study center until the results of the C-SSRS are reviewed and the patient is not considered to be at risk. If there is doubt about whether a patient is at risk, the Investigator must obtain appropriate psychiatric consultation. The results of the C-SSRS will be recorded in the eCRF.

9.5.3 Investigational Product Concentration Measurements

PK blood samples will be collected from assented/consented patients ***aged 7-11 years*** to determine plasma concentrations of levomilnacipran. The blood sample will be processed, stored, and shipped as indicated in Appendix IV. The population PK of levomilnacipran will be characterized using serial and sparse plasma concentration-time data. The plasma concentration-time data collected will provide estimates of PK parameters, eg, area under the curve (AUC), half-life, maximum plasma drug concentration, and time of maximum plasma concentration.

Sparse PK blood samples will be collected during Visits 5, 6, and 7, as follows:

- Visit 5, at predose and at 1-4 hour postdose
- Visit 6, 4-6 hours postdose
- Visit 7, 6-8 hours postdose

In case of scheduling constraints and with prior notification of AGN, the sampling times above may be collected in a different sequence among specified visits.

From a subset of consented patients instead of sparse PK samples, 7 serial PK blood samples will be collected at Visit 5 (or at any 24-hour period between Visit 5 and Visit 7, inclusive) at the following time points: predose (20-24 hours after the most recent dose), and 2, 4, 6, 8, 10-12, and 24-hours postdose.

To allow for a predose sampling, patients may be instructed to hold their daily dose on the sampling day and take it when instructed at the study center.

PK samples will not be obtained from patients who missed investigational product dosing for 2 or more consecutive days before the sampling date.

The actual date and clock times of the reference dose (the last dose taken before the PK sample) and all blood draws will be recorded in the eCRF along with the date and time of the 2 doses before the reference dose for each patient who undergoes PK sampling.

9.5.4 Health Economic and Outcomes Research Assessments

Not applicable.

9.5.5 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.0 and Section 2.1. The descriptions of the procedures to be performed at each visit are provided below.

The screening period should be 1 week (± 3 days) before Visit 2, but may be extended up to a total of 5 weeks to accommodate prior medication washout or to repeat assessments. The reason for the extended screening will be recorded in the source documents.

If necessary, visits may be conducted up to 3 days before or after the indicated postbaseline weeks relative to Visit 2 (Baseline).

9.5.5.1 Visit 1 (Screening)

At Visit 1 (Screening), study procedures will be reviewed with the patient, parent/guardian/LAR, and caregiver. Documentation of informed assent (from patient), parent/guardian/LAR permission and caregiver consent will be obtained (See Section 5.3). Then, patients will be assigned a unique PID number (see Section 9.4.3).

The following procedures will be performed:

- Obtain and record medical, psychiatric history
- Obtain and record medication history, non-drug psychiatric treatment history, and current medication status
- Administer placebo capsule to confirm patient is able to successfully swallow
- Administer CDRS-R (caregiver and patient)
- Administer C-SSRS (Baseline C-SSRS). Results should be evaluated by the Investigator or designee before the patient leaves the study center
- Administer K-SADS-PL (caregiver and patient; all findings recorded in the source documents only)
- Administer CGI-S
- Measure vital signs (including height, measured by stadiometer)
- Complete physical examination
- Perform ECG
- Collect blood and urine samples for clinical laboratory determinations, hepatitis screening, blood alcohol, thyroid tests
- Serum β-hCG pregnancy test (females of childbearing potential only)

- Collect urine samples for UDS
- Review of all inclusion/exclusion criteria
- Schedule Visit 2 for approximately 1 week after Visit 1
- Record AEs after consent/assent during the screening period

9.5.5.2 Visit 2 (Baseline Visit)

The Baseline Visit (Visit 2) will be conducted approximately 1 week (up to a maximum of 5 weeks to accommodate prior medication washout) after Visit 1 (Screening) to determine whether the patient and caregiver are eligible to continue into the double-blind treatment period.

At the Baseline Visit, the following procedures will be performed:

- Review of all inclusion/exclusion criteria
- Review and record AEs
- Review prior medications and non-drug psychiatric treatment history
- Measure vital signs
- Complete efficacy evaluations
    - Administer CDRS-R (caregiver and patient)
    - Administer CGI-S
- Administer C-SSRS (Since-Last-Visit) and have the results evaluated by the Investigator or designee before the patient leaves the study center
- If the patient and caregiver are eligible to continue in the study, a randomization number will be assigned to the patient and double-blind investigational product will be dispensed per IWRS assignment. Written and verbal instructions for dosing will be provided to patient and caregiver. Document that instructions were given in source documents
- If Visit 2 is done remotely, the study drug may be sent to patients via preferred courier or via curbside pickup and must be approved in advance by the Sponsor

- Schedule next visit:
    - Visit 3: 1 week (± 3 days) after Visit 2

9.5.5.3 Visit 3 (End of Week 1)

At this visit, the following procedures will be performed:

- Review and record AEs
- Review concomitant medications
- Measure vital signs
- Complete efficacy evaluations
    - Administer CDRS-R (caregiver and patient)
    - Administer CGI-S
    - Administer CGI-I
- Administer C-SSRS (Since-Last-Visit). Results should be evaluated by the Investigator or designee before the patient leaves the study center
- Confirm investigational product return and assess investigational product compliance
- Dispense double-blind investigational product for the next visit per IWRS assignment and provide written and verbal instructions for dosing to patient and caregiver. Document that instructions were given in source documents
- If Visit 3 is done remotely, the study drug may be sent to patients via preferred courier or via curbside pickup must be approved in advance by the Sponsor
- Schedule next visits
    - Visit 4: 2 weeks (± 3 days) after Visit 2 and
    - Visit 5: 3 weeks (± 3 days) after Visit 2

9.5.5.4 Visits 4 (End of Week 2) and 5 (End of Week 3)

At these visits, the following procedures will be performed:

- Review and record AEs
- Review concomitant medications
- Measure vital signs
- Perform ECG (Visit 5 only)
- Complete efficacy evaluations
    - Administer CDRS-R (caregiver and patient)
    - Administer CGI-S
    - Administer CGI-I
- Administer C-SSRS (Since-Last-Visit). Results should be evaluated by the Investigator or designee before the patient leaves the study center
- Obtain PK samples (Visit 5 only; see Section 9.5.3 for details)
- Confirm investigational product return and assess investigational product compliance
- Dispense double-blind investigational product for the next visit per IWRS assignment and provide written and verbal instructions for dosing to patient and caregiver. Document that instructions were given in source documents
- If Visit 4 and 5 are done remotely, the study drug may be sent to patients via preferred courier or via curbside pickup must be approved in advance by the Sponsor
- Schedule next visits
    - Visit 6: 4 weeks (± 3 days) after Visit 2 and
    - Visit 7: 6 weeks (± 3 days) after Visit 2

9.5.5.5 Visits 6 (End of Week 4) and 7 (End of Week 6)

At these visits, the following procedures will be performed:

- Review and record AEs

- Review concomitant medications
- Measure vital signs
- Complete efficacy evaluations
    - Administer CDRS-R (caregiver and patient)
    - Administer CGI-S
    - Administer CGI-I
- Administer C-SSRS (Since-Last-Visit). Results should be evaluated by the Investigator or designee before the patient leaves the study center
- Obtain PK samples (if applicable; see Section 9.5.3 for details)
- Confirm investigational product return and assess investigational product compliance
- Dispense double-blind investigational product for the next visit per IWRS assignment and provide written and verbal instructions for dosing to patient and caregiver. Document that instructions were given in source documents
- If Visit 6 and Visit 7 are done remotely, the study drug may be sent to patients via preferred courier or via curbside pickup must be approved in advance by the Sponsor
- Schedule next visit
    - Visit 8: 8 weeks (± 3 days) after Visit 2

9.5.5.6 Visit 8 (End of Week 8 or Early Termination Visit)

All randomized patients should be seen for a final assessment at Visit 8/ET. A *final assessment* will be defined as completion of the evaluations scheduled at the end of Week 8 or ET Visit. The following procedures will be performed at Visit 8:

- Review and record AEs
- Review concomitant medications
- Measure vital signs (including height, measured by stadiometer)
- Perform ECG
- Complete physical examination

- Collect blood and urine samples for clinical laboratory determinations
- Serum β-hCG pregnancy test (females of childbearing potential only)
- Complete efficacy evaluations
    - Administer CDRS-R (caregiver and patient)
    - Administer CGI-S
    - Administer CGI-I
- Administer C-SSRS (Since-Last-Visit). Results should be evaluated by the Investigator or designee before the patient leaves the study center
- Confirm investigational product return and assess investigational product compliance
- If entering down-taper period: dispense double-blind down-taper investigational product for the next visit per IWRS assignment and provide written and verbal instructions for dosing to patient and caregiver. Document that instructions were given in source documents
- If Visit 8 is done remotely, the study drug may be sent to patients via preferred courier or via curbside pickup must be approved in advance by the Sponsor. All attempts must be made to collect safety labs
- Schedule Visit 9/SFU: 1 week (± 3 days) after Visit 8

Any clinical findings observed during this visit, including clinically significant laboratory abnormalities observed at prior visits, will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the investigational product.

9.5.5.7 Visit 9 (End of Week 9/Safety Follow-up Visit)

All randomized patients must complete Visit 8/ET Visit and, at the end of the double-blind down-taper period, return for Visit 9/SFU Visit. Patients who do not enter the double-blind down-taper period must return for Visit 9/SFU Visit approximately 1 week after Visit 8/ET.

The following procedures will be performed at Visit 9:

- Review and record AEs
- Review concomitant medications

- Measure vital signs
- Administer C-SSRS (Since-Last-Visit). Results should be evaluated by the Investigator or designee before the patient leaves the study center
- Confirm investigational product return and assess investigational product compliance (for patients who enter the double-blind down-taper period)

Any clinical findings observed during this visit, including clinically significant laboratory abnormalities observed at prior visits, will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to the investigational product. If a follow-up visit is necessary, it should take place within 30 days of investigational product termination.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

Before any patient enters the study, a representative of AGN will meet with the Investigator and the study center staff to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train Investigators and authorized designees on recording the data in the eCRFs using the EDC system. After the first patient is enrolled, the AGN representative, a Regional Site Manager (RSM) or designee, will periodically monitor the progress of the study by conducting on-site visits. This RSM or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the Investigator and the study center staff. The Investigator will make available to the RSM or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study center staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system, and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording and Documentation

Data collection will involve the use of the AGN EDC system, to which only authorized personnel will have access. Patient's data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring, and reviews, queries may be electronically issued to the site and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date, and time) to assist AGN and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator before the final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents) will be retained at the site, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by AGN, its authorized representatives, and the FDA or other health authorities.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Patient Populations

Four populations will be considered in the statistical analysis of the study as specified below.

9.7.1.1 Screened Population

The Screened Population will consist of all patients who underwent a Screening Visit and received a screening number, and for whom informed consent was obtained.

9.7.1.2 Randomized Population

The Randomized Population will consist of all patients in the Screened Population who were randomized to a treatment group in the study.

9.7.1.3 Safety Population

The Safety Population will consist of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product.

9.7.1.4 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who had the baseline and at least 1 postbaseline assessment of the CDRS-R total score.

9.7.2 Patient Disposition

The number of patients in the Screened Population will be summarized overall by study center. The number of patients in the Randomized, Safety, and ITT Populations will be summarized by treatment group and study center. Patients who were impacted by the COVID-19 pandemic (ie, had protocol deviations, missing safety assessments, AEs [as determined by investigator], or withdrew from the study due to the COVID-19 pandemic, or whose anxiety appeared to be affected by the pandemic) will also be summarized.

Screen failures (ie, patients who were screened but not included in the Randomized Population) and the associated reasons for failure will be tabulated overall. Patients completing 8 weeks of double-blind treatment (Visits 2-8) will be considered completers. The number and percentage of patients who complete the double-blind treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups. The reasons for premature discontinuation from the double-blind treatment period as recorded on the disposition pages of the eCRF will be summarized (number and percentage) by treatment group for the safety population.

The number and percentage of patients with important protocol deviations will be summarized overall and by treatment group for the Safety Population. Deviations related to the following categories will be included:

- Inclusion or exclusion criteria
- Withdrawal criteria
- Treatment or dose

- Concomitant medications

These and any additional important protocol deviations will be reviewed and documented before database lock and unblinding of treatment codes.

Protocol deviations that occur due to COVID-19 will be summarized and listed separately.

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, body mass index) and other baseline characteristics will be summarized by treatment group for the Safety and ITT populations. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented for continuous variables, and frequency distributions (counts and percentages) will be presented for categorical variables.

Prior medication is defined as any recorded medication taken before the date of the first dose of double-blind investigational product. Concomitant medication is defined as any recorded medication taken on or after the date of the first dose of double-blind investigational product.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a patient will only be counted once. Any recorded medications started after last dose of double-blind investigational product will not be summarized but will be included in listings.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

9.7.4.1.1 Investigational Product

Exposure to double-blind investigational product for the Safety Population during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind investigational product taken to the date of the last dose taken, inclusive. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment group.

In addition, weekly and overall mean daily dose of investigational product will be summarized by treatment group for the Safety Population.

9.7.4.2 Measurement of Treatment Compliance

Dosing compliance for a specified period will be defined as the total number of capsules actually taken by a patient during that period divided by the number of capsules prescribed to be taken for the same period multiplied by 100. This information will be obtained from the investigational product record of the patient's eCRF.

The total number of capsules actually taken during a specific time period is calculated based on the study medication record. The number of capsules prescribed to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules to be taken per day.

Descriptive statistics for investigational product compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the entire double-blind treatment period.

9.7.5 Efficacy Analyses

The efficacy analyses will be based on the ITT Population. Baseline for efficacy is defined as the last nonmissing efficacy assessment recorded at or prior to Visit 2. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with less than 2 patients in at least 1 treatment group in the ITT population. Small centers will be pooled to form pseudo centers so that each treatment group includes at least 2 ITT patients within the center. Pooling will be done using the following algorithm:

Based on the number of ITT patients, small centers will be ordered from the largest to the smallest, and centers of the same size will be ordered from the largest center code to the smallest center code. The pooling process starts with the largest small center from the top, which will be pooled with the smallest from the bottom until a non-small center is formed. The process will be repeated using the small centers left out after the first pass. If any centers are left out at the end of the process, they will be pooled with the smallest pseudo center. If there is more than 1 smallest pseudo center, the pseudo center with the smallest center code will be selected. In case the pseudo center formed by pooling all small centers is still a small center, it will be pooled with the smallest non-small center. If there is more than 1 smallest non-small center, the one with the smallest center code will be selected.

By-visit analysis based on the mixed-effects model for repeated measures (MMRM) using the observed case approach will be performed for all continuous efficacy parameters.

In addition, by-visit analyses using the last-observation-carried-forward (LOCF) approach will be presented for all continuous efficacy parameters. For the LOCF approach, only the postbaseline total score of a parameter will be imputed using the LOCF approach; individual item scores will not be carried forward. Baseline total score will be carried forward only for the intermittent missing scores immediately after baseline. If all the postbaseline values are missing, the baseline value will not be carried forward.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the change from baseline to end of Week 8 in the CDRS-R total score. The primary analysis will be performed using an MMRM with treatment group, study center, visit, and treatment group–by-visit interaction as the fixed effects and the baseline value and baseline value-by-visit interaction as the covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and Roger, 1997) will be used to estimate denominator degrees of freedom. This analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values. In the MMRM analysis, if the model fails to converge based on the unstructured covariance matrix, then structures of Heterogenous Toeplitz, Toeplitz, and Compound symmetry will be applied, only if necessary, in the specified order until the model converges.

In addition, 2 sensitivity analyses, LOCF and pattern-mixture model, will be performed on the primary efficacy parameter. For the LOCF approach, the between-treatment group comparison will be performed by means of an analysis-of-covariance model with treatment group and pooled study center as factors and the baseline CDRS-R total score as the covariate. The LOCF approach will be used to impute missing postbaseline values, provided that at least 1 postbaseline assessment is available. Missing values between the baseline and the first nonmissing postbaseline will be imputed with the baseline value. If all the postbaseline values are missing, baseline value will not be carried forward. Only the total score of a parameter will be imputed using the LOCF approach; individual item scores will not be carried forward.

In the other sensitivity analysis, a pattern-mixture model based on non-future dependent missing value restrictions (Kenward 2003) will be performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at–random missingness assumption. The non-future dependent missing value restriction states that the probability of drop-out at a specific visit can only depend on the observed value and the possibly missing value up to that visit, but not future values beyond that visit. The details of this sensitivity analyses are as follows:

The pattern for the pattern-mixture model will be defined by the patient's last visit with observed value. The observed CDRS-R total score at a visit is assumed to have a linear relationship with the patient's prior measurements. The dataset with missing values will be imputed under the assumption that the distribution of a missing observation differs from the observed only by a shift parameter value Δ. The dataset with missing values will be analyzed using the same model as the primary analysis for between-treatment group comparisons at Week 8. The imputation of missing values and the analysis will be performed multiple times and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The values for Δ will be selected as 0 to 6 based on experience with historical data.

9.7.5.2 Secondary Efficacy Parameter

The secondary efficacy parameter is the change from baseline to the end of Week 8 in CGI-S score. This parameter will be analyzed similarly to the primary efficacy parameter.

A sensitivity analysis will also be performed using the LOCF approach as described in Section 9.7.5.1.

9.7.5.3 Additional Efficacy Parameters

The additional efficacy parameters will include the following at each postbaseline visit:

- CGI-I score
- Change from baseline in CGI-S score
- CDRS-R response (≥ 40% reduction in CDRS-R from baseline) rate
- CDRS-R remission (CDRS-R ≤ 28) rate

CGI-I score and the change in CGI-S will be analyzed using the MMRM and LOCF approaches similar to those used for the primary efficacy parameter. For CGI-I score, the baseline CGI-S score will be used as the baseline variable.

The CDRS-R response rate and CDRS-R remission rate will be analyzed using a generalized linear mixed model (GLMM), based on logit link function, with random intercept and flexible terms of treatment group, visit, treatment-by-visit interaction, and baseline score. If the GLMM does not converge, a logistic regression model with treatment group and the baseline score as explanatory variables will be used. For the logistic regression analysis, the postbaseline missing data will be imputed using the LOCF approach.

9.7.6 Safety Analyses

The safety analysis will be performed for the double-blind treatment period and double-blind down-taper period separately using the Safety Population. The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, ECG parameters, C-SSRS, and growth evaluations. For each safety parameter, the last assessment made before the first dose of double-blind investigational product will be used as the baseline for all analyses of that safety parameter.

9.7.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the double-blind treatment period or during the double-blind down-taper treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present before the date of the first dose of double-blind investigational product or was present before the date of the first dose of double-blind investigational product and increased in severity during the double-blind treatment period or during the double-blind down-taper period, respectively. If more than 1 AE is reported before the date of the first dose of double-blind investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the double-blind treatment period or during the double-blind down-taper period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of double-blind investigational product will not be counted as a TEAE.

An AE occurring during the double-blind down-taper period will be considered a newly emergent AE if it was not present before the start of the double-blind down-taper period or was present before the start of the double-blind down-taper period but increased in severity during the double-blind down-taper period. The newly emergent AEs during the double-blind down-taper period will be summarized by body system, preferred term, and treatment group.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and causal relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group.

The incidence of common (≥ 2% of patients in any treatment group) TEAEs during the double-blind treatment period will be summarized separately by preferred term and treatment group and will be sorted by decreasing frequency for the test treatment. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of double-blind investigational product and within 30 days of the date of the last dose of double-blind investigational product.

The incidence of SAEs and AEs leading to premature discontinuation of the study will also be summarized by study period, system organ class, preferred term, and treatment group.

Listings will be presented for SAEs, AEs leading to discontinuation, and death (if any).

9.7.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) postbaseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (ie, pulse rate, systolic and diastolic BP, and body weight) and changes from baseline values at each visit and at end of study will be presented by treatment group. In addition, height and weight z-scores will be calculated based on growth charts (see Section 9.7.6.5.2).

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline–value criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values.

9.7.6.4 Electrocardiogram

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and changes from baseline values at each assessment time point will be presented by treatment group. The QTc interval is calculated using the Bazett and Frederica corrections.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated by treatment group. The criteria for PCS ECG values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values.

A listing of patients with postbaseline clinically significant ECG abnormalities, as reported by the Investigator or by the central cardiologist, will also be provided.

The number and percentage of patients with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. A supportive listing of patients with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTcF values (including changes from baseline). A listing of all AEs for patients with postbaseline QTcF increases > 30 msec will also be provided.

9.7.6.5 Other Safety Parameters

9.7.6.5.1 Columbia-Suicide Severity Rating Scale

For the C-SSRS, the number and percentage of patients with suicidal ideation or suicidal behavior as recorded on the C-SSRS scale will be presented by treatment group. The distribution of responses for most severe suicidal ideation and suicidal behavior during the lifetime history, the double-blind treatment period and the down-taper period will also be presented by treatment group for the Safety Population. Supportive listings will be provided and will include the PID number, treatment group, visit number, lifetime history, and postbaseline values for each patient. Intensity of ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings.

9.7.6.5.2 Growth Evaluation

Weight and height will be presented as standardized z-scores adjusted for gender and age, using the lambda-mu-sigma method (Cole TJ 1990). To assess the impact of treatment on growth, the change from baseline in the age and gender adjusted height will be analyzed using an analysis of variance model with treatment as factor. A non-parametric (Wilcoxon) test will also be performed.

9.7.6.6 Investigational Product Plasma Concentration Parameters

Plasma samples will be analyzed for the concentrations of levomilnacipran using validated bioanalytical methods. Population PK parameters will be estimated using nonlinear mixed-effects modeling methods. The study will be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for levomilnacipran ER, with at least 80% power.

9.7.7 Health Economics and Outcomes Research Analyses

Not applicable.

9.7.8 Interim Analysis

The interim analysis was conducted 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) on ITT population was based on the conditional power as described in Lan et al. 1999. In calculating the conditional power, it was assumed that the future patients to be enrolled into the Study will have similar efficacy as those of the existing patients of the same treatment group. The non-binding futility criteria was set when the conditional power for detecting a statistically significant treatment difference between the levomilnacipran treatment group

(40-80 mg/day) and placebo at the final analysis was 0.2 (20%) or lower given the interim analysis results. After the futility analysis results were reviewed by a data monitoring committee member, it was determined that this study will continue until the planned study end.

9.7.9 Determination of Sample Size

The effect size (treatment group difference relative to pooled SD) of 0.36 for both levomilnacipran and fluoxetine is based on a treatment difference of 4 units with a common pooled SD of 11.1 for the primary efficacy parameter, change from baseline to Week 8 in CDRS-R total score. A sample size of 480 patients (160 per treatment group) will be needed to provide 85% power for primary analysis (levomilnacipran vs placebo) based on an MMRM model using simulation method (Lu 2012). The simulation assumed a correlation of 0.7 between the repeated measures and a dropout rate of 17% based on historical data in pediatric patients.

9.7.10 Computer Methods

Statistical analyses will be performed using version 9. 3 (or newer) of SAS on a LINUX operating system.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by AGN. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the Investigator, has been received by AGN. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS AND VIOLATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing, or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, scheduling of visits not in accordance with specifications.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patient and must immediately be reported to AGN. Protocol deviations, including those that may be due to the COVID-19 pandemic, should be reported to AGN (either verbally or electronically) in a timely manner from the date of discovery.

Protocol deviations that may impact a patient's rights (eg, failure to obtain informed consent prior to initiating study procedures), safety or well-being (eg, deviations that resulted in an SAE, exposure during pregnancy), or the integrity and authenticity of the study data should be reported to AGN within 24 hours, if possible.

The IRB/IEC must be notified according to the criteria and time period dictated by the IRB/IEC associated with this study.

9.10 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee to evaluate safety study outcomes such as suicidal ideation and suicidal behavior during study conduct will be established and will operate based on a charter drafted to comply with FDA guidance (FDA 2006).

10.0 STUDY SPONSORSHIP

This study is sponsored by AGN.

10.1 STUDY TERMINATION

AGN reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 REPORTING AND PUBLICATION

All data generated in this study are the property of AGN. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and AGN and will follow the AGN's Standard Operating Procedure on publications.

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must provide the following to AGN before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to AGN for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all Subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 5.1
- A copy of the IRB/IEC-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the Investigator
- Financial disclosure agreement completed and signed by the Investigator and all Subinvestigators listed on Form FDA 1572. The Investigator and all Subinvestigators will provide an updated financial disclosure agreement to AGN 1 year after the completion of the study

11.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Subinvestigators listed on Form FDA 1572. The investigational products must be stored and locked in a secured location. At study initiation, a representative from AGN will inventory the investigational products at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. AGN will supply forms on which to record the date the investigational products were received and a dispensing record in which to record each patient's use. All unused investigational products must be returned to AGN. It is the Investigator's responsibility to ensure that patients return their investigational product.

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a DTP study drug shipment can be made from the study site to the subject if allowed by local regulations.

11.4 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by AGN through the EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to AGN. The Investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and ECGs) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by AGN.

No study records shall be destroyed without notifying AGN and providing AGN the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of AGN or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. AGN must be notified in writing of the name and address of the new custodian in advance of the transfer.

11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by PID number. Patients' names are not to be transmitted to AGN. The Investigator will keep a master patient list on which the PID number and the full name, address, and telephone number of each patient are listed.

12.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol (Protocol LVM-MD-14) and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____
Investigator's Signature Date

_____
Investigator's Name

13.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's LAR. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation

- A description of any reasonably foreseeable risks or discomforts to the patient

- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; AGN; the IRB/IEC; or an authorized contract research organization may inspect the records

- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained

- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB/IEC may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of consent (eg, "I agree to participate . . .")
- A place for the patient's signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the patient.

APPENDIX II. CONTACT INFORMATION

Contact information for AGN personnel will be provided in the study reference binder.

APPENDIX III. CONCOMITANT MEDICATIONS

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Name or Class	***Episodic Use (PRN)***	***Chronic Use***	***Restrictions***
ADHD Medications	N	Y	Oral or transdermal methylphenidate, amphetamine products or prodrugs, pseudoephedrine, modafinil (Provigil), and armodafinil (Nuvigil) are allowed if the patient has been stable on the same dose for at least 2 months prior to Screening and the patient is to remain on the same dose throughout the double-blind treatment period. Catapres (clonidine), Strattera (atomoxetine), Tenex (guanfacine), and Intuniv (guanfacine extended-release) are not allowed.
Analgesics	Y	Y	• Non-narcotic analgesics are allowed. • Tramadol, pregabalin, and indomethacin are not allowed. • Clinically appropriate episodic use of narcotic analgesics for acute medical indications limited to 3 days for an episode is allowed, except on days of efficacy evaluations.
Anesthetics, local	Y	N	
Anorexics/appetite suppressants/anti-absorption agents	N	N	
Antacids	Y	Y	
Anti-acne agents	Y	Y	Isotretinoin (Accutane) is not allowed.
Antianginal agents	N	N	
Antiarrhythmics	N	N	
Anti-asthma agents	Y	Y	• Systemic corticosteroids are not allowed. • Inhaled steroids at approved dosages and other asthma medications are allowed.
Antibiotics (antibacterial)	Y	N	• Chronic use of topical antibiotics for acne is allowed. • Linezolid (Zyvox), and monoamine oxidase inhibitors [MAOI]) and isoniazid are not allowed. • Erythromycin, clarithromycin, telithromycin, chloramphenicol, rifampicin, and rifabutin are not allowed. • Azithromycin is recommended if a macrolide antibiotic is needed.
Anticonvulsants	N	N	

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Name or Class	***Episodic Use (PRN)***	***Chronic Use***	***Restrictions***
Antidiarrheal preparations	Y	N	Only loperamide HCl (Imodium), bismuth subsalicylate (Pepto-Bismol), and kaolin preparations are allowed.
Antiemetics/antinauseants	Y	N	• Antidopaminergic agents (such as metoclopramide, domperidone, and phenothiazines), scopolamine, 5-HT3 receptor antagonists (eg, ondansetron) and sedating (H1) antihistamines are not allowed. • Phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto Bismol), and cola syrup are allowed.
Antifungals, systemic	N	N	
Antifungals, topical	Y	Y	
Antihistamines	Y	Y	• Sedating antihistamines are not allowed. • Only fexofenadine (Allegra), loratadine (Claritin), desloratadine (Clarinex), cetirizine (Zyrtec), and levocetirizine (Xyzal) are allowed for episodic or chronic use. • See cough and cold preparations for combination products.
Antihypertensives	N	Y[a]	The medication and dosage should be stable for 1 month before screening (for diuretics, the patient should have been treated with the diuretic for at least 3 months, with at least 1 month on the current dose).
Anti-inflammatory drugs	Y	Y[b]	• Chronic use is allowed if dosage is stable for 1 month before screening. • Indomethacin (Indocin) and systemic corticosteroids are not allowed.

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Name or Class	***Episodic Use (PRN)***	***Chronic Use***	***Restrictions***
Antimigraine	Y	Y	• Triptans should be used with some caution. Note that cases of serotonin syndrome have been reported with the concomitant use of triptans and serotonergic reuptake inhibitors. • Ergotamine or ergot derivatives, antidepressants, and anticonvulsants are not allowed for migraine treatment or prophylaxis.
Antineoplastics	N	N	
Antiobesity agents	N	N	
Antipsoriatic treatments	Y	Y	Acitretin (Soriatane) is not allowed.
Antipsychotics	N	N	
Antismoking medications	N	N	• Varenicline (Chantix) and bupropion (Zyban) are not allowed. • Nicotine replacement therapies are allowed.
Antiviral agents	Y	Y	• Only acyclovir, famciclovir, valacyclovir, penciclovir, docosanol, trifluridine, and vidarabine are allowed. • Amantadine and rimantadine are permitted for influenza prophylaxis, but use is limited to a 7- to 14-day course. • Interferons are not allowed.
Anxiolytics	N	N	
Cough and cold preparations	Y	N	• Cough/cold preparations containing dextromethorphan or narcotics are not allowed. • Decongestant preparations containing pseudoephedrine or phenylpropanolamine are not allowed. • Phenylephrine nasal sprays are allowed for brief clinically appropriate use, for up to 5 days. • Combination products containing the word “Nighttime” or some synonym routinely include a sedating antihistamine and are not allowed. • Combination products ending in “D” routinely contain a stimulant such as pseudoephedrine or phenylpropanolamine and are not allowed (also see antihistamines).

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Name or Class	***Episodic Use (PRN)***	***Chronic Use***	***Restrictions***
Strong CYP3A4 Inhibitors	N	N	Following are examples of strong CYP3A4 inhibitors which are prohibited: Indinavir, nelfinavir, ritonavir, saquinavir, itraconazole, ketoconazole, clarithromycin, telithromycin, nefazodone, and suboxone. Refer to the following website for the most up to date list of strong CYP3A4 inhibitors: http://medicine.iupui.edu/clinpharm/DDIs/table.aspx
H_2 blockers/proton pump inhibitors	Y	Y[a]	Tagamet (cimetidine) is not allowed; all others acceptable.
Hormones, non-reproductive	N	N	Thyroid replacement is allowed if not for depression and condition and dose stable for 1 month.
Hormones: reproductive	N	Y	Hormonal contraception such as oral contraceptives (estrogen-progestin combination or progestin alone), transdermally delivered contraceptives (eg, Ortho Evra), depot injections (eg, Depo-Provera), vaginal contraceptive ring (eg, NuvaRing), and contraceptive implant (eg, Implanon, Norplant) are allowed.
Hormone suppressants	N	N	
Hypoglycemic agents	Y	Y	
Hypolipidemics	N	Y[a]	Statins are allowed.
Laxatives	Y	Y[b]	• Episodic and chronic use of bulk laxatives and emollient laxatives are allowed. • Episodic use of stimulant laxatives containing senna, bisacodyl, and anthraquinone derivatives is allowed. • Episodic use of osmotic laxatives such as oral magnesium hydroxide (milk of magnesia), oral sodium citrate, and sodium biphosphate is allowed. • Hyperosmotic laxatives such as sorbitol, lactulose, and polyethylene glycol (eg, Miralax) are not allowed.

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Name or Class	***Episodic Use (PRN)***	***Chronic Use***	***Restrictions***
Muscle relaxants	N	N	
Psychotropic drugs not otherwise specified (including herbal products)	N	N	No drugs with psychomotor effects or with anxiolytic, antidepressant, stimulant, antipsychotic, or sedative properties are allowed except as stipulated by the protocol. Herbal/dietary products and supplements with potential psychoactive actions, including St. John's wort, ginkgo biloba, kava, SAMe, valerian root, DHEA, tyrosine, tryptophan and 5-HTP are not allowed. Omega-3 supplements are allowed if the dose of EPA is ≤ 1000 mg/day, and the patient has been taking same for at least 1 month.
Sedatives/Hypnotics	Y	N	Only zolpidem (Ambien up to 5 mg/day and Ambien CR up to 6.25 mg/day), zaleplon (Sonata) up to 10 mg/day, and eszopiclone (Lunesta) up to 3 mg/day and melatonin are permitted up to 3 times a week, if required for sleep. Sedatives/hypnotics may not be used in the 8 hours preceding any behavioral assessments.
Corticosteroids, systemic	N	N	
Corticosteroids, topical	Y	Y	
Corticosteroids, inhalant	Y	Y	
Corticosteroids, intra-articular	Y	NA	
Vaccines	Y	NA	

a If being taken for at least 3 months before study and dose is stabilized.

b If being taken before admission to the study.

ADHD = attention deficit hyperactivity disorder; MAOI = monoamine oxidase inhibitor; NA = not applicable; N = no; PRN = *pro re nata* (as needed); Y = yes.

APPENDIX IV. PHARMACOKINETIC BLOOD SAMPLING AND SHIPPING INSTRUCTIONS (ONLY IN PARTICIPANTS AGED 7-11 YEARS)

Specimen Tube Collection Preparation

- Adhere the provided label to a 3-mLVacutainer K_2EDTA containing tube
- Prechill (eg, in an ice bath or refrigerator) the labeled Vacutainer tube and a polypropylene tube

Plasma Collection Procedure

- Collect blood into the prechilled Vacutainer tube; invert the tube gently 8-10 times to mix the blood and anticoagulant. Place the tube in an ice-water bath (use crushed ice).
- Centrifuge the tube (within 30 minutes from the time the blood is drawn) at 2500 rpm to 3750 rpm for 10 minutes at approximately 4°C (ie, refrigerated centrifuge). In absence of a refrigerated centrifuge, the blood tubes should be chilled in ice for at least 10 minutes prior to centrifuging. Blood samples should still be centrifuged within 30 minutes of blood collection.
- After centrifugation, transfer harvested plasma immediately into a prechilled, labeled, polypropylene tube provided by the central laboratory. Ensure the tube has the appropriate label marked with study number, patient identification number, date, and time of collection.
- The tube must then be immediately placed in the freezer and should be stored at approximately –70°C (or up to 6 weeks at –20°C).
- Enter the actual time that the blood sample was collected on the appropriate form of the eCRF.
- Send the frozen sample to the central laboratory according to the central laboratory sample shipment guide.

Shipping Guide from the Study Center to the Central Laboratory

Samples will be shipped from the study center to the central laboratory on the first available appropriate date after sample collection, and can be batch-shipped but no later than 6 weeks after sample collection. The central laboratory will provide packaging, labeling, and shipping instructions to the study center. Plasma samples will be shipped on sufficient dry ice to keep them frozen for at least 96 hours.

APPENDIX V. CHILDREN'S DEPRESSION RATING SCALE–REVISED

1. ***IMPAIRED SCHOOLWORK***

Performance is consistent with ability	1
	2
Decrease in school performance and/or ability to concentrate	3
	4
Major interference with performance in most subjects	5
	6
No motivation to perform	7

Comment:

2. ***DIFFICULTY HAVING FUN***

Interest and activities realistically appropriate for age, personality, and social environment. No appreciable change from usual behavior during at least the past 2 weeks. Any feelings of boredom are seen as transient	1
	2
Describes some activities as enjoyable that are realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.	3
	4
Is easily bored. Complains of "nothing to do" as characteristic of daily experience. Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.	5
	6
Has no initiative to become involved in any activities. Describes himself/herself as primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.	7

Comment:

3. ***SOCIAL WITHDRAWAL***

Enjoys friendships with peers at school and at home.	1
	2
Does not actively seek out friendships but waits instead for others to initiate a relationship. Occasionally rejects opportunities to play, without having a describable alternative.	3
	4
Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.	5
	6
Does not currently relate to other children. States that he/she has "no friends" or actively rejects new or former friends.	7

Comment:

4. ***SLEEP DISTURBANCE***

No difficulty or occasional difficulty that is situationally explainable.	1
	2
Frequently has mild difficulty with sleep.	3
	4
Has difficulty with sleep nearly every night.	5

Supplemental information (not scored)
Indicate when sleep disturbance occurs (check all applicable items):

____ Upon first going to bed
____ In the middle of the night
____ Early in the morning

Comment:

5. ***APPETITE DISTURBANCE***

No problems or changes in eating pattern.	1
	2
Mild but notable change from usual eating habits.	2
	3
Avoids eating and/or is not hungry most of the time OR describes a noteworthy increase in appetite and/or excessive food intake.	5

Supplemental information (not scored)
If applicable, indicate type of appetite disturbance:
____ Increased appetite
____ Decreased appetite

Comment:

6. ***EXCESSIVE FATIGUE***

No unusual complaints of "feeling tired" during the day.	1
	2
Complains of fatigue seem somewhat excessive and are not related to boredom or increased activity levels.	3
	4
Daily complaints of feeling tired.	5
	6
Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Degree of fatigue interferes with play activities.	7

Comment:

7. ***PHYSICAL COMPLAINTS***

Occasional complaints that do not appear to be excessive.	1
	2
Complaints appear mildly excessive.	3
	4
Complains daily of aches and pains. These occasionally interfere with his/her ability to function.	5
	6
Preoccupied with aches and pains. These regularly interfere with play activities.	7

Comment:

8. ***IRRITABILITY***

Rarely irritable.	1
	2
Easily irritable. Periods of irritability occur several times a week, but do not last long.	3
	4
Frequently irritable. Extended periods of irritability occur several times a week and are difficult to break out of.	5
	6
Constant experience of irritability. Nothing changes this mood.	7

Comment:

9. ***EXCESSIVE GUILT***

Does not express any undue feelings of guilt. Reported guilt appears appropriate to precipitating event.	1
	2
Exaggerates guilt and/or shame out of proportion to the event described.	3
	4
Feels guilty over things not under his/her control. These feelings interfere with everyday functioning.	5
	6
Severe delusions of guilt.	7

Comment:

10. ***LOW SELF-ESTEEM***

Describes himself/herself in primarily positive terms.	1
	2
Describes one important or prominent area where he/she feels there is a deficit.	3
	4
Describes himself/herself in predominantly negative terms or gives bland answers to questions asked.	5
	6
Refers to himself/herself in derogatory terms. Reports that other children frequently refer to him/her by using derogatory nicknames. Puts himself/herself down.	7

Comment:

11. ***DEPRESSED FEELINGS***

Occasionally feelings of unhappiness that quickly disappear.	1
	2
Describes sustained periods of unhappiness that appear excessive for events described.	3
	4
Feels unhappy most of the time without a major precipitating cause.	5
	6
Feels unhappy all of the time; characterized by a sense of psychic pain (eg, "I can't stand it").	7

Comment:

12. ***MORBID IDEATION***

No morbid thinking reported.	1
Strongly denies morbid thoughts.	2
Discusses morbid thoughts that relate to a real event but seem excessive.	3
	4
Describes preoccupation with morbid thoughts several times a week. These morbid thoughts extend beyond external reality.	5
	6
Preoccupied on a daily basis with death themes or morbid thoughts that are elaborate, extensive, or bizarre.	7

Comment:

13. ***SUICIDAL IDEATION***

Understands the word *suicide*, but does not apply the term to himself/herself.	1
Sharp denial of suicidal thoughts.	2
Has thoughts about suicide, or of hurting himself/herself (if he/she does not understand the concept of suicide), usually when angry.	3
	4
Has recurrent thoughts of suicide.	5
	6
Has made a suicide attempt within the last month or is actively suicidal.	7

Comment:

14. ***EXCESSIVE WEEPING***

Report appears normal for age.	1
Suggestive statements that he/she cries, or feels like crying, more frequently than peers.	2
Cries more often than peers, occasionally without clear precipitant.	3
	4
Cries or feels like crying frequently (several times a week). Admits to crying without knowing the reason why.	5
	6
Cries nearly every day.	7

Comment:

15. ***DEPRESSED FACIAL AFFECT***

Facial expression and voice animated during the interview. No sign of depressed affect.	1
Mild suppression of affect. Some loss of spontaneity.	2
Overall loss of spontaneity. Looks unhappy during parts of the interview (eg, sullen face, lowered eyes, lack of animation in face). Is capable of smiling, however, and does not avoid eye contact when discussing non-threatening areas.	3
	4
Moderate restriction of affect throughout most of the interview. Has longer and frequent periods of looking distinctly unhappy. Nothing seems to enliven him/her.	5
	6
Severe restriction of affect. Looks distinctly sad and withdrawn. Minimal verbal interaction throughout the interview. Cries or may appear tearful.	7

Comment:

16. ***LISTLESS SPEECH***

Quality of speech seems situationally sensitive without any noteworthy deviations.	1
Slowed tempo, monotone, or overly soft speech.	2
Slowed tempo with many pauses where he/she appears to drift. Hesitations include sighing. Voice qualities are distinctly monotonic and unanimated, and convey a sense of distress and psychic discomfort.	3
	4
Extreme sense of psychic distress exhibited in voice or by a profound sense of hollowness or emptiness. Has difficulty conducting the interview.	5

Comment:

17. ***HYPOACTIVITY***

Bodily movements are animated. (Note that a hyperactive, agitated child is not distinguished here from what would be seen as normal nondistracting behavior; hyperactivity should be noted).	1
	2
Bodily movements appear somewhat restricted and/or slowed.	3
	4
Definite restriction in bodily movements and an overall sense of motor retardation.	5
	6
Severe sense of motor retardation with catatonic-like qualities.	7

Comment:

APPENDIX VI. CLINICAL GLOBAL IMPRESSIONS–SEVERITY

SEVERITY OF ILLNESS

Considering your total clinical experience with this population, how mentally ill is the patient at this time? (Check one)

1 Normal, not at all ill

2 Borderline ill

3 Mildly ill

4 Moderately ill

5 Markedly ill

6 Severely ill

7 Among the most extremely ill patients

APPENDIX VII. CLINICAL GLOBAL IMPRESSIONS–IMPROVEMENT

GLOBAL IMPROVEMENT

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his/her condition at **BASELINE**, how much has the patient changed? (Check one)

1 Very much improved

2 Much improved

3 Minimally improved

4 No change

5 Minimally worse

6 Much worse

7 Very much worse

APPENDIX VIII. BASELINE COLUMBIA–SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** /Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX IX. SINCE LAST VISIT COLUMBIA–SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) *Description of Ideation*

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of* act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	**Most Lethal Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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