LURASIDONE

D1050302

A 104-WEEK, FLEXIBLE-DOSE, OPEN-LABEL, MULTICENTER, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFECTIVENESS OF LURASIDONE IN PEDIATRIC SUBJECTS

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader		Head of Global Clinical Research, Psychiatry Sunovion Pharmaceuticals Inc.
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SAE Reporting in EU and Africa		Principal Drug Safety Scientist Sunovion Pharmaceuticals Europe, Ltd.

1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: Lurasidone (lurasidone HCl)

Title of Study: A 104-Week, Flexible-Dose, Open-Label, Multicenter, Extension Study to Evaluate the Long-Term Safety and Effectiveness of Lurasidone in Pediatric Subjects

Study Centers: Multicenter study in the United States and Worldwide

Phase of Development: 3

Study Objectives:

Primary: To evaluate the long-term safety, tolerability, and effectiveness of lurasidone (20, 40, 60 or 80 mg/day, flexibly dosed) in pediatric subjects who have completed a prior lurasidone study.

Secondary:

For all subjects, the following will be assessed:

- Proportions of subjects with adverse events (AEs), discontinuations due to AEs, and serious AEs (SAEs).

For subjects continued from Study D1050301, the following will be assessed:

- Change in Positive and Negative Syndrome Scale (PANSS) total, positive, negative, general psychopathology, and excitability subscale scores;
- Change in the Clinical Global Impression – Severity (CGI-S);
- Change in the Clinician-rated Children's Global Assessment Scale (CGAS);
- Change in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q).

For subjects continued from Study D1050325, the following will be assessed:

- Change in Aberrant Behavior Checklist (ABC) irritability subscale, and the following subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal);
- Change in the Clinical Global Impression – Severity (CGI-S);
- Change in Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs);
- Change in the Caregiver Strain Questionnaire (CGSQ).

For subjects continued from Study D1050326, the following will be assessed:

- Change in the Children's Depression Rating Scale, Revised (CDRS-R);
- Change in the Clinical Global Impression Bipolar Version – Severity (CGI-BP-S);
- Change in the Clinician-rated Children's Global Assessment Scale (CGAS);
- Change in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
- Change in anxiety symptoms as measured by the Pediatric Anxiety Rating Scale (PARS);
- Change in attention-deficit/hyperactivity symptoms as measured by the Attention-Deficit/ Hyperactivity Disorder Rating Scale (ADHD-RS) total score.

Study Design:

This is an open-label, 104-week, multicenter, extension study designed to evaluate the long-term safety, tolerability and effectiveness of flexibly dosed lurasidone (20, 40, 60 or 80 mg/day) in pediatric

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subjects who have completed the 6-week treatment period in the preceding studies, D1050301, D1050325, or D1050326.

Subjects who complete participation in the preceding studies, D1050301, D1050325, or D1050326 will be eligible for enrollment in this study. Informed consent/assent will be obtained from all subjects (where developmentally appropriate) before any study procedures are performed. Subjects who meet entry criteria will transition to this study directly from Study D1050301, D1050325, or D1050326. All subjects will be treated with flexibly dosed lurasidone during the trial.

A reliable informant (eg, parent, legal guardian, or caregiver) of the subject must accompany the subject at each visit. For subjects entering from Study D1050325, the reliable caregiver will also oversee the administration of the study drug throughout the study.

All eligible subjects will be treated with lurasidone 40 mg/day for Days 1-7. Beginning with Day 8, dose adjustments (20, 40, 60 or 80 mg/day) will be permitted, based on investigator judgment, to optimize tolerability and effectiveness.

Dose adjustment of study drug should occur at the regularly scheduled visits and in increments or decrements of 1 dose level. However, dose reductions for tolerability or safety purposes may occur beginning on Day 2, based on investigator judgment. These dose reductions may be between study visits and at more than 1 dose level at a time (maximum of 2 dose levels at a time). If dose reductions are required between regular study visits, the subject must return to the study site for an unscheduled visit to receive new medication kits and return all used/unused medication kits at the time of dose adjustment.

Safety and effectiveness assessments will be conducted at scheduled visits during the study.
A follow-up visit will occur 1 week post last dose of study drug.

A Data and Safety Monitoring Board (DSMB) will review safety and clinical outcome data including data on adverse events (AEs) and serious adverse events (SAEs) at regular intervals until the D1050301, D1050325, and D1050326 studies are complete and as long as necessary for the D1050302 study, as determined by the Sponsor. The DSMB will be independent of the Sponsor, contract research organization (CRO), and the investigators and will be empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility. The membership of the DSMB and its mandate is denoted in the DSMB charter.

Number of Subjects (planned): The estimated number of subjects eligible for enrollment is approximately 702 subjects.

Diagnosis and Main Criteria for Inclusion:

Subject has completed Study D1050301 (Visit 9), Study D1050325 (Visit 9), or Study D1050326 (Visit 8); is judged to be appropriate for long-term treatment with lurasidone; has provided informed assent/consent (where developmentally appropriate); and has met all other entry criteria.

Investigational Product, Dosage and Mode of Administration: Subjects will receive lurasidone (lurasidone HCl) administered orally, 20, 40, 60 or 80 mg (flexibly dosed), once daily in the evening with food (at least 350 calories) or within 30 minutes after eating.

Duration of Treatment: 24 months (104 weeks)

Reference Therapy, Dosage and Mode of Administration: Not applicable

Criteria for Evaluation:

Safety Assessments:

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All Subjects:

- Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation and serious AEs (SAEs);
- Laboratory tests, vital signs, body weight and body mass index (BMI), waist circumference, physical examination, height (as measured by stadiometer), electrocardiogram (ECG), hormonal parameters;
- Movement disorders as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS);
- Tanner staging, and menstrual cyclicity (female subjects).

For subjects continued from Study D1050301 and D1050326:

- Columbia Suicide Severity Rating Scale (C-SSRS);
- CogState Computerized Cognitive Test Battery;
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU).

For subjects continued from Study D1050326:

- Young Mania Rating Scale (YMRS) score.

Effectiveness Assessments:

For subjects continued from Study D1050301:

- Positive and Negative Syndrome Scale (PANSS);
- Clinical Global Impression-Severity (CGI-S) scale;
- Clinician-rated Children's Global Assessment Scale (CGAS);
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q).

For subjects continued from Study D1050325:

- Aberrant Behavior Checklist (ABC);
- Clinical Global Impression-Severity (CGI-S) scale.
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs);
- Caregiver Strain Questionnaire (CGSQ).

For subjects continued from Study D1050326:

- Children's Depression Rating Scale, Revised (CDRS-R);
- Clinical Global Impression Bipolar Version -Severity (CGI-BP-S) scale;
- Clinician-rated Children's Global Assessment Scale (CGAS);
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
- Pediatric Anxiety Rating Scale (PARS);
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS).

Statistical Methods:

The safety population will include all subjects who receive at least one dose of study medication. A total of three analysis groups will be formed based on a subject's previous participation status in double-blind studies D1050301, D1050325, or D1050326. Safety and efficacy analyses will be

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presented by the above analysis groups, respectively. In efficacy and safety analyses, the pre-treatment baseline from studies D1050301, D1050325, or D1050326 will be referred to as the double-blind study baseline or "DB baseline," and the last assessment prior to the first dose in the open-label study D1050302 will be referred to as the open label study baseline or "OL baseline." No statistical comparisons will be conducted for treatment groups.

Safety Analyses:

For all subjects:

The incidence of AEs, SAEs, and discontinuations due to AEs. AEs (or SAEs) will be summarized by presenting the number and percentage of subjects having each individual AE (or SAE) by analysis group. Discontinuations due to AEs and SAEs will be summarized by presenting number and percentage of subjects terminated prematurely due to AEs or SAEs by analysis group.

Descriptive statistics will also be provided for the following safety variables and the corresponding changes from baseline: body weight, height, body mass index (BMI), waist circumference, vital signs, electrocardiogram (ECG) parameters, movement disorders as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS), Tanner staging, and menstrual cyclicity (female subjects), physical examination results, and standard laboratory tests covering hematology, chemistry, hormonal parameters, and urinalysis.

For subjects continued from Study D1050301 and D1050326:

Descriptive statistics will also be provided for the CogState Computerized Cognitive Test Battery, and Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU) by visit for each analysis group. For C-SSRS data, number and percentage of subjects with suicidal ideations and behaviors will be summarized.

For subjects continued from Study D1050326:

Descriptive statistics will be presented for YMRS result by analysis group and study visit.

For above safety analyses, continuous variables will be summarized using descriptive statistics of number of subjects, mean, standard deviation, median, minimum and maximum values. Categorical variables will be reported as frequencies and percentages.

Effectiveness Analyses

This open-label study includes subjects coming from three different studies (D1050301, D1050325, and D1050326). Efficacy variables to be summarized for this study will include:

For subjects continued from Study D1050301:

Descriptive statistics of observed value and change from DB baseline and OL baseline in PANSS total score and positive, negative, general psychopathology, and excitability subscale scores, CGI-S, CGAS, and PQ-LES-Q scores will be provided by visit and by analysis group.

For subjects continued from Study D1050325:

Descriptive statistics of observed value and change from DB baseline and OL baseline in ABC subscale scores (irritability, hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal), CGI-S, CY-BOCS, and CGSQ scores will be provided by visit and by analysis group.

For subjects continued from Study D1050326:

Descriptive statistics of observed value and change from DB baseline and OL baseline in CDRS-R, CGI-BP-S, CGAS, PQ-LES-Q, PARS, and ADHD-RS scores will be provided by visit and by analysis group.

For above effectiveness analyses, descriptive statistics, including number of subjects, mean, standard

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deviation, median, minimum, maximum, and a 95% confidence interval, will be provided. Since this is an uncontrolled open-label extension of studies D1050301, D1050325, or D1050326, no inferential statistics on effectiveness will be presented.

Sample Size:

Subjects who complete the respective double-blind studies D1050301, D1050325 or D1050326, sign the consent, and meet all entry criteria will be included in this study. Studies D1050301, D1050325, and D1050326 have finished, with a total of 271 subjects from D1050301, 125 subjects from D1050325, and 306 subjects from D1050326 enrolling into D1050302. Based on an estimated attrition rate of approximately 30% of subjects over six months, it is expected that at least 100 subjects will be exposed to lurasidone for a minimum of 6 months for subjects continued from Studies D1050301 and D1050325 in Study D1050302.

Data Analyses of Interim Data for FDA Filing

After studies D1050301 and D1050325 are completed, when at least 100 subjects previously from these two studies complete the Week 28 visit (ie, exposed to study drug for at least 6 months), data analyses based on these interim data will be done to prepare a safety/effectiveness report in support of the initial health authority filing for US regulatory submission for the lurasidone pediatric program. A subsequent final analysis of study D1050302 will be performed after every subject previously enrolled from study D1050301, D1050325, and D1050326 complete the study.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

For the purposes of standardization, the following definitions will be used:

Abbreviation	Term
5-HT	5-hydroxytryptamine
ABC	Aberrant Behavior Checklist
ADHD-RS	Attention-Deficit/ Hyperactivity Disorder Rating Scale
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ATC	Anatomic Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
β-hCG	beta-subunit of human chorionic gonadotropin
BMI	Body Mass Index
CDRS-R	Children's Depression Rating Scale, Revised
CFR	Code of Federal Regulations
CGAS	Clinician-rated Children's Global Assessment Scale
CGI-BP-S	Clinical Global Impression Bipolar Version – Severity
CGI-S	Clinical Global Impression-Severity Scale
CGSQ	Caregiver Strain Questionnaire
CNS	central nervous system
CRA	clinical research associate
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scales
CYP	cytochrome P
DSMB	Data and Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture
EPS	extrapyramidal symptoms

Abbreviation	Term
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IXRS	Interactive Voice/Web Response System
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
PANSS	Positive and Negative Syndrome Scale
PARS	Pediatric Anxiety Rating Scale
PDD	Pervasive developmental disorders
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
QD	once-daily
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
UKU	Udvalg for Kliniske Undersogelser Side Effect Rating Scale
WHO	World Health Organization
YMRS	Young Mania Rating Scale

- CRF: A printed, optical, or electronic document designed to record all of the protocol required information to report to the sponsor for each study subject.
- Screened Subject: Any subject who signed the study specific informed consent.
- Screen Failures: Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled.

- Study Drug (or study medication): Term to cover investigational drug.
- Treatment Phase: The period of the study in which the study drug is administered.
- Enrolled Subject: Any subject who was successfully screened and enter the treatment phase of the study.
- Completed Subject: Any subject who participated throughout the duration of the study, up to and including the end of study visit.
- Early Termination Subject: Any subject who was successfully screened and enrolled into the treatment phase of the study, but did not complete the study.

4. INTRODUCTION

4.1. Previous Human Experience in Pediatric Subjects

There has been 1 completed pediatric clinical study evaluating the safety, tolerability, and pharmacokinetics of single and multiple doses of lurasidone in adolescents (12-17 years of age) and children (6-11 years of age) with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders (Study D1050300).

Preliminary results from this study revealed that exposure in the pediatric population (6-17 years of age) are similar to observed exposure in adults across the dose range (20-160 mg). The most frequently observed AEs (≥10%) across the dose range in this population were somnolence (42%), sedation (18%), nausea (17%), and vomiting (15%).

4.2. Study Rationale

Lurasidone is a novel compound being developed by Sunovion Pharmaceuticals Inc, and is an approved agent for the treatment of adult patients with schizophrenia. Lurasidone has a unique chemical structure that differs from conventional and atypical antipsychotic agents. Lurasidone is a novel compound with high affinities for dopamine D_2, serotonin 5-HT_{2A} and 5-HT_7 receptors, moderate affinity for serotonin 5-HT_{1A} and noradrenaline α_{2C} and α_{2A} receptors, and little or no affinity for histamine H_1 and muscarinic M_1 receptors which are thought to be responsible for some important side effects (weight gain, sedation) and worsening of the cognitive function. Clinical studies in adults with schizophrenia treated with lurasidone have shown significant beneficial effects on the amelioration of positive and negative symptoms with a minimal effect on weight gain, glucose metabolism, and lipid parameters.

Based on its pharmacologic profile as well as clinical studies in adult subjects with schizophrenia and bipolar depression, lurasidone is expected to be associated with few extrapyramidal symptoms (EPS) and to be effective in ameliorating a broad range of symptoms in adolescents with schizophrenia, autistic disorder, and bipolar depression.

This open-label extension study is designed to evaluate the longer-term safety, tolerability, and effectiveness of lurasidone over 104 weeks for the treatment of pediatric patients that have completed a previous lurasidone study. The 104-week study duration will provide an adequate timeframe within which to evaluate the longer-term effects of lurasidone in this patient population.

4.3. Dose Justification

Based on the therapeutic dose ranges evaluated in prior lurasidone clinical studies, doses of 20, 40, 60 or 80 mg/day will be used in this study. Lurasidone will be taken with food for optimal exposure to the administered dose. The dose of lurasidone may be adjusted to optimize efficacy and tolerability, as deemed clinically appropriate.

5. STUDY OBJECTIVES

5.1. Primary Objective

To evaluate the long-term safety, tolerability, and effectiveness of lurasidone (20, 40, 60 or 80 mg/day, flexibly dosed) in pediatric subjects who have completed a prior lurasidone study.

5.2. Secondary Objectives

For all subjects:

- Proportions of subjects with adverse events (AEs), discontinuations due to AEs, and serious AEs (SAEs).

For subjects continued from Study D1050301, the following will be assessed:

- Change in Positive and Negative Syndrome Scale (PANSS) total, positive, negative, general psychopathology, and excitability subscale scores;
- Change in the Clinical Global Impression – Severity (CGI-S);
- Change in the Clinician-rated Children's Global Assessment Scale (CGAS);
- Change in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q).

For subjects continued from Study D1050325, the following will be assessed:

- Change in Aberrant Behavior Checklist (ABC) irritability subscale, and the following subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal);
- Change in the Clinical Global Impression – Severity (CGI-S);
- Change in Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs);
- Change in the Caregiver Strain Questionnaire (CGSQ).

For subjects continued from Study D1050326, the following will be assessed:

- Change in the Children's Depression Rating Scale, Revised (CDRS-R);
- Change in the Clinical Global Impression Bipolar Version – Severity (CGI-BP-S);
- Change in the Clinician-rated Children's Global Assessment Scale (CGAS);
- Change in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
- Change in anxiety symptoms as measured by the Pediatric Anxiety Rating Scale (PARS);
- Change in attention-deficit/hyperactivity symptoms as measured by the Attention-Deficit/ Hyperactivity Disorder Rating Scale (ADHD-RS) total score.

6. STUDY ENDPOINTS

6.1. Safety Assessments

All Subjects:

- Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation and serious AEs (SAEs);
- Laboratory tests, vital signs, body weight and body mass index (BMI), waist circumference, physical examination, height (as measured by stadiometer), electrocardiogram (ECG), hormonal parameters;
- Movement disorders as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS);
- Tanner staging, and menstrual cyclicity (female subjects).

For subjects continued from Study D1050301 and D1050326:

- Columbia Suicide Severity Rating Scale (C-SSRS);
- Composite Score of the CogState Computerized Cognitive Test Battery;
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU).

For subjects continued from Study D1050326:

- Young Mania Rating Scale (YMRS) score.

6.2. Effectiveness Assessments

For subjects continued from Study D1050301:

- Positive and Negative Syndrome Scale (PANSS);
- Clinical Global Impression-Severity (CGI-S) scale;
- Clinician-rated Children's Global Assessment Scale (CGAS);
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q).

For subjects continued from Study D1050325:

- Aberrant Behavior Checklist (ABC);
- Clinical Global Impression-Severity (CGI-S) scale;
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs);
- Caregiver Strain Questionnaire (CGSQ).

For subjects continued from Study D1050326:

- Children's Depression Rating Scale, Revised (CDRS-R);
- Clinical Global Impression Bipolar Version -Severity (CGI-BP-S) scale;

- Clinician-rated Children's Global Assessment Scale (CGAS);
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
- Pediatric Anxiety Rating Scale (PARS);
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS).

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, 104-week, multicenter, extension study designed to evaluate the long-term safety, tolerability and effectiveness of flexibly dosed lurasidone (20, 40, 60 or 80 mg/day) in pediatric subjects who have completed a 6-week treatment period in one of the preceding studies, D1050301, D1050325, or D1050326.

Subjects who complete participation in one of the preceding studies, D1050301, D1050325 or D1050326, will be eligible for enrollment in this study. Informed consent/assent will be obtained from all subjects (where developmentally appropriate) before any study procedures are performed. Subjects who meet entry criteria will transition to this study directly from Study D1050301, D1050325 or D1050326. All subjects will be treated with flexibly dosed lurasidone during the trial.

A reliable informant (eg, parent, legal guardian, or caregiver) of the subject must accompany the subject at each visit. For subjects entering from Study D1050325, the reliable caregiver will also oversee the administration of the study drug throughout the study.

All eligible subjects will be treated with lurasidone 40 mg/day for Days 1-7. Beginning with Day 8, dose adjustments (20, 40, 60 or 80 mg/day) will be permitted, based on investigator judgment, to optimize tolerability and effectiveness.

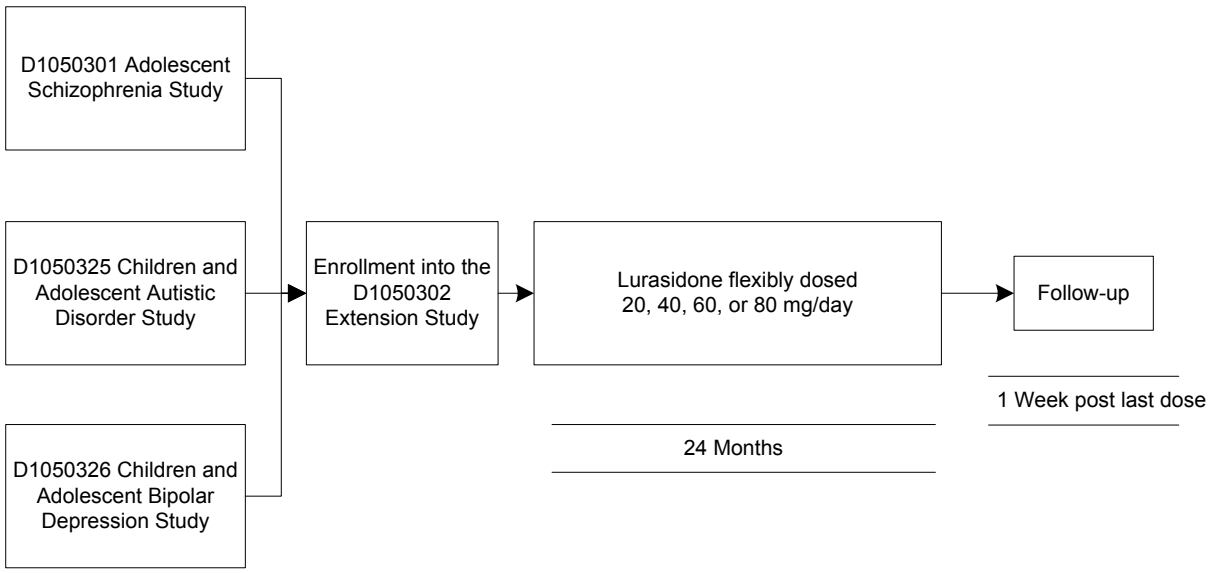
Dose adjustment of study drug should occur at the regularly scheduled visits and in increments or decrements of 1 dose level. However, dose reductions for tolerability or safety purposes may occur beginning on Day 2, based on investigator judgment. These dose reductions may be between study visits and at more than 1 dose level at a time (maximum of 2 dose levels at a time). If dose reductions are required between regular study visits, the subject must return to the study site for an unscheduled visit to receive new medication kits and return all used/unused medication kits at the time of dose adjustment.

Safety and effectiveness assessments will be conducted at scheduled visits during the study. A follow-up visit will occur 1 week post last dose of study drug.

A DSMB will review safety and clinical outcome data including data on AEs and SAEs at regular intervals until the D1050301, D1050325, and D1050326 studies are complete and as long as necessary for the D1050302 study, as determined by the Sponsor. The DSMB will be independent of the Sponsor, contract research organization (CRO), and the investigators and will be empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility. The membership of the DSMB and its mandate is denoted in the DSMB charter.

A study schematic is presented below in Figure 1. Details of study assessments and other procedures to be performed at each visit are presented in Table 3, Schedule of Assessments, and Section 11, Treatment Plan.

Figure 1: Study Schematic



7.2. Study Termination Criteria

The study may be terminated at any time by the sponsor for any reason.

Table 3: Schedule of Assessments Enrollment to Week 40

Study Visit Number **Study Visit Week (±3 days)**	**V 1E** **Day 1**	**V 2E** **W2**	**V 3E** **W4**	**V 4E** **W6**	**V 5E** **W8**	**V 6E** **W12**	**V 7E** **W16**	**V 8E** **W20**	**V 9E** **W24**	**V 10E** **W28**	**V 11E** **W32**	**V 12E** **W36**	**V 13E** **W40**
Obtain informed consent/assent	X												
Inclusion/exclusion criteria	X												
Interactive Voice/Web Response System (IXRS) subject registry/visit	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication	X	X[a]	X	X[a]	X	X	X	X	X	X	X	X	X
Study drug accountability/assess compliance		X	X	X	X	X	X	X	X	X	X	X	X
Clinical and Laboratory Evaluations: ALL SUBJECTS													
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event (AE) monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	These clinical evaluations were to have been performed at Study Visit Number 9 in study D1050301 or D1050325 or at Study Visit Number 8 in study D1050326 and will serve as the baseline evaluations for this study.									X			X
Height as measured by stadiometer				X		X				X			X
Tanner staging										X			X
Menstrual cyclicity (female subjects)		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[b]		X	X	X	X	X	X	X	X	X	X	X	X
Weight				X		X				X			X
Waist circumference measurement						X				X			X
Electrocardiogram (ECG)										X			
Hematology, chemistry, and urinalysis						X				X			
Hormonal Parameters[c]						X				X			
Serum prolactin						X				X			
Glycosylated hemoglobin (HbA_{1c})						X				X			
Glucose and lipid panel[d]						X				X			
Serum insulin and C-reactive protein						X				X			

Study Visit Number **Study Visit Week (±3 days)**	**V 1E** **Day 1**	**V 2E** **W2**	**V 3E** **W4**	**V 4E** **W6**	**V 5E** **W8**	**V 6E** **W12**	**V 7E** **W16**	**V 8E** **W20**	**V 9E** **W24**	**V 10E** **W28**	**V 11E** **W32**	**V 12E** **W36**	**V 13E** **W40**
Urine drug screen			X		X	X	X	X	X	X	X	X	X
Urine β-hCG[e, f]			X		X	X	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS)	These clinical evaluations were to have been performed at Study Visit Number 9 in study D1050301 or D1050325 or at Study Visit Number 8 in study D1050326 and will serve as the baseline evaluations for this study.	X	X	X	X	X	X	X	X	X	X	X	X
Barnes Akathisia Rating Scale (BARS)		X	X	X	X	X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Evaluations: **SUBJECTS from D1050301 ONLY**													
Children's Global Assessment Scale (CGAS)				X		X				X			X
Clinical Global Impression – Severity (CGI-S)		X	X	X	X	X	X	X	X	X	X	X	X
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)				X		X				X			X
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)		X		X		X				X			X
Columbia Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X	X	X	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)				X		X				X			X
CogState Computerized Cognitive Test Battery						X				X			
Clinical Evaluations: **SUBJECTS from D1050325 ONLY**													
Aberrant Behavior Checklist (ABC)				X		X				X			X
Clinical Global Impression – Severity (CGI-S)		X	X	X	X	X	X	X	X	X	X	X	X
Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)				X		X				X			X
Caregiver Strain Questionnaire (CGSQ)				X		X				X			X

Study Visit Number **Study Visit Week (±3 days)**	**V 1E** **Day 1**	**V 2E** **W2**	**V 3E** **W4**	**V 4E** **W6**	**V 5E** **W8**	**V 6E** **W12**	**V 7E** **W16**	**V 8E** **W20**	**V 9E** **W24**	**V 10E** **W28**	**V 11E** **W32**	**V 12E** **W36**	**V 13E** **W40**
Clinical Evaluations: **SUBJECTS from D1050326 ONLY**	These clinical evaluations were to have been performed at Study Visit Number 9 in study D1050301 or D1050325 or at Study Visit Number 8 in study D1050326 and will serve as the baseline evaluations for this study.												
Children's Depression Rating Scale, Revised (CDRS-R)				X		X				X			X
Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)		X	X	X	X	X	X	X	X	X	X	X	X
Children's Global Assessment Scale (CGAS)				X		X				X			X
Young Mania Rating Scale (YMRS)				X		X				X			X
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)				X		X				X			X
Columbia Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X	X	X	X	X	X	X	X
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)		X		X		X				X			X
Pediatric Anxiety Rating Scale (PARS)				X		X				X			X
Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)				X		X				X			X
CogState Computerized Cognitive Test Battery						X				X			

Abbreviations: V = Visit; Wk = Week

[a] Study drug will be dispensed only if a dose change is required.

[b] Vital sign measurements to include orthostatic changes in blood pressure and heart rate.

[c] Hormonal Parameters include the following measures: follicle stimulating hormone; luteinizing hormone; testosterone (male subjects only); estradiol (female subjects only).

[d] Subjects will fast for laboratory tests.

[e] Any positive urine β-hCG test will be confirmed by serum β-hCG.

[f] Females subjects ≥ 11 years of age only.

If a subject discontinues from the study, all Visit 29E procedures will be performed at the discontinuation visit, within 48 hours of the last dose of study medication.

Table 4: Schedule of Assessments - Week 44 to 92

Study Visit Number Study Visit Week (±3 days)	V 14E W44	V 15E W48	V 16E W52	V 17E W56	V 18E W60	V 19E W64	V 20E W68	V 21E W72	V 22E W76	V 23E W80	V 24E W84	V 25E W88	V 26E W92
Interactive Voice/Web Response System (IXRS) subject registry/visit	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability/assess compliance	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical and Laboratory Evaluations: ALL SUBJECTS													
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination			X						X				
Height as measured by stadiometer			X			X			X			X	
Tanner staging			X						X				
Menstrual cyclicity (female subjects)	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight			X			X			X			X	
Waist circumference measurement			X			X			X			X	
Electrocardiogram (ECG)			X						X				
Hematology, chemistry, and urinalysis			X						X				
Hormonal Parameters[b]			X						X				
Serum prolactin			X						X				
Glycosylated hemoglobin (HbA_{1c})			X						X				
Glucose and lipid panel[c]			X						X				
Serum insulin and C-reactive protein			X						X				
Urine drug screen	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[d, e]	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Visit Number Study Visit Week (±3 days)	V 14E W44	V 15E W48	V 16E W52	V 17E W56	V 18E W60	V 19E W64	V 20E W68	V 21E W72	V 22E W76	V 23E W80	V 24E W84	V 25E W88	V 26E W92
Simpson-Angus Scale (SAS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Barnes Akathisia Rating Scale (BARS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Evaluations: SUBJECTS from D1050301 ONLY													
Children's Global Assessment Scale (CGAS)			X			X			X			X	
Clinical Global Impression – Severity Scale (CGI-S)	X	X	X	X	X	X	X	X	X	X	X	X	X
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)			X			X			X			X	
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)			X			X			X			X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)			X			X			X			X	
CogState Computerized Cognitive Test Battery			X						X				
Clinical Evaluations: SUBJECTS from D1050325 ONLY													
Aberrant Behavior Checklist (ABC)			X			X			X			X	
Clinical Global Impression – Severity Scale (CGI-S)	X	X	X	X	X	X	X	X	X	X	X	X	X
Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)			X			X			X			X	
Caregiver Strain Questionnaire (CGSQ)			X			X			X			X	
Clinical Evaluations: SUBJECTS from D1050326 ONLY													

Study Visit Number Study Visit Week (±3 days)	V 14E W44	V 15E W48	V 16E W52	V 17E W56	V 18E W60	V 19E W64	V 20E W68	V 21E W72	V 22E W76	V 23E W80	V 24E W84	V 25E W88	V 26E W92
Children's Depression Rating Scale, Revised (CDRS-R)			X			X			X			X	
Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)	X	X	X	X	X	X	X	X	X	X	X	X	X
Children's Global Assessment Scale (CGAS)			X			X			X			X	
Young Mania Rating Scale (YMRS)			X			X			X			X	
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)			X			X			X			X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)			X			X			X			X	
Pediatric Anxiety Rating Scale (PARS)			X			X			X			X	
Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)			X			X			X			X	
CogState Computerized Cognitive Test Battery			X						X				

Abbreviations: V = Visit; Wk = Week

[a] Vital sign measurements to include orthostatic changes in blood pressure and heart rate.

[b] Hormonal Parameters include the following measures: follicle stimulating hormone; luteinizing hormone; testosterone (male subjects only); estradiol (female subjects only).

[c] Subjects will fast for laboratory tests.

[d] Any positive urine β-hCG test will be confirmed by serum β-hCG.

[e] Females subjects ≥ 11 years of age only.

If a subject discontinues from the study, all Visit 29E procedures will be performed at the discontinuation visit, within 48 hours of the last dose of study medication.

Table 5: Schedule of Assessments - Week 96 to 105

Study Visit Number Study Visit Week (±3 days)	V 27E Wk96	V 28E Wk100	EOS/ET V 29E [a] Wk104	F/U V 30E Wk105
Interactive Voice/Web Response System (IXRS) subject registry/visit	X	X	X	X
Dispense study medication	X	X		
Study drug accountability/assess compliance	X	X	X	
Clinical and Laboratory Evaluations: ALL SUBJECTS				
Prior/concomitant medication review	X	X	X	X
Adverse event monitoring	X	X	X	X
Physical examination			X	
Height as measured by stadiometer			X	
Tanner staging			X	
Menstrual cyclicity (female subjects)	X	X	X	X
Vital signs[b]	X	X	X	X
Weight			X	
Waist circumference measurement			X	
Electrocardiogram (ECG)			X	
Hematology, chemistry, and urinalysis			X	
Hormonal Parameters[c]			X	
Serum prolactin			X	
Glycosylated hemoglobin (HbA_{1c})			X	
Glucose and lipid panel[d]			X	
Serum insulin and C-reactive protein			X	
Urine drug screen	X	X	X	
Urine β-hCG[e, f]	X	X	X	X

Study Visit Number Study Visit Week (±3 days)	V 27E Wk96	V 28E Wk100	EOS/ET V 29E [a] Wk104	F/U V 30E Wk105
Simpson-Angus Scale (SAS)	X	X	X	X
Barnes Akathisia Rating Scale (BARS)	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)	X	X	X	X
Clinical Evaluations: SUBJECTS from D1050301 ONLY				
Children's Global Assessment Scale (CGAS)			X	
Clinical Global Impression – Severity Scale (CGI-S)	X	X	X	
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)			X	
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)			X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)			X	
CogState Computerized Cognitive Test Battery			X	
Clinical Evaluations: SUBJECTS from D1050325 ONLY				
Aberrant Behavior Checklist (ABC)			X	
Clinical Global Impression – Severity Scale (CGI-S)	X	X	X	
Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)			X	
Caregiver Strain Questionnaire (CGSQ)			X	
Clinical Evaluations: SUBJECTS from D1050326 ONLY				
Children's Depression Rating Scale, Revised (CDRS-R)			X	
Clinical Global Impression-Bipolar Version, Severity of	X	X	X	

Study Visit Number Study Visit Week (±3 days)	V 27E Wk96	V 28E Wk100	EOS/ET V 29E [a] Wk104	F/U V 30E Wk105
Illness (CGI BP-S)				
Children's Global Assessment Scale (CGAS)			X	
Young Mania Rating Scale (YMRS)			X	
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)			X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)			X	
Pediatric Anxiety Rating Scale (PARS)			X	
Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)			X	
CogState Computerized Cognitive Test Battery			X	

Abbreviations: V = Visit; Wk = Week; F/U = follow-up

[a] If a subject discontinues from the study, all Visit 29E procedures will be performed at the discontinuation visit, within 48 hours of the last dose of study medication.

[b] Vital sign measurements to include orthostatic changes in blood pressure and heart rate.

[c] Hormonal Parameters include the following measures: follicle stimulating hormone; luteinizing hormone; testosterone (male subjects only); estradiol (female subjects only).

[d] Subjects will fast for laboratory tests.

[e] Any positive urine β-hCG test will be confirmed by serum β-hCG.

[f] Females subjects ≥ 11 years of age only.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

The following inclusion/exclusion criteria must be met prior to enrolling the subject into the study.

8.1. Subject Inclusion Criteria

1. Written informed consent from parent(s) or legal guardian(s) with sufficient intellectual capacity to understand the study and support subjects' participation in the study procedures must be obtained for subjects who are not emancipated. In accordance with Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements, the subject will complete an informed assent when developmentally appropriate, to participate in the study before conduct of any study-specific procedures.
2. Subject has completed Study D1050301 (Visit 9);
   OR
   Subject has completed Study D1050325 (Visit 9);
   OR
   Subject has completed Study D1050326 (Visit 8).
3. Subject is judged by the investigator to be appropriate for participation in a 104-week clinical trial in an outpatient setting involving open-label lurasidone treatment, and is able to comply with the protocol.
4. A reliable informant (eg, parent, legal guardian, or caregiver) must be available to accompany the subject at each visit. For subjects entering from Study D1050325, the reliable caregiver must also oversee the administration of the study drug throughout the study.
5. Females who participate in this study:
   - are unable to become pregnant (eg, premenarchal, surgically sterile, etc.)

   -OR-

   - practices true abstinence (consistent with lifestyle) and must agree to remain abstinent from signing informed consent to at least 7 days after the last dose of study drug has been taken;

   -OR-

   - are sexually active and willing to use a medically effective method of birth control (eg, male using condom and female using condom, diaphragm, contraceptive sponge, spermicide, contraceptive pill, or intrauterine device) from signing informed consent to at least 7 days after the last dose of study drug has been taken.
6. Males must be willing to remain sexually abstinent (consistent with lifestyle) or use an effective method of birth control (eg, male using condom and female using condom, diaphragm, contraceptive sponge, spermicide, contraceptive pill, or intrauterine device)

from signing informed consent to at least 7 days after the last dose of study drug has been taken.

8.2. Subject Exclusion Criteria

1. Subject is considered by the investigator to be at imminent risk of suicide.
2. Exhibits evidence of moderate or severe extrapyramidal symptoms, dystonia, tardive dyskinesia, or any other moderate or severe movement disorder. Severity to be determined by the investigator.

9. TREATMENT OF SUBJECTS

9.1. Concomitant Medications

Any medication or non-pharmacological therapy that is taken by or administered to the subject at any point during the course of this study must be recorded in the electronic case report form (eCRF). The entry must include the dose, regimen, route, indication, and dates of use.

Potent inducers or inhibitors of the CYP3A4 enzyme system (Appendix B) and any medications that consistently prolong the QTc interval are prohibited. In addition, the use of herbal supplements (for psychotropic reasons, eg, Gingko Biloba, Kava Kava, St. John's Wort, etc.) or other complementary or alternative medications except melatonin during the study are not permitted.

Initiation of new non-pharmacologic therapy (eg, a new course of psychotherapy or behavior modification) is permitted during the study. Subjects who have participated in ongoing psychotherapy or other non-pharmacological treatment during Study D1050301, D1050325, or D1050326 will be permitted to continue this treatment during the study.

9.1.1. Concomitant Non-psychotropic Medications

Non-psychotropic medications may be used to treat mild, chronic medical conditions if the dose and regimen have been stable (± 25%) during Study D1050301, D1050325, or D1050326. β-adrenergic antagonists used to treat stable hypertension can be continued throughout the study. In addition, use of non-prescription pain medications (eg, acetaminophen or ibuprofen) are allowed provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study drug. Medications for short-term treatment of a medical condition (no more than 14 days) are allowed provided that the medications are not CYP3A4 inhibitors/inducers and do not consistently prolong the QTc interval.

9.1.2. Concomitant Psychotropic Medications

Subjects may be treated with any approved benzodiazepines or antidepressants provided that the medications are not potent CYP3A4 inhibitors/inducers (Appendix B), during the course of the study, at the discretion of the investigator in a manner consistent with labeling recommendations and conventional medical practice. Monoamine oxidase inhibitors (MAOI) and additional antipsychotic medications (with the exception of lurasidone) will be prohibited.

Treatment with stimulants (provided that the medications are not potent CYP3A4 inhibitors/inducers), guanfacine or atomoxetine will be permitted during the course of the study for treatment of attentional deficits, at the discretion of the investigator in a manner consistent with labeling recommendations and conventional medical practice.

Treatment with benztropine (≤ 6 mg/day) will be permitted as needed for movement disorders. In cases where benztropine is not available, or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute EPS: biperiden (≤ 16 mg/day) or trihexyphenidyl (≤ 15 mg/day) or diphenhydramine (≤ 100 mg/day for subjects entering from Study D1050301 or Study D1050326; ≤ 50 mg/day for subjects entering from Study D1050325). Treatment with propranolol (≤ 120 mg/day) will be

permitted as needed for akathisia. Medications used to treat movement disorders should not be given prophylactically.

Concomitant use of lorazepam, or equivalent benzodiazepine, is permitted at the discretion of the investigator (≤ 6 mg/day or equivalent dose) for intolerable anxiety/agitation, as clinically indicated. In regions where lorazepam or other specified medications are not available, another similar agent at equivalent doses will be permitted as specified by the Medical Monitor and/or the Operations Manual. Benzodiazepines administered orally or as a rapid acting IM injection should be used sparingly, and only when clinically required per investigator judgment. The date and time of last dose of lorazepam (or equivalent benzodiazepine) must be recorded at each visit. Subjects should be encouraged to avoid taking these medications within 8 hours prior to scheduled study assessments.

Temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zaleplon (≤ 20mg/day), zolpidem (≤ 10 mg/day for males; ≤ 5 mg/day for females), zolpidem CR (≤ 12.5 mg/day for males; ≤ 6.25 mg/day for females), diphenhydramine (≤ 100 mg/day for subjects entering from Study D1050301 or D1050326; ≤ 50 mg/day for subjects entering from Study D1050325), melatonin (≤ 5 mg/day), or clonidine immediate release (≤ 0.1 mg/day) may be administered at bedtime for insomnia, as needed. For those subjects taking melatonin, over the counter melatonin should be used; combination melatonin products are not allowed. Sedative-hypnotic agents should be administered no more than once nightly and should not be used in combination.

Since the list of prohibited potent CYP3A4 inhibitors and inducers (Appendix B) is not comprehensive, investigators should use medical judgment when a subject presents with a medication not on the list or consult with the Medical Monitor for clarification.

9.2. Treatment Compliance

All subjects and caregivers will be reminded at each study visit of the importance of strict compliance with taking study medication as directed, with food. Compliance with study medication must be monitored closely at each visit. Subjects will be instructed to bring all unused study medication with them to each visit. Subjects missing more than 25% or taking more than 125% of scheduled doses between visits must be immediately reported to and discussed with the Medical Monitor.

9.3. Hospitalization

Subjects who were hospitalized at the conclusion of the previous core study (either D1050301 or D1050326) can continue to be hospitalized for up to 14 days in this study at the discretion of the investigator. The investigator must evaluate the subject to determine the length of hospitalization based on his/her clinical judgment. After these initial 14 days, subjects must be transitioned to an outpatient setting for the remainder of the study. If the subject cannot be transitioned to an outpatient setting, they must be discontinued from the study.

If a subject discontinues and is clinically unstable, additional hospitalization (beyond the original 14 days allowed) may be allowed on a case-by-case basis with pre-approval of the Medical Monitor.

For hospitalized subjects, they must be clinically stable, in the judgment of the investigator, to warrant discharge to the appropriate living environment. In making a discharge determination, investigators should also consider the following additional factors: appropriateness for outpatient

treatment; a stable residence with adequate caregiver support; and the ability of the subject to be compliant with study medications and study visits.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of Study Drug

The study drug is lurasidone 20 mg tablets and lurasidone 40 mg tablets.

Table 6: Investigational Product

Investigational Drug:	Lurasidone
Active Ingredient:	Lurasidone hydrochloride (HCl)
Formulation:	Film-coated lurasidone 20 mg active tablets and film-coated lurasidone 40 mg active tablets.
Frequency:	20 mg, 40 mg, 60 mg, or 80 mg once daily (QD)
Packaged as:	20 mg or 40 mg tablets in Aluminum-Aluminum blister package
Manufactured by:	Dainippon Sumitomo Pharma Co., Ltd.
Storage Conditions:	Store between 15-25ºC (59-77ºF). Protect from light and moisture
Packaging Description:	Aluminum-Aluminum blister package.

10.2. Study Drug Packaging and Labeling

Supplies will be packaged in blister cards as described below. Study medication will be labeled with the clinical trial number and all appropriate investigational labeling requirements.

10.2.1. Blister Cards

All study medication will be packaged in uniquely identifiable 7-day supply (plus 2 days) blister cards. At each dispensing visit a subject will receive a 4-week carton which contains four blister cards. The 20 mg per day and 40 mg per day blister cards will contain one column and 9 rows. The 60 mg per day and 80 mg per day blister cards will contain two columns and 9 rows. Subjects assigned to the 20 mg per day or 40 mg per day dose will be requested to take 1 tablet (one row) each day, according to dosing instructions. Subjects assigned to the 60 mg per day or 80 mg per day dose will be requested to take 2 tablets (one row), each day according to dosing instructions.

The labeling and packaging of the study medication will be based on the guidance described in US Code of Federal Regulations, CFR 21, Part 312.6, Annex 13 and any other local applicable regulatory requirements. Container label text for study medication blister cards may include the following information listed in Table 7 below:

Table 7: Blister Card and Carton Label Example

1) Med ID #: XXXXXX (IXRS identifying number) 2) Protocol # D1050302 3) Space for subject number (assigned by IXRS) 4) Fill Count & Dosage Form 5) Visit # _____ 6) Packaging batch number XXXXXXXX-XX 7) Expiry Date: MM/YYYY 8) Investigator Information (contact information –if applicable) 9) Sponsor Address: Sunovion Pharmaceuticals Inc. One Bridge Plaza, Suite 510 Fort Lee, NJ 07024, USA	10) Directions for Use 11) "Keep out of reach of children" statement 12) For Oral Use 13) Storage Conditions: Store between 15- 25°C (59-77°F). Protect from light and moisture. 14) Caution: New Drug–Limited By Federal (or United States) Law to Investigational Use. 15) For Clinical Trial Use Only and other Country Regulatory Requirements

NOTE: Item 7, Expiration will not be on the US and Puerto Rico ONLY label

10.3. Study Drug Storage

The clinical study drug lurasidone should be stored between 15-25°C (59-77°F) and protected from light and moisture. The subject will be instructed to store the medication at room temperature.

The study drug storage area will be monitored for temperature. A monitoring system recording temperature 24 hours a day, 7 days a week will be employed. Appropriate temperature records will be maintained. If the storage conditions fall outside of the indicated range, 15-25°C (59-77°F), the sponsor must be contacted to discuss the potential implications and any actions(s), if necessary.

The investigator is responsible for the proper storage of the study drug according to the sponsor's recommendations and all applicable federal and state regulatory guidelines. The investigator agrees not to dispense or store the study drug at any location other than that listed on Form FDA 1572.

10.4. Study Drug Dispensation and Handling

A 4-week supply of study drug will be dispensed according to the visit schedule. The subject (or caregiver as appropriate) will be instructed to use the 2-day reserve if they miss their regularly scheduled visit. The subject (or caregiver as appropriate) will be instructed to return all unused study medication and empty blister cards to the clinical trial site at each visit.

10.5. Interactive Voice Response/Web Response System (IXRS)

IXRS is an integrated phone and web, subject and drug management system. The interactive system that will assign unique subject numbers and medication identification numbers (Med ID #) corresponding to the appropriate cartons and blister cards.

10.6. Administration

The study drug will be dispensed by appropriately qualified site study staff. Under the supervision from the subject's caregiver, as appropriate, subjects will take the study drug following the directions given to them in the clinic.

All study medication will be taken once daily in the evening by mouth with food (at least 350 calories; eg, dinner) or within 30 minutes after eating. Subjects who, in the judgment of the investigator, are intolerant to evening dosing may be allowed for take study medication in the morning. Exceptions to the evening dosing of study medication are acceptable on a case-by case basis, and must be recorded appropriately in the eCRF. Subjects who change to morning dosing should continue morning dosing for the duration of the study.

10.7. Study Drug Accountability

Study drug must be received by the investigator or a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and/or designated assistants have access. Study medication is to be dispensed only in accordance with the protocol.

The investigator (or qualified designee) is responsible for maintaining accurate records of the study drug received from the Sponsor, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. At the end of the study, all study medication including unused, partially used, and empty blister cards must be returned to the Sponsor, or designee, after confirmation with the CRA. The investigator will be provided with instructions on the return of all study drug. The following information is to be included in the eCRF: visit medication dispensed, blister card number, time of dose, dosing start/stop dates, number of tablets dispensed, blister card return status and number of tablets returned.

If the investigation is terminated, discontinued, suspended, or completed, all unused study drug will be returned to the Sponsor’s designee, unless other instructions are provided in writing by CRO/Sponsor.

11. TREATMENT PLAN

11.1. Study Assessments

11.1.1. Effectiveness

Aberrant Behavior Checklist (ABC): The ABC is a symptom checklist for assessing problem behaviors of children and adults with intellectual disability and developmental disorders at home, in residential facilities, intermediate care facilities for individuals with intellectual disability, and work training center. It is also useful for classifying problem behaviors of these children and adolescent in educational settings, residential and community-based facilities, and developmental centers. The 58 items resolve into five subscales: (1) irritability and agitation, (2) lethargy and social withdrawal, (3) stereotypic behavior, (4) hyperactivity and noncompliance, and (5) inappropriate speech. The ABC irritability subscale contains 15 items that rate symptoms such as "injures self", "aggressive to other children and adults", "irritable", "temper outbursts", "depressed mood", "mood changes", and "yells or screams inappropriately" on a scale ranging from 0 (not at all a problem) to 3 (severe). The checklist is completed by the subject's parent/caregiver and the same parent/caregiver should complete all ABC assessments for a given subject whenever possible. The ABC-C (community) version will be used.

Clinical Global Impression – Severity Scale (CGI-S): The CGI-S is a clinician-rated assessment of the subject's current illness state on a 7 point scale, where a higher score is associated with greater illness severity (eg, schizophrenia or irritability associated with autism). Following a clinical interview, the CGI-S can be completed in 1-2 minutes (Guy 1976; Williams 2000). The CGI-S will be administered by a qualified rater at the site and the same study site rater should perform all CGI-S assessments for a given subject whenever possible.

Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs): The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) modified for pervasive developmental disorders (PDDs) (Scahill, 2006) is a clinical-administered semistructured clinician rating that measures to measure the severity of obsessive-compulsive disorder. The modification for PDDs eliminates the obsessions checklist and severity scales of the CY-BOCS, while expanding the compulsions checklist to include repetitive behaviors more commonly seen in children with PDD. In addition, the modified for PDDs version relies more on parental input than on the child's input. The CY-BOCS will be administered by a qualified rater at the site and the same study site rater should perform all CY-BOCS assessments for a given subject whenever possible.

Children's Global Assessment Scale (CGAS): The CGAS is a clinician-rated assessment of the overall severity of disturbance in children, with a range of scores from 1 to 100. It anchors at 10-point intervals include descriptors of functioning and psychopathology for each interval. A second version of the CGAS, designed for nonclinicians who have conducted a standardized diagnostic assessment of the child (usually in community surveys), was constructed similarly, except that the descriptors of psychopathology and functioning are written in lay terminology. The single numerical score representing severity of disturbance ranges from 1 (most impaired) to 100 (healthiest). On the basis of the descriptors, raters are expected to synthesize their knowledge about the child's social and symptomatic functioning and condense this information

into a score. For example, a score of 61–70 indicates that the child has some difficulty in a single area but is generally functioning pretty well. Scores above 70 are considered to be in the normal range, whereas scores on the low end of the continuum indicate a need for constant supervision (1–10) or considerable supervision (11–20). The CGAS will be administered by a qualified rater at the site and the same study site rater should perform all CGAS assessments for a given subject whenever possible.

Caregiver Strain Questionnaire (CGSQ): The CGSQ is a caregiver reported assessment that assesses the extent to which caregivers are affected by the special demands associated with caring for a child with emotional and behavioral problems. The CGSQ is comprised of three subscales which range in severity from 1 to 5. Objective Strain refers to observable disruptions in family and community life (eg, interruption of personal time, lost work time, financial strain). Subjective Externalized Strain refers to negative feelings about the child such as anger, resentment, or embarrassment. Subjective Internalized Strain refers to the negative feelings that the caregiver experiences such as worry, guilt, or fatigue. Higher scores on each of these scales indicate greater strain. A Global Strain score is calculated by summing the three subscales (ie, Objective Strain, Subjective Externalized Strain, and Subjective Internalized Strain) to provide an indication of the total impact of the special demands on the family. Global Strain scores range from 3 to 15. As with the individual subscales, higher scores indicate greater strain.

Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q): The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) is a 15-item measure that assesses the quality of life in children and adolescents. This scale focuses on the child's or adolescent's views about general health, well-being, and feelings about the medical condition. Response categories range from "very poor" to "very good". The PQ-LES-Q is a subject self-reported assessment.

Positive and Negative Syndrome Scale (PANSS): The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 scales: the Positive scale assesses hallucinations, delusions, and related symptoms; the Negative scale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology scale addresses other symptoms such as anxiety, somatic concern, and disorientation. An anchored Likert scale from 1-7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item. Individual items are then summed to determine scores for the 3 scales, as well as a total score. A Composite scale score (Positive scale score minus Negative scale score) can also be calculated to show the relative valence of positive and negative symptoms. Total time required for the PANSS interview and scoring is approximately 30-40 minutes (Kay, 1994; Perkins, 2000; Opler, 1992). PANSS raters will be required to meet specific training and education criteria before they are certified to rate for this study. In addition, raters will receive specific training and education regarding all of the assessments prior to study initiation. The PANSS will be administered by a qualified rater at the site and the same study site rater should perform all PANSS assessments for a given subject whenever possible.

Children's Depression Rating Scale, Revised (CDRS-R): The CDRS-R is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6-17 years. It contains 17 ordinally-scaled items that evaluate the presence and severity of symptoms commonly associated with depression in childhood. The CDRS-R score ranges from

17-113. The CDRS-R will be administered separately to the patient and to the caregiver. For each item, the rating that provides the best description of the patient will be selected by the clinician administering the interviews. The CDRS-R will be administered by a qualified rater at the site and the same study site rater should perform all CDRS-R assessments for a given subject whenever possible.

Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S): The CGI-BP-S is a three-part clinician-rated assessment of the subject's current illness state (depression, mania, and overall) using a 7-point scale for each part, where a higher score is associated with greater illness severity. Following a clinical interview, the CGI-BP-S can be completed in 1-2 minutes. The CGI-BP-S will be administered by a qualified rater at the site and the same study site rater should perform all CGI-BP-S assessments for a given subject whenever possible.

Pediatric Anxiety Rating Scale (PARS): The PARS is a clinician-rated instrument for assessing over time the severity of anxiety symptoms associated with common DSM-IV anxiety disorders (generalized anxiety disorder, separation anxiety, and social phobia) in children ages 6-17 years. The PARS will be administered separately to the subject and to the caregiver. The instrument has 2 sections. The first section includes a 50-item symptom checklist, which the clinician rates as present or absent during the past week. The second section is comprised of 7 severity impairment items that are rated on a 6 point Likert scale. The 7 severity impairment items reflect the severity/impairment of all symptoms endorsed in Section 1 of the PARS (during the past week). The PARS will be administered by a qualified rater at the site and the same study site rater should perform all PARS assessments for a given subject whenever possible.

Attention-Deficit/ Hyperactivity Disorder Rating Scale (ADHD-RS): The ADHD-RS IV was developed to measure the behaviors of children with ADHD. The ADHD-RS IV is a validated scale that consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV-TR criteria. Each item is scored from a range of zero (reflecting no symptoms) to three (reflecting severe symptoms) with total scores ranging from zero to 54. The 18 items may be grouped into two sub-scales: hyperactivity/impulsivity (even number items 2 through 18) and inattentiveness (odd number items 1 through 17). The ADHD-RS will be administered to the caregiver by a qualified rater at the site and the same study site rater should perform all ADHD-RS assessments for a given subject whenever possible.

11.1.2. Safety

Vital Signs: Vital signs following 5 minutes of seated rest will consist of supine systolic and diastolic blood pressures, respiration rate, heart rate, and oral body temperature.

Blood pressure and heart rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and heart rate throughout the study. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and heart rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

Orthostatic effects: Orthostatic changes with clinically significant symptoms should be recorded as AEs. The categorization of orthostatic effects is intended for the data analysis and reporting of group effects and does not constitute guidance as to whether individual assessments reflect clinically meaningful changes.

Physical Examination Assessments: A full physical examination will be performed. The physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

Weight, height, and waist circumference: Weight and height should be measured in street clothing with no shoes. Waist circumference measurement should be taken around the body at the level of the abdomen and just above the hip bone. The waist circumference measurement is usually taken immediately after exhalation.

Centrally-read ECG: All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 10 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability.

Clinical Laboratory: For detailed instructions regarding laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified. See Appendix A for a list of required clinical laboratory tests. Hyperglycemia will be defined as any glucose result of ≥ 126 mg/dL; dyslipidemia will be defined as any result of total cholesterol ≥ 240 mg/dL or triglycerides ≥ 200 mg/dL.

Adverse Events: As a discussion guide, subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Appendix C.

Concomitant Medications and Medical History: Subject and caregiver self-report will be acceptable for listing all concomitant medication use, medical history, psychiatric history, and evaluation for inclusion/exclusion except where specific protocol procedures are mandated to ensure appropriate enrollment (eg, certain baseline lab values).

Simpson-Angus Scale (SAS): The SAS is a clinician-rated assessment of neuroleptic-induced parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale, and address rigidity, gait (bradykinesia), tremor, glabellar tap, and salivation (Simpson, 1970). SAS raters will be required to meet specific credential and educational criteria before they are certified to rate for this study. The same study site rater should perform all SAS assessments for a given subject whenever possible.

Barnes Akathisia Rating Scale (BARS): The BARS (Barnes, 1989, Barnes, 2003, Schooler, 2000) is a rating scale geared toward assessment of neuroleptic-induced akathisia, though it can be used to measure akathisia associated with other drugs as well. The BARS consists of 4 items, including one item assessing objective restlessness, 2 items targeting

subjective restlessness (awareness and related distress), and one global clinical assessment item. All items are anchored and utilize a 4-point scale, except for the global rating which has a 6-point scale (from absence of akathisia through severe akathisia). The subjective and objective items are summed to yield a total score. The BARS can be administered in about 10 minutes. The BARS will be administered by a qualified rater at the site. The same study site rater should perform all BARS assessments for a given subject whenever possible.

Abnormal Involuntary Movement Scale (AIMS): The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk. There are 2 items related to dental status, as well as 3 global impression items assessing overall severity, incapacitation, and the subject's awareness of abnormal movements (Guy, 1976; Munetz, 1988). AIMS raters will be required to meet specific credential and educational criteria before they are certified to rate for this study. The same study site rater should perform all AIMS assessments for a given subject whenever possible.

Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU): The Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingiaerde, 1987) is a comprehensive, clinician-rated scale, designed to assess the side effects in patients treated with psychotropic medications. The UKU contains information obtained via interviews with the patient, as well as observations made by the clinician. The UKU consists of 48 questions. A rating can typically be assessed within 30 minutes. Each point on the UKU is assigned a degree of zero, one, two or three. Zero indicates normal; one indicates mild symptoms; two indicates moderate symptoms; and three indicates severe symptoms. The same study site rater should perform all UKU assessments for a given subject whenever possible.

Columbia Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the trial. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional. The same study site rater should perform all C-SSRS assessments for a given subject whenever possible.

Young Mania Rating Scale (YMRS): The YMRS is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar disorder. The 11 items are: Elevated Mood, Increased Motor Activity Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language-Thought Disorder, Content, Disruptive-Aggressive Behaviour, Appearance and Insight. The YMRS is a clinician-rated assessment and uses operationally-defined anchor points. Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score). The YMRS will be administered separately to the subject and to the caregiver by a qualified rater at the site and the same study site rater should perform all YMRS assessments for a given subject whenever possible.

CogState Computerized Cognitive Test Battery: The CogState Computerized Cognitive Test Battery is a computerized testing platform designed to provide brief, standardized, and easily administered assessment of a range of cognitive functions. The CogState test battery to be used in this study consists of four tasks each designed to specifically assess functioning in the following cognitive domains: psychomotor speed (detection task); attention (identification task); learning/memory (one card learning task); and working memory (one back task). The computerized test will be administered to each subject using the computer interface at the study site.

Tanner Staging: a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, testicular volume and development of pubic and axillary hair.

Menstrual cyclicity (female subjects only): Menstrual cyclicity will be monitored in female subjects who have begun menses. Female subjects will be given a calendar to mark the beginning and end of each menses. This calendar will be reviewed at each visit.

11.2. Standardization of Data Capture

Study Schematic and Schedule of Assessments: A schematic of the study design and summary of assessments to be conducted at each visit are presented in Figure 1 and Table 3, Table 4, and Table 5, respectively.

Assessment Windows: Assessments will be conducted within the time frames specified (ie ± 3 days). All times are relative to the time of dosing for individual subjects

11.3. Electronic Data Capture (EDC)

The study sites will use a validated EDC system to enter subject data onto CRFs. Medidata RAVE will be used for this clinical study. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the investigator.

11.4. Study Visits and Assessments

11.4.1. Visit 1E (Day 1)

Visit 1E (Day 1) – this visit will occur on the same day as Study Visit Number 9 in Study D1050301 and Study D1050325 and Study Visit Number 8 in Study D1050326.

Note: Assessments specific to this study are listed below; all other assessments will be carried over from Study Visit Number 9 in Study D1050301 and Study D1050325 and Study Visit Number 8 in Study D1050326.

- Obtain informed consent/assent
- Inclusion/exclusion criteria

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring

11.4.2. Visit 2E (Week 2)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.3. Visit 3E (Week 4)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.4. Visit 4E (Week 6)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Height as measured by stadiometer
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Children's Global Assessment Scale (CGAS)
- Clinical Global Impression – Severity Scale (CGI-S)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)

11.4.5. Visit 5E (Week 8)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen

- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.6. Visit 6E (Week 12)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Height as measured by stadiometer
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Hematology, chemistry, and urinalysis
- Hormonal Parameters
- Serum prolactin
- Glycosylated hemoglobin (HbA1c)
- Glucose and lipid panel
- Serum insulin and C-reactive protein
- Urine drug screen

- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Children's Global Assessment Scale (CGAS)
- Clinical Global Impression – Severity Scale (CGI-S)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)
- CogState Cognitive Test Battery

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
- CogState Cognitive Test Battery

11.4.7. Visit 7E (Week 16)

- Interactive Voice/Web Response System (IXRS) subject registry/visit

- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.8. Visit 8E (Week 20)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)

- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.9. Visit 9E (Week 24)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.10. Visit 10E (Week 28)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Physical examination
- Height as measured by stadiometer
- Tanner staging
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Electrocardiogram (ECG)
- Hematology, chemistry, and urinalysis
- Hormonal Parameters
- Serum prolactin
- Glycosylated hemoglobin (HbA1c)
- Glucose and lipid panel
- Serum insulin and C-reactive protein
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Global Assessment Scale (CGAS)

- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)
- CogState Cognitive Test Battery

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
- CogState Cognitive Test Battery

11.4.11. Visit 11E (Week 32)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs

- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.12. Visit 12E (Week 36)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.13. Visit 13E (Week 40)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Physical examination
- Height as measured by stadiometer
- Tanner staging
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Global Assessment Scale (CGAS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)

11.4.14. Visit 14E (Week 44)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.15. Visit 15E (Week 48)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.16. Visit 16E (Week 52)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication

- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Physical examination
- Height as measured by stadiometer
- Tanner staging
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Electrocardiogram (ECG)
- Hematology, chemistry, and urinalysis
- Hormonal Parameters
- Serum prolactin
- Glycosylated hemoglobin (HbA1c)
- Glucose and lipid panel
- Serum insulin and C-reactive protein
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Global Assessment Scale (CGAS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)
- CogState Cognitive Test Battery

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
- CogState Computerized Cognitive Test Battery

11.4.17. Visit 17E (Week 56)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.18. Visit 18E (Week 60)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.19. Visit 19E (Week 64)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Height as measured by stadiometer
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Global Assessment Scale (CGAS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)

11.4.20. Visit 20E (Week 68)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.21. Visit 21E (Week 72)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.22. Visit 22E (Week 76)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Physical examination
- Height as measured by stadiometer

- Tanner staging
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Electrocardiogram (ECG)
- Hematology, chemistry, and urinalysis
- Hormonal Parameters
- Serum prolactin
- Glycosylated hemoglobin (HbA1c)
- Glucose and lipid panel
- Serum insulin and C-reactive protein
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Global Assessment Scale (CGAS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)
- CogState Cognitive Test Battery

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
- CogState Computerized Cognitive Test Battery

11.4.23. Visit 23E (Week 80)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)

- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.24. Visit 24E (Week 84)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.25. Visit 25E (Week 88)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Height as measured by stadiometer

- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Global Assessment Scale (CGAS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)

11.4.26. Visit 26E (Week 92)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.27. Visit 27E (Week 96)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs

- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.28. Visit 28E (Week 100)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Dispense study medication
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Columbia Suicide Severity Rating Scale (C-SSRS)

11.4.29. Visit 29E EOS/ET (Week 104)

- Interactive Voice/Web Response System (IXRS) subject registry/visit
- Study drug accountability/assess compliance

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Physical examination
- Height as measured by stadiometer
- Tanner staging
- Menstrual cyclicity (female subjects)
- Vital signs
- Weight
- Waist circumference measurement
- Electrocardiogram (ECG)
- Hematology, chemistry, and urinalysis
- Hormonal Parameters
- Serum prolactin
- Glycosylated hemoglobin (HbA1c)
- Glucose and lipid panel
- Serum insulin and C-reactive protein
- Urine drug screen
- Urine β-hCG (female subjects ≥ 11 years of age only)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Clinical Global Impression – Severity Scale (CGI-S)

- Children's Global Assessment Scale (CGAS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Positive and Negative Syndrome Scale (PANSS)
- CogState Cognitive Test Battery

Clinical Evaluations: SUBJECTS from D1050325 ONLY

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impression – Severity Scale (CGI-S)
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Caregiver Strain Questionnaire (CGSQ)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Children's Depression Rating Scale, Revised (CDRS-R)
- Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)
- Children's Global Assessment Scale (CGAS)
- Young Mania Rating Scale (YMRS)
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Pediatric Anxiety Rating Scale (PARS)
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
- CogState Computerized Cognitive Test Battery

11.4.30. Visit 30E (Week 105)

- Interactive Voice/Web Response System (IXRS) subject registry/visit

Clinical and Laboratory Evaluations: ALL SUBJECTS

- Prior/concomitant medication review
- Adverse event (AE) monitoring
- Menstrual cyclicity (female subjects)
- Vital signs
- Urine β-hCG (female subjects ≥ 11 years of age only)

- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)

Clinical Evaluations: SUBJECTS from D1050301 ONLY

- Columbia Suicide Severity Rating Scale (C-SSRS)

Clinical Evaluations: SUBJECTS from D1050326 ONLY

- Columbia Suicide Severity Rating Scale (C-SSRS)

12. DISCONTINUATION AND REPLACEMENT OF SUBJECTS/ CLINICAL ASSESSMENTS AFTER STUDY MEDICATION DISCONTINUATION

Subjects may withdraw from the study at any time for any reason.

12.1. Study Participation Termination Criteria

The reason for early discontinuation from study participation is to be recorded as one of the following:

- Adverse event (specify)
- Lack of efficacy (specify)
- Lost to follow-up (specify)
- Other (specify)
- Protocol violation (specify)
- Withdrawal by subject (specify)

Discontinuations due to an adverse event may include laboratory, vital signs, or other test abnormalities that result in early discontinuation. Please note that all AEs are to be recorded on the AE page. Serious adverse events that result in discontinuation or that result in death (an outcome resulting from an AE) are to be recorded on the AE page. The investigator or study coordinator must notify the Sponsor or Sponsor designee as soon as possible when a subject has been discontinued/withdrawn due to an AE (telephone or fax).

Subjects whose study participation is prematurely terminated will not be replaced.

12.2. Follow-up Procedures Upon Discontinuation/Withdrawal

If a subject discontinues study medication treatment due to an AE, then the subject should be evaluated until resolution or stabilization of the adverse event. When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. A termination eCRF page should be completed for every subject who received study medication whether or not the subject completed the study. The reason for discontinuation should be indicated on the eCRF. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 13. Subjects who discontinue from the study will not be replaced. Subjects who discontinue from the study must be referred by the Investigator for appropriate follow-up care.

For all subjects a follow-up visit will be scheduled for 7 (± 3) days after the last dose of study medication to monitor AEs and SAEs. If an in-person visit is not possible, telephone contact will be made with the subject to assess any post study discontinuation adverse effects.

13. ADVERSE EXPERIENCE REPORTING

13.1. Adverse Events

An adverse event (AE) is any new, untoward medical occurrence or worsening of a pre-existing medical condition that occurs during study participation, whether or not the event is considered drug related.

AEs will be collected from the time the informed consent is signed to the end of the study. Serious adverse events (SAEs) will be collected and reported on the SAE form, from the time of informed consent to 14 days post last dose and will be followed until resolution or lost to follow up. SAEs occurring from the time of informed consent to the end of study must be recorded on the CRF and the data recorded should match that on the SAE form.

Non-leading questions will be used to ask subjects about the possible occurrence of AEs. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study medication, must be documented in the subject's study records/source documents, in accordance with the investigator's normal clinical practice, and on the AE page of the CRF. Each AE is to be evaluated for duration, intensity, seriousness, and causal relationship to the study medication. Appendix C (Definitions for Reporting Adverse Events) provides definitions for severity of an adverse event, relationship to study medication, frequency, and action taken. An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the experience may have been caused by the drug" (21 CFR 312.32 [a]).

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

13.2. Objective Findings

New and worsening signs and symptoms of underlying or emerging disease must be recorded as AEs. Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded on the Adverse Event page of the CRF from signing of the informed consent onwards. When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by an investigator as they become available. The investigator must determine the clinical significance of all out of range values. Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the investigator. Laboratory reports will be initialed and dated on all pages by a Form FDA 1572-listed investigator.

All on site ECG tracings and ECG over-read reports will be reviewed by an investigator as they become available. The investigator must determine the clinical significance of all abnormal ECG interpretations on the machine read tracing. Possibly drug-related or clinically relevant abnormal ECGs of uncertain causality must be repeated. Any abnormal ECGs that persist should be followed at the discretion of the investigator. ECG tracings will be initialed and dated on all pages by a Form FDA 1572-listed investigator.

13.3. Immediately Reportable Events

There are two categories of medical events that could occur during participation in a clinical study that must be immediately reported:

- SAE, including death.
- The incidence of pregnancy.

The appropriate Pharmacovigilance (PVG) group must be contacted immediately upon first knowledge of the incident.

Emergency contact information can be found in Table 1 of this protocol.

An AE or suspected adverse reaction is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or 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 upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form might have caused death.

If an investigator or study site staff becomes aware of a SAE that occurs in a study subject from the time that informed consent is signed through 14 days following the last dose of study medication, this must be reported immediately to PVG.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and sent via fax to PVG within 1 business day of an investigator or study site staff becoming aware of the event. Sunovion Pharmaceuticals Inc. provides the SAE form used to report SAEs as a part of the document package necessary to conduct this clinical study.

Sunovion Pharmaceuticals Inc. will promptly notify all research sites of an AE that is determined to be reportable to the Regulatory Authorities. These AEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Principal investigator.

If a subject becomes pregnant during the course of the study, she will be instructed to immediately stop taking study medication. Further, the subject will be instructed to return within 48 hours of the first notification of pregnancy to the research site and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the subject will no longer receive any additional

study medication and will continue to be followed. All pregnancies, whether or not the subject received any study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

If a pregnancy is reported for the study subject's partner, the Sponsor's representative will provide instructions on how to collect pregnancy information in accordance with local requirements. Proper consent to collect the partner's information will be obtained prior to the collection of any information.

To report a pregnancy, the Pregnancy Event Form must be completed and sent via facsimile to PVG within 1 business day of first knowledge by the research personnel of the pregnancy. Sunovion Pharmaceuticals Inc. provides the Pregnancy Event Form as a part of the document package necessary to conduct this clinical study. Pregnancies occurring from the time the informed consent is signed through 7 days following the last dose of study medication, will be followed quarterly until birth or termination of the pregnancy.

13.3.1. Bone Fractures

All confirmed cases of bone fracture, regardless of seriousness or presumed relationship to study drug, must be reported as SAEs. All procedures for reporting of SAEs as detailed in the current protocol are to be followed for these events.

13.4. Preplanned Hospitalizations or Procedures

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled prior to the subject entering the study (ie, before the subject signed the informed consent form [ICF]) for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of an SAE. It should have been clearly documented prior to signing the ICF. However, if the event/condition worsens during the study, it must be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

13.5. Data and Safety Monitoring Board

A DSMB will review safety and clinical outcome data including data on AEs and SAEs at regular intervals until the D1050301, D1050325, and D1050326 studies are complete and as long as necessary for the D1050302 study, as determined by the Sponsor. The DSMB will be independent of the Sponsor, CRO, and the investigators and will be empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility. The membership of the DSMB and its mandate is denoted in the DSMB charter.

14. STATISTICS

A Statistical Analysis Plan (SAP) will provide details on the statistical methods planned for this study and will be finalized prior to the 1st interim data cut, which will happen when at least 100 subjects continued from studies D1050301 and D1050325 complete the Week 28 Visit.

14.1. Randomization and Blinding

This is an open-label study, therefore randomization and blinding will not be employed.

14.2. Unblinding Procedures

This section is not applicable to this study.

14.3. Hypotheses

Because of the nature of an open-labeled study, no hypotheses are planned.

14.4. Variables and Timepoints

14.4.1. Primary Safety Variables

The primary safety variables include treatment-emergent AEs and SAEs, and discontinuations due to AEs.

14.4.2. Other Safety Variables

Safety and tolerability will further be assessed by the following variables: laboratory values, ECGs, physical examinations, movement disorders (AIMS, BARS, and SAS scores), vital signs, height, weight, BMI, waist circumference, tanner staging, menstrual cyclicity (female subjects), and hormonal parameters. For subjects previously enrolled in the D1050301 and D1050326, safety will further be assessed by CogState Cognitive Test Battery, C-SSRS, and UKU. In addition, for subjects previously enrolled in study D1050326, Young Mania Rating Scale (YMRS) will be also assessed.

14.5. Sample Size Considerations

Subjects who complete the respective double-blind studies D1050301, D1050325 or D1050326, sign the consent, and meet all entry criteria will be included in this study. Studies D1050301, D1050325, and D1050326 have finished, with a total of 271 subjects from D1050301, 125 subjects from D1050325, and 306 subjects from D1050326 enrolling into D1050302. Based on an estimated attrition rate of approximately 30% of subjects over six months, it is expected that at least 100 subjects will be exposed to lurasidone for a minimum of 6 months for subjects continued from Studies D1050301 and D1050325 in Study D1050302.

14.6. Data Analyses of Interim Data for FDA Filing

After studies D1050301 and D1050325 are completed, when at least 100 subjects complete the Week 28 visit (ie, exposed to study drug for at least 6 months), data analyses based on these

interim data will be done to prepare a safety/effectiveness report in support of the initial health authority filing for US regulatory submission for the lurasidone pediatric program. A subsequent final analysis of study D1050302 will be performed after every subject previously enrolled from study D1050301, D1050325, and D1050326 complete the study. The details of the interim data analyses and final data analyses are provided below in Section 14.7, and the SAP.

14.7. Data Analyses

All data collected in this 104 week open-label study will be summarized and presented in final data analyses report. All data collected through the cut-off time point when at least 100 subjects previously from studies D1050301 and D1050325 complete the Week 28 Visit will be summarized separately for a study report for FDA filing.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation or standard error, minimum and maximum values, and 95% confidence interval) by visit. Categorical variables will be reported as frequencies and percentages by visit. Standard laboratory shift tables will be reported. Where changes are reported, the reference will be to the pre-treatment baseline from double-blind studies D1050301, D1050325, or D1050326, as indicated as “DB baseline”. Where relevant, changes from baseline for the open-label study, as defined as the Week 6 assessment in the double-blind study or the last assessment prior to the first dose of the open label study, will also be reported, and will be referred to as the open-label study baseline or "OL baseline."

14.7.1. Analysis Population

Safety population:

The safety population will consist of all subjects who receive at least one dose of study medication.

14.7.2. Definitions of Assessments

The following definitions will be used for efficacy assessments:

- DB Baseline (ie, Baseline assessment of the double-blind studies [D1050301, D1050325, or D1050326]): the last assessment made on or before double-blind randomization as described in the protocols;
- OL Baseline (ie, Endpoint assessment of the double-blind studies [D1050301, D1050325, or D1050326]) or Baseline assessment of the open-label study (D1050302): the last assessment made during the double-blind studies, as described in the protocols;
- Week 28 Endpoint assessment: the last post-baseline assessment made prior to or at Week 28 visit.
- Week 104 Endpoint assessment: the last post-baseline assessment made during the open-label study (D1050302), as described in the protocol;
- Scheduled assessment: assessment made during the open-label study (D1050302).

14.7.3. Analysis Group

A total of three analysis groups will be formed based on a subject's previous participation in double-blind studies D1050301, D1050325, and D1050326:

- All subjects previously enrolled in Study D1050301 and enrolled into this extension study.
- All subjects previously enrolled in Study D1050325 and enrolled into this extension study.
- All subjects previously enrolled in Study D1050326 and enrolled into this extension study.

Summary tables, wherever applicable, will be presented for all subjects in the study by above analysis group, respectively.

14.7.4. Statistical Methods

Unless otherwise specified, analysis outputs will be presented for subjects who complete double-blind studies D1050301, D1050325, or D1050326, respectively and analyses presented will be based on the safety population.

14.7.4.1. Efficacy Evaluation

All efficacy evaluations will be summarized for all subjects and by analysis group listed Section 14.7.3.

The efficacy variables to be summarized for this study will include:

For subjects continued from Study D1050301:

- Positive and Negative Syndrome Scale (PANSS) total, positive, negative, general psychopathology, cognition, and excitability subscale scores;
- Clinical Global Impression severity (CGI-S) scale;
- Clinician-rated Children's Global Assessment Scale (CGAS);
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q).

For subjects continued from Study D1050325:

- Aberrant Behavior Checklist (ABC) subscale scores (irritability, hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal);
- Clinical Global Impression severity (CGI-S) scale;
- Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs);
- Caregiver Strain Questionnaire (CGSQ).

For subjects continued from Study D1050326:

- Children's Depression Rating Scale, Revised (CDRS-R);
- Clinical Global Impression Bipolar Version -Severity (CGI-BP-S) scale;

- Clinician-rated Children's Global Assessment Scale (CGAS);
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
- Pediatric Anxiety Rating Scale (PARS);
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS).

Since this is an uncontrolled open-label extension of studies D1050301, D1050325, and D1050326, no inferential statistics on efficacy will be presented. For all of the efficacy assessments, summary statistics (number of subjects, mean, standard deviation, minimum, median, and maximum and a 95% confidence interval) will be presented for all subjects by analysis group for the DB baseline, OL baseline, each of the scheduled assessments, and the endpoint assessments in the open-label study. All analyses for the scheduled assessments will be based on observed cases (OC). Confidence intervals will be based on means and standard deviations estimated without adjustment for any center or baseline effects. In addition, for all efficacy evaluations, differences from DB baseline and OL baseline will be presented in a similar way using summary statistics, as described above.

For time to early discontinuation, Kaplan-Meier curves will be plotted by analysis group.

14.7.4.2. Safety Evaluation

All safety evaluations will be summarized for all subjects by analysis group for the safety population.

Safety evaluations include:

- AEs, SAEs, Discontinuation due to AEs and SAEs;
- Laboratory safety tests (chemistry, including liver function tests and bilirubin; hematology including HbA_{1c}; serum lipids; glucose; hormonal parameters; and urinalysis);
- Body weight, height, BMI, waist circumference, vital signs, physical examinations, and ECG parameters;
- Simpson-Angus Scale (SAS);
- Barnes Akathisia Rating Scale (BARS);
- Abnormal Involuntary Movement Scale (AIMS);
- Tanner staging, and menstrual cyclicity (female subjects).

For subjects continued from Study D1050301 and D1050326:

- Columbia Suicide Severity Rating Scale (C-SSRS);
- CogState Cognitive Test Battery;
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU).

For subjects continued from Study D1050326:

- Young Mania Rating Scale (YMRS) score.

The primary analysis for the study is to assess the incidence of AEs, SAEs, and discontinuations due to AEs. The terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset on or after the first dose of study drug during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis.

AEs will be summarized by presenting the number and percentage of subjects having any AE, having an AE by body system, and having each individual AE. The incidence of an AE is determined by occurrence of at least one AE regardless of the frequency, severity and/or relationship to study medications. AEs will also be summarized by maximum severity and relationship to study medication (as assessed by the investigator), and action taken.

Special attention will be given to those subjects who discontinue treatment due to an adverse event, or who experienced a severe or a serious adverse event (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

Descriptive statistics will be provided for the all other safety variables or tests and the corresponding changes from baseline (including double-blind study baseline and open-label study baseline) by scheduled visit. Notable values will be flagged, and any other information collected will be listed as appropriate. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum values). Categorical variables will be reported as frequencies and percentages. For weight, height, and BMI, descriptive statistics will be also summarized for the age-adjusted standardized scores.

For subjects continued from study D1050301 and D1050326, descriptive statistics will be provided for Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU) and the age-adjusted standardized CogState composite score. For C-SSRS, number and percentage of subjects with suicidal ideations and behaviors will be summarized.

For subjects continued from study D1050326, descriptive statistics will be presented for YMRS result by analysis group and study visit.

Frequency distribution of the tanner staging will be tabulated by visit and gender.

15. COMPUTERIZED SYSTEMS USED FOR SOURCE DATA

A list of the computerized systems that will be used at each step to create, modify, maintain, archive, retrieve, or transmit source data are presented below, per the *Guidance for Industry Computerized Systems Used in Clinical Investigations*, May 2007.

Table 8: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent/assent	NA
Inclusion/exclusion criteria	A
Prior/concomitant medication review	A
Interactive Voice/Web Response System (IXRS) subject registry/study medication assignment	G
Study drug accountability/assess compliance	A
Clinical and Laboratory Evaluations: ALL SUBJECTS	
Physical examination	A
Height as measured by stadiometer	A
Tanner staging	A
Vital signs	A
Weight	A
Waist circumference measurement	A
Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B
Hormonal Parameters	B
Serum prolactin	B
Glycosylated hemoglobin (HbA_{1c})	B
Glucose and lipid panel	B
Serum insulin and C-reactive protein	B
Urine β-hCG	NA
Adverse event (AE) monitoring	A
Barnes Akathisia Rating Scale (BARS)	A
Abnormal Involuntary Movement Scale (AIMS)	A
Simpson-Angus Scale (SAS)	A
Clinical Evaluations: SUBJECTS from D1050301 ONLY	
Children's Global Assessment Scale (CGAS)	A
Clinical Global Impression – Severity Scale (CGI-S)	A
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)	A
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)	A

Protocol Step	Computerized System Type or Description
Columbia Suicide Severity Rating Scale (C-SSRS)	A
Positive and Negative Syndrome Scale (PANSS)	A
CogState Cognitive Test Battery	E
Clinical Evaluations: SUBJECTS from D1050325 ONLY	
Aberrant Behavior Checklist (ABC)	A
Clinical Global Impression – Severity Scale (CGI-S)	A
Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)	A
Caregiver Strain Questionnaire (CGSQ)	A
Clinical Evaluations: SUBJECTS from D1050326 ONLY	
Children's Depression Rating Scale, Revised (CDRS-R)	A
Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)	A
Children's Global Assessment Scale (CGAS)	A
Young Mania Rating Scale (YMRS)	A
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)	A
Columbia Suicide Severity Rating Scale (C-SSRS)	A
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)	A
Pediatric Anxiety Rating Scale (PARS)	A
Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)	A
CogState Computerized Cognitive Test Battery	E

A = EDC (Medidata RAVE); B = LIMS; C = Core Lab Over-read; D = LIMS/ASCII; E = Computerized Assessment System; F = ePRO; G = IXRS.
Abbreviations: EDC = electronic data capture; CDR = clinical data repository; ePRO = electronic patient reported outcomes; IXRS = Interactive Voice/Web Response System; LIMS = laboratory information management system.

16. ETHICAL AND REGULATORY OBLIGATIONS

16.1. Study Conduct

The investigator agrees that the study will be conducted according to the protocol, the US Code of Federal Regulations (CFR), Good Clinical Practice (GCP) (E6) and the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The investigator will assure that study staff cooperate with monitoring and current audits, and will demonstrate due diligence in recruiting and screening study subjects.

The investigator must sign and return to CRO/Sponsor the "Study Acknowledgment" page and provide a copy of current curriculum vitae (CV), including a copy of a current medical license, current Drug Enforcement Agency (DEA) license, where applicable, and financial disclosure. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on CV.
- Appropriate diploma number stated on CV.
- Copy of the diploma.

For all studies conducted under an Investigational New Drug (IND), the investigator must sign and return a completed Form FDA 1572 "Statement of investigator" to CRO/Sponsor.

16.2. Institutional Review Board or Independent Ethics Committee

Before initiation of the study, the investigator/CRO must obtain approval or favorable opinion of the research protocol, informed consent form, and any advertisement for subject recruitment, from an IRB or IEC complying with the provisions specified in 21 CFR Part 56 or in ICH GCP, as applicable, and applicable pertinent government regulations. The investigator must assure IRB or IEC compliance with the applicable regulations.

A copy of written IRB or IEC approval or favorable opinion of the protocol, informed consent form and advertising (if applicable) must be provided to CRO/Sponsor prior to initiation of the study. The approval or favorable opinion letter must be signed by the IRB or IEC chairman or designee, identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB or IEC complies with the requirements in 21 CFR Part 56 for a study conducted under an IND or ICH GCP, as applicable.

The investigator/CRO is responsible for obtaining continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not

exceeding one year or otherwise specified by the IRB or IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The investigator must promptly inform their IRB/IEC of all SAEs or other safety information reported from CRO/Sponsor in accordance with 21 CFR 312.66, or when dictated by applicable local regulations (ie, Directive 2001/20/EC), the Sponsor/CRO is responsible for reporting to the IEC (eg, reporting of serious AEs).

16.3. Informed Consent

The investigator will prepare the informed consent form and provide the form to CRO/Sponsor for approval prior to submission to the IRB or IEC. CRO/Sponsor may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by the FDA or governing regulatory authority and ICH guidelines and will be subject to CRO/Sponsor approval as well as IRB or IEC approval. CRO/Sponsor may submit informed consent forms to a central IRB or IEC for review and approval or favorable opinion contingent upon prior investigator permission and review.

Before recruitment and enrollment, where developmentally appropriate, each prospective candidate will be given a full explanation of the study, allowed to read the approved informed consent form or assent form for prospective candidates < 18 years of age and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the investigator is assured that the individual or parent or legal guardian for individuals < 18 years of age understands the implications of participating in the study, the subject will be asked to give consent or assent for subjects < 18 years of age to participate in the study by signing the informed consent/assent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review and regulatory inspection. The investigator will provide a copy of the signed informed consent form to each subject. For subjects < 18 years, the parent or legal guardian will be required to provide written informed consent. For subjects who become 18 years of age during the course of this study, they will need to give informed consent upon becoming 18 years of age (or as soon as possible thereafter).

For this study, the parents or guardians must give permission for their children to participate and demonstrate their agreement by signing the informed consent document. The child or teenager will be provided with a form that explains, in age-appropriate terms, the purpose of the research, what they will be asked to do, and what procedures they will undergo. For this study, where developmentally appropriate, the assent of the child/or adolescent is deemed required. The assent process is an ongoing, interactive conversation between the research team and the child or young adult. If at any time the child or young adult shows signs of dissent, the assessment should be stopped, the situation assessed and assent established to continue. It should always be made clear that the young person has the right to leave the trial, at any time and for any reason, without penalty or consequences, and that any information gathered will be kept confidential.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the informed consent form must be revised, submitted to the IRB or IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he

or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the amendment.

16.4. Subject Privacy

The Sponsor's staff or any designees affirm and uphold the subject's confidentiality. Throughout this study, all data forward to the Sponsor will be identified only by an identification number, date of birth, gender, and initials. The investigator agrees that its representatives, its designee, representatives of the relevant IRB/IEC or representatives of the regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, clinical laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation and autopsy reports for deaths occurring during the study).

For the studies conducted in the US, in accordance with the Healthcare Insurance, Portability, and Accountability Act of 1996, the investigator will prepare a privacy authorization form and provide the form to CRO/Sponsor for approval prior to submission to the IRB/IEC or to a Privacy Board. CRO/Sponsor may provide a template privacy authorization form to be qualified by each research facility to conform to local requirements. The content of the privacy authorization form must comply with the regulations governing the authorization. All prospective study candidates will be given full explanation of the privacy authorization form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the investigator is assured that the individual understands the implications of the privacy authorization form, the subject will be asked to sign the privacy authorization. The authorization remains in effect until revoked by the subject. The investigator will provide a copy of the signed privacy authorization form to each subject. Subjects who do not sign the privacy authorization form will not be permitted to participate in the study.

16.5. Protocol Amendments and Emergency Deviations

Changes to the research covered by this protocol must be implemented by formal protocol amendment. Amendments to the protocol may be initiated by the Sponsor or at the request of the investigator. In either case, a formal amendment cannot be initiated until the Sponsor has approved it, the investigator has signed it off, and it has been reviewed and has received approval or favorable opinion by the IRB or IEC.

Emergency deviations or modifications may be initiated without the Sponsor's or IRB/IEC approval or favorable opinion, only in cases where the change is necessary to eliminate an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to CRO/Sponsor and the IRB/IEC within five business days of the occurrence, or in accordance with applicable regulatory requirements.

16.6. Monitoring and Auditing of the Study

A clinical monitor, whether an employee of the Sponsor or its designated representative, has the obligation to follow this study closely. In doing so, the monitor will visit the clinical study sites at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of

study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Quality assurance auditors, whether an employee of the Sponsor or its designated representative, may evaluate the conduct of the study by the clinical study sites. These parties must have access to any and all study-related documentation including source documentation, regardless of location and format. The Sponsor audit reports will be kept highly confidential.

16.7. Study Documentation

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate source documentation and CRFs as part of the case histories.

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source documentation is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or is in support of the protocol specifications, eg, clinical lab reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires, telephone logs, ECGs, etc. All draft, preliminary and pre final iterations of a final report are also considered to be source documents, eg, faxed lab reports and hard copy lab reports, faxed initial results and hard copy, final report.

CRO/Sponsor will supply CRFs. All requested information must be entered on the CRFs. Every effort should be made to complete all forms in their entirety. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. Each set of completed CRFs must be reviewed, electronically signed and dated by the investigator.

16.8. Laboratory Certification and Normal Values

A central laboratory will be used for analysis for most of the clinical labs for this study. The central laboratory will provide the investigator, CRO, and Sponsor with laboratory certification(s), a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens, and the lab director's CV. If an exception is granted to use a local laboratory, the investigator must supply the CRO/Sponsor with laboratory certification, lab director's CV and a current, dated copy of normal range values.

16.9. Records Retention

The investigator agrees to retain study records for the time periods stated below. The investigator agrees to contact CRO/Sponsor before destroying any study documentation. Should the investigator leave the site at which the study was conducted, CRO/Sponsor will be contacted regarding the disposition of document storage.

Records will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH

region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Dates marking the beginning of the final record retention periods will be sent in writing from CRO/Sponsor. If an investigator withdraws from the study (eg, relocation), the records will be transferred to a mutually agreed upon designee (ie, another investigator). This transfer is subject to Sponsor approval and will be documented in writing and a copy sent to the Sponsor.

Electronic Data Capture/ePRO Data Archiving:

In compliance with data retention requirements, and after the capture phase of the study is complete, the site will receive a copy of all eSource data and accompanying audit trail from the EDC and/or ePRO vendors. The vendors shall certify the integrity of the copy (certified copy) and send it on commonly readable storage material (CD or DVD); if necessary, software for viewing the data files and instruction on installation and use of the software will also be included. This read-only archive will be retained, protected, and made accessible by the site throughout the required retention period.

16.10. Inspection of Records

In the event of an inspection, the investigator agrees to allow representatives of the Sponsor, its representative, the Food and Drug Administration or other regulatory authorities' access to all study records. The investigator will promptly notify CRO/Sponsor of all requests to inspect by government agencies and will promptly forward a copy of all such inspection reports.

16.11. Financial Disclosure

Prior to the start of the study, investigators will release sufficient and accurate financial information that permits CRO/Sponsor to demonstrate that an investigator and all sub-investigators listed on the Form FDA 1572, if appropriate, have no personal or professional financial incentive regarding the future approval or disapproval of the study medication such that his or her research might be biased by such incentive. Investigators will provide an update of the above financial information at the end of the study and one year following the end of the study.

17. STUDY ACKNOWLEDGMENT

I have read the foregoing protocol, D1050302, Version 4.0, "A 104-Week, Flexible-Dose, Open-Label, Multicenter, Extension Study to Evaluate the Long-Term Safety and Effectiveness of Lurasidone in Pediatric Subjects", and agree that it contains all necessary details for conducting this study and to conduct the study in strict accordance with the specifications outlined herein.

By signing the protocol, the investigator agrees to keep all information provided by Sunovion Pharmaceuticals Inc. in strict confidence and to request the same from his/her staff and the Institutional Review Board/Independent Ethics Committee. Study documents provided by Sunovion Pharmaceuticals Inc. (protocols, Investigator Brochures, case report forms, and other materials) will be stored appropriately to ensure their confidentiality. The information provided by Sunovion Pharmaceuticals Inc. to the investigator may not be disclosed to others without direct written authorization from Sunovion Pharmaceuticals Inc., except to the extent necessary to conduct the study.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB or IEC approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

18. REFERENCES

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APPENDIX A.CLINICAL LABORATORY TESTS

The following laboratory tests are to be performed:

Blood Chemistry Tests
aspartate aminotransferase
alanine aminotransferase
albumin
alkaline phosphatase
bicarbonate
blood urea nitrogen
calcium
chloride
creatinine
gamma-glutamyl transferase
phosphorous
potassium
sodium
total bilirubin[a]
total protein
lactate dehydrogenase
fasting (non-random) triglycerides
fasting (non-random) serum cholesterol
fasting (non-random) serum high-density lipoprotein cholesterol
fasting (non-random) serum low-density lipoprotein cholesterol
fasting glucose
prolactin
whole blood hemoglobin A1c
creatine phosphokinase
Endocrine Tests
free thyroxine test
thyroid-stimulating hormone test
Hormonal Parameters
follicle stimulating hormone (female subjects only)
luteinizing hormone (female subjects only)
testosterone (male subjects only)
estradiol (female subjects only)
serum human chorionic gonadotropin (β-hCG) (female subjects ≥ 11 years of age only)
urine human chorionic gonadotropin (β-hCG) (female subjects ≥ 11 years of age only)
Hematology Tests
white blood cell count
white blood cell differential
eosinophilic leukocyte count
basophilic leukocyte count
neutrophil count
lymphocyte count
monocyte count
platelet count
hemoglobin
blood hematocrit
red blood cell count

red cell distribution width
red blood cell indices:
mean corpuscular volume
mean corpuscular hemoglobin concentration
mean corpuscular hemoglobin
Urinalysis Tests
color
appearance
total ketones
urobilinogen
bilirubin
red blood cells
leukocyte esterase
nitrite
pH
protein
specific gravity
glucose
microscopic evaluation[b]
Urine Drug Screen
amphetamines
benzodiazepines
barbiturates
cocaine
tetrahydrocannabinol
ethanol
methadone
methamphetamine
opiates
phencyclidine

[a] Bilirubin will be fractionated (direct serum bilirubin test/indirect serum bilirubin test) if elevated 2.0 times the upper limit of the normal range.

[b] Microscopic evaluation will be performed if the Chemstrip 9™ (or equivalent dipstick analysis) indicates the presence of any significant abnormality.

Table 9: Total Blood Drawn For Laboratory Tests

Visit	Total mL
6E	8.5
10E	8.5
16E	8.5
22E	8.5
29E/ET	8.5
Total	**42.5 mL**

APPENDIX B. POTENT INHIBITORS AND INDUCERS OF THE CYP3A4 ENZYME SYSTEM

CYP3A4 Inhibitors:

Azole antifungals

- Butoconazole
- Fluconazole
- Itraconazole
- Ketoconazole
- Miconazole
- Sulconazole
- Tioconazole

HIV protease inhibitors

- Amprenavir
- Indinavir
- Nelfinavir
- Ritonavir
- Saquinavir

Macrolide antibiotics

- Clarithromycin
- Dirithromycin
- Erythromycin
- Troleandomycin

Miscellaneous

- Nefazodone
- Diltiazem
- Verapamil
- Amiodarone
- Cimetidine
- Grapefruit juice

CYP3A4 Inducers:

Barbiturates

- Amobarbital
- Butabarbital
- Butalbital compound
- Mephobarbital
- Methohexital
- Pentobarbital
- Phenobarbital
- Primidone
- Secobarbital
- Thiopental

Miscellaneous

- Carbamazepine
- Hypericin (St. John's Wort)
- Phenytoin
- Rifampin
- Oxcarbazepine
- Topiramate

APPENDIX C.DEFINITIONS FOR REPORTING ADVERSE EVENTS

The investigator must assess the severity of the AE using the following:

- **Mild** - awareness of event but easily tolerated.
- **Moderate** - discomfort enough to cause some interference with normal activity.
- **Severe** - inability to carry out usual activity.

The investigator must assess the relationship of the AE to the study medication using the following:

- **Unrelated** – improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Unlikely** - occurs with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other medications, chemicals, or underlying disease provide plausible explanations.
- **Possible** - occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
- **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
- **Related** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

Frequency will be defined using the following terms and definitions:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken regarding study drug will be defined as follows:

- **Dose Not Changed** – no change.
- **Dose Increased.**
- **Dose Reduced.**
- **Drug Interrupted** – study drug stopped temporarily.
- **Drug Withdrawn** – study drug stopped permanently.
- **Not Applicable.**