A PHASE 3, MULTICENTER, FOUR-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY TRIAL OF FLEXIBLE DOSES OF ORAL ZIPRASIDONE IN CHILDREN AND ADOLESCENTS WITH BIPOLAR I DISORDER (CURRENT OR MOST RECENT EPISODE MANIC)

Compound:	CP-88,059-1
Compound Name (if applicable):	Ziprasidone Hydrochloride
United States (US) Investigational New Drug (IND) Number (if applicable):	CCI [redacted]
European Clinical Trial Database (EudraCT) Number (if applicable):	N/A
Protocol Number:	A1281198
Phase:	3

Document History

Document	Version Date	Summary of Changes
Original protocol	08 October 2013	N/A
Amendment 1	7 August 2018	For this amendment there is one substantial change and several non-substantial changes noted below: Substantial: The requirement that female subjects have two pregnancy tests separated by a 2 week period before they can be randomized to study drug has posed significant challenges to investigators due to the fact that these subjects are in a current manic state and treatment of their mania is being delayed. In several cases, investigators have withdrawn female subjects during the screening period so they could be more rapidly medicated for treatment of their manic symptoms. We are proposing instead to obtain pregnancy tests in all female subjects at all study visits and believe this approach should provide adequate surveillance of female subjects for pregnancy while avoiding further delaying the treatment of their manic symptoms. Pregnancy testing will be done weekly with no 14 day screening window. Weekly and follow-up laboratory testing for such testing has been addressed within sections below. Section 3. STUDY DESIGN, paragraphs 4, 6 and 7. Section 6.2. Visit 2 (Day 1) - Baseline, paragraph 1 and bullet 6. Section 6.3.1. Visit 3 (Day8/Week

		1) bullet 3. Section 6.3.2. Visit 4 (Day 15/end of Week 2) bullet 3. Section 6.3.3 Visit 5 (Day 22/end of Week 3) bullet 3. Section 6.4. Visit 6 (Day 29/end of Week 4) - End of Treatment (or Early Termination), last paragraph. Section 6.5. Visit 7, Follow-up Visit (Day 36/end of Week 5), paragraphs 1,3 bullet 4. Section 7.1 Pregnancy Testing. Section 7.2.1. Laboratory Assessments paragraph 3, last bullet. Non-substantial: This protocol amendment details the addition of an open-label extension study, removal of the SBQR scale and clarity on inclusion criteria. The CSSR-S is performed at Screening, Baseline and every post-baseline visit. Including the SBQ-R at screening is redundant and has not provided any additional benefit in detection of suicidal ideation/behavior over and beyond the CSSR-S. Removal of the SBQ-R rating also reduces the assessment burden to patients. In addition clerical and grammar updates have been addressed and new approved template language was applied to this amendment. 1)Open Label Study sections noted below: Schedule of Activities. PROTOCOL SUMMARY, Study Design, LAST 2 PARAGRAPHS. Section 3.1. Post Study Care

		Program, paragraphs 2, 3 and 5. Section 5.3.3.6. Dose Reductions. Section 7.2.6. 12-lead Electrocardiogram (ECG), last sentence. 2) Removal of SBRQ scale and updated language to inclusion and exclusion criteria. Section 4.1. Inclusion Criteria. Section 4.2. Exclusion Criteria, bullet 3 and criteria 40. Section 7.2.9.1. Suicidality Assessments at Screening, bullet 3. 7.2.9.4. Suicidal Behaviors Questionnaire-Revised (SBQ-R) on inclusion criteria. 3) New protocol template language was addressed in sections noted below: Section 4.4. Life Style Guidelines. Section 5.3.3.7. Medication Errors. Section 8.1. Adverse Events. Section 8.2. Reporting Period. Section 8.3. Definition of an Adverse Event bullet 13. Section 8.4. Medication Errors. Section 8.6.2. Potential Cases of Drug-Induced Liver Injury. Section 8.7. Hospitalization. Section 8.10. Exposure During Pregnancy. Section 8.11. Occupational Exposure. Section 8.12. Withdrawal Due to Adverse Events (See Also Section 6.7 Subject Withdrawal). Section 8.14.1. Serious Adverse Event Reporting Requirements,

		paragraphs 2 and 4. Section 15.1. Communication of Results by Pfizer. 4) Clerical and grammar errors were corrected in sections noted below: 1.2.2. Background on Ziprasidone (CP-88,059). Section 1.2.2.1.1. Study A1281123: Open Label Safety and Tolerability. Section 1.2.2.1.2. Study A1281132 and Extension Study A1281133: Pediatric Bipolar I Disorder. Section 5.1. Allocation to Treatment. Section 5.5. Concomitant Medication(s). Section 6.1. Screening. Section 6.7. Subject Withdrawal, paragraph 4. Section 6.7.1. Specific Withdrawal Criteria. Section 7.4. Rater Qualifications/Training/Certification for Diagnostic, Efficacy, and Safety Rating Scales 2nd paragraph, last sentence and Table Criteria for Training Approval without Sponsor Review. CCI [redacted] CCI [redacted] Section 12.3. Subject Information and Consent, paragraph.
Amendment 2	19 February 2019	For this amendment there are five substantial changes and several non-substantial changes noted below: Substantial

		Language was applied to reflect the FDA agreed upon increase in sample size due to the rater training issue and adding a separate Sensitivity Analysis of Final Data Set. The study analysis section was updated to reflect the new power applied to the study. Language was added to speak to country specific rater training qualifications. Summary, Study Design, paragraphs 3-5. Summary, Statistical Methods, paragraphs 1, 3-5. Section 3. Study Design, paragraph 3, sentence 1. Section 6.1. Screening, paragraphs 3, 4. Section 9.1. Sample Size Determination, paragraphs 3, 5-6. Non substantial: Language added for country specific guidance on alternative treatment. Language added for country specific guidance on alternative treatment. In addition, clerical and grammar updates have been addressed and new approved template language was applied to this amendment. Summary, Study Treatments, paragraph 6, sentence 1. Schedule of Activities Section 3. Study Design, paragraph 3, sentence 1 Section 3. Study Design, Schema. Section 3.1 Post Study Care Program, paragraphs 2-3, and 6. Section 4.2 Exclusion Criteria, bullet 1, numbers 8, 22, 38, 39 and 40. Section 5.5. Concomitant

		Medication (s), Table, row 3. Section 6.3.2. Visit 4 (Day 15/end of Week 2), bullet 3. Section 6.5. Visit 7, Follow up Visit (Day 36/end of Week 5), paragraphs 1 and 3. 7.2.9.3 Columbia Suicide Severity Rating Scale (C-SSRS). Section 8.2. Reporting Period.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

The present protocol has been designed to satisfy a Pediatric Research Equity Act (PREA) requirement issued by the Food and Drug Administration (FDA) to Pfizer, on August 19, 2004, that stipulated: "You are required to assess the safety and effectiveness of Geodon® as a treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents)." The overall goal of the present study is to assess the safety profile and efficacy of ziprasidone in the treatment of pediatric mania in association with Bipolar Disorder, and to develop other relevant information, eg, CCI [redacted]

OBJECTIVES

Primary Objectives

The primary objectives of the study are:

1. To assess the efficacy of oral ziprasidone compared with placebo in the treatment of children and adolescents aged 10-17 with Bipolar I Disorder (current or most recent episode manic), as measured by the change from baseline to Week 4 in the Young Mania Rating Scale (YMRS) total score.

2. To evaluate the safety and tolerability of oral ziprasidone over 4 weeks in the treatment of children and adolescents with Bipolar I Disorder (current or most recent episode manic).

Secondary Objectives

The key secondary objective of the study is to evaluate the efficacy of oral ziprasidone as compared with placebo in the treatment of children and adolescents with Bipolar I Disorder (current or most recent episode manic) as measured by the change from baseline in the Clinical Global Impression of Severity (CGI-S) score.

Other secondary objectives of the study include:

1. An evaluation of the efficacy of oral ziprasidone as compared with placebo as measured by the Clinical Global Impression of Improvement (CGI-I) score.

CCI [redacted]

STUDY DESIGN

This will be a Phase 3, multicenter, 4-week, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and tolerability of flexibly dosed ziprasidone compared with placebo for the treatment of Bipolar I Disorder (current or most recent episode manic) in children and adolescents aged 10 to 17 years (inclusive).

Ziprasidone (or placebo) will be administered as oral capsules given twice daily (BID) with food. Ziprasidone (or placebo) will be titrated over the first 7-14 days of treatment, and then flexibly dosed through the end of the double-blind treatment period (Week 4, Day 29).

Sample Size

Shortly after enrollment into this study commenced, Pfizer was informed by the rater training vendor (on 29 September 2014) that an internal audit had revealed an error in their internal processes. This error resulted in some sites being notified that they could start screening subjects before all raters at the sites had completed all of the required rater training activities. The primary endpoint assessments (YMRS) and/or the diagnostic interviews (KSADS) of 14 subjects were impacted by the rater training issue.

In agreement with the FDA to ensure the robustness of the inferential analysis, Pfizer will recruit an additional 14 subjects into the study and conduct a sensitivity analysis excluding these 14 subjects to mitigate the effect of the rater training issue that was identified.

The original sample size for this study was 180 subjects. For the revised sample size, a total of 194 subjects (97 ziprasidone: 97 placebo) will be recruited from approximately 60 -70 worldwide sites. The power of the study including the additional subjects is 88%. It is estimated that approximately 300 subjects will be required to be screened to achieve this enrollment target with an anticipated screen failure rate of approximately 40%.

The study will begin with a screening visit to determine subject eligibility, followed by a 1-14 day period to allow for wash-out of exclusionary medications. Subjects who qualify will be randomized at baseline to receive either double-blind oral ziprasidone or placebo (randomization ratio 1:1).

Eligible subjects will remain in the treatment period for 4 weeks. After completion of the treatment phase, subjects will return for a post-treatment follow-up visit at week 5. Subjects who complete the study or who terminate early may be eligible for continuation of treatment in the open label extension study A1281201.

Subjects with a body weight ≥45 kg who cannot tolerate a dose of 80 mg/day and subjects weighing <45 kg who cannot tolerate a minimum dose of 40 mg/day will discontinue from the double blind study and will not be eligible for continuation of treatment in the open-label extension study. These subjects will be eligible for the Post Study Care program (see Section 3.1).

STUDY TREATMENTS

Study drug will be provided by Pfizer and will include oral ziprasidone capsules of 20 mg, 40 mg, 60 mg, and 80 mg strength and matching placebo capsules. All medication will be packaged in child resistant blister cards with columns for AM and PM capsules.

Study medication will be dispensed at the baseline visit after all baseline assessments have been completed. A single titration card will be dispensed based on the subject's weight (≥45 kg or <45 kg) for the first week of dosing. The titration cards that will be used for the first week of the trial will have a maximum of 80 mg/day for subjects ≥45 kg and a maximum of 60 mg/day for subjects <45 kg. Subsequent dosing will follow as per the parameters of Section 5 of the protocol. Dosing flexibility is allowed based on the clinical judgment of the investigator regarding tolerability and efficacy of the subject.

In general, the target dose should be attained by Days 7-14. For subjects with a body weight ≥45 kg, the target dose range is 120-160 mg/day. A dose of 160 mg/day should not be achieved before Day 14 of treatment, however. For subjects with a body weight <45 kg, the target dose range is 60-80 mg/day. A dose of 80 mg/day should not be achieved before Day 8 of treatment.

After subjects have been titrated to the target dose range, double-blind dosing will continue to the end of Week 4, during which time the dose should be kept stable except that downward adjustments of the dose are allowed if required in the judgment of the investigator for safety and tolerability concerns.

All study medication is to be taken with food.

At the end of the double-blind treatment period, subjects may be switched to one of the alternative therapies for treatment of pediatric bipolar disorder approved within their country for the U.S. (including lithium, Abilify®, Risperdal®, Zyprexa®, and Seroquel®) if in the judgment of the investigator or treating physician, continued pharmacotherapy is warranted. Based on accumulated safety data from the pre-marketing clinical trials with ziprasidone, short term treatment with ziprasidone does not appear to be associated with a marked withdrawal syndrome and it should be feasible and well tolerated to immediately switch the subjects from ziprasidone treatment to an alternative treatment. Following the last dose of study drug, ziprasidone plasma concentrations should self-taper over 2 to 3 days, during which time the alternative medication can be titrated up to ensure that treatment of the subject is not interrupted.

STATISTICAL METHODS

This study has been designed to have 85% statistical power to show a difference between drug and placebo at conventional levels (ie, 5% level, 2-sided) of statistical significance. Based on the previous Pfizer pediatric study A1281132, the estimated difference in change from baseline of the YMRS total score for ziprasidone versus placebo is –4.55 points (from descriptive and LSMEANs at week 4) with an approximate within-group standard deviation of 8.0. Using EAST (version 5.4) for a two-sample t-test, the sample size needed to detect

this difference with 85% power at a two-sided significance level of 5% was determined to be 111 randomized subjects. Adjusting for dropouts (approximately 38% at week 4) and including the additional 14 subjects being enrolled to mitigate the impact of the rater training issue, the total sample necessary is 194 subjects (1:1 enrollment with 97 on ziprasidone and 97 on placebo). The power for this study has now increased to 88%. The randomization will be stratified by weight group (weight <45 kg, weight ≥45 kg) to ensure treatment balance within each of the two weight groups.

Both the Intent-to-Treat (ITT) and Per-Protocol (PP) analysis sets will be used in the analyses of all efficacy endpoints, with the ITT being primary. The Safety Analysis Set will be used in the analyses of the safety data. Only the ITT analysis set will be used in the analyses of the outcome and special safety assessments.

Sensitivity Analysis of Final Data Set

The YMRS data of 14 subjects was impacted by the rating training issue, representing about 7% of the target sample size of 194 subjects. While we remain confident of the validity of these data, we plan to conduct a sensitivity analysis of the treatment effect on the primary endpoint, excluding these 14 subjects from the analysis. The power for this sensitivity analysis is 85%, to detect a difference in means of -4.5, with a standard deviation of 8, and assuming a dropout at week 4 of 38%.

The sensitivity analysis excluding these 14 patients will use the same statistical methodology as the pre-specified primary efficacy analysis.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

	Screening[m,n]	Baseline[m]	Treatment			End of Treatment (or Early Termination)[a,o]	Follow Up[o]	Follow Up[p]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Day -14 to -1	Day 1	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 36 Week 5	
Study Windows			(±3 days)[b]					
Informed consent, assent[c]	X							
Demography	X							
Diagnostic eligibility; K-SADS administration; prepare diagnostic narrative for external review	X							
Medical/psychiatric history; family history	X							
Full physical exam including body temperature	X					X		
Height; weight; BMI; BMI z-score; waist circumference	X					X		
12-lead ECG[e]	X	XXX[f]	X	X	X	XXX[f,h]	X[d]	
Blood pressure; pulse	X	X	X	X	X	X[h]	X[d]	
CCI						C		
Laboratory evaluations								
Blood chemistry	X	X[d]	X			X	X[d]	
Hematology	X	X[d]	X			X	X[d]	
Urinalysis	X	X[d]	X			X	X[d]	
Hormones (free T4 &TSH, prolactin)	X	X[d]				X	X[d]	
Fasting glucose, lipid profile, insulin, HbA1c[j]	X	X[d]				X	X[d]	
Hepatitis serology	X							
Pregnancy test[l,m]	X	X	X	X	X	X	X	

	Screening[m,n]	Baseline[m]	Treatment			End of Treatment (or Early Termination)[a,o]	Follow Up[o]	Follow Up[p]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Day -14 to -1	Day 1	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 36 Week 5	
Urine drug screen[l]	X	X				X		
Inclusion/exclusion criteria review	X	X						
Randomization		X						
Dispense study drug		X	X	X	X			
Drug accountability			X	X	X	X		
Subject contact[l] (telephone or in-person)		X	X					X[p]
Efficacy assessments								
YMRS	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X		
CGI-I			X	X	X	X		
CCI [redacted]	[redacted]	[redacted]				[redacted]		
CDRS-R	X	X	X	X	X	X		
C-SSRS[k]	X	X	X	X	X	X	X	
Movement disorder scales: SARS, BAS, AIMS		X	X	X	X	X	X[d]	
Adverse events	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	

K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; BMI = Body Mass Index; ECG = Electrocardiogram; T4 = Thyroxin 4; TSH= Thyroid-Stimulating Hormone; HbA1c = glycated hemoglobin; YMRS = Young Mania Rating Scale; CGI-S = Clinical Global Impressions of Severity; CGI-I = Clinical Global Impression of Improvement; CCI [redacted]; CDRS-R = Child Depression Rating Scale - Revised; SARS = Simpson-Angus Rating Scale; BAS = Barnes Akathisia Rating Scale; AIMS = Abnormal Involuntary Movement Scale; C-SSRS = Columbia Suicide Severity Rating Scale.

a. In the case of early termination, all procedures specified for Visit 6 (Week 4) are to be completed.

b. Every effort should be made to bring the subject back to the office on the designated study days; however, office visits will have a ±3 day visit window to allow for slight variations in subject schedules unless approved on an individual subject basis by the sponsor. When scheduling subsequent visits, the overall treatment period in the protocol should be maintained.

c. Subjects who turn 18 years old during the study need to give a written consent.

d. Collect/perform procedure only if clinically significant abnormalities present at the previous visit.

e. All ECGs will be collected before or at least 3 hours after food intake, before BP/pulse measurements and before any blood draw. ECGs showing a QTcF of ≥480 msec or a suspected increase from baseline of 60 msec or greater must be repeated within the same visit. If the QTcF value persists at ≥480 msec and/or the change from baseline persists at ≥60 msec, the study drug must be discontinued immediately and a pediatric cardiologist, or an adult cardiologist experienced in the interpretation of pediatric ECGs should be contacted to discuss the ECG result.

f. Triplicate ECGs should be performed.

g. CCI [redacted]

h. Subjects will be required to take their last AM dose of study medication in the clinic. Prior to dosing, all subjects will have an ECG followed by measurement of blood pressure and pulse. CCI [redacted] Subjects will then take breakfast and their morning dose of study medication.

i. Unscheduled UDS and/or pregnancy tests can be performed at additional visits at the investigator's discretion. Pregnancy tests should also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

j. Subjects should remain fasting for at least 8 hours prior to glucose, lipid profile, insulin and HbA1c samples.

k. A risk assessment should be done to determine if it is safe for the subject to participate in the trial or continue to participate in the trial, if the subject's responses during the suicidality assessments indicate that the subject has had suicide ideation associated with actual intent and/or plan at any time in their lifetime or any previous lifetime history of suicide behaviors. See Section 7.2.9.

l. Contact should be made with the subject by the investigator or designated staff member, either by telephone or in person as an unscheduled visit, after the baseline visit but before Visit 3 and after Visit 3 but before Visit 4 to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability, safety, and efficacy of the study drug.

m. At all required visits, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive. Female subjects must have a negative urine pregnancy test at screening, at baseline prior to randomization, and at all post-baseline visits in order to continue to receive study drug.

   In addition, if a subject is not sure whether they might be pregnant at the time of screening, ie, they have had unprotected sex within the last 2 weeks prior to screening, then that subject would be required to have 2 negative pregnancy tests two weeks apart before they could receive study drug.

n. Screening procedures may be completed over 1 or multiple days based on the needs of the site and/or the subject/parent/guardian.

o. Subjects who do not enter the open extension study A1281201 will return for a post-treatment follow-up clinic visit at Week 5.

p. Contact may occur via telephone and must occur 28 to 35 days from administration of the final dose of investigational product to capture any potential adverse events (see the Adverse Events Information section) and to confirm appropriate contraception usage (see the Life Style Guidelines section) for subjects who do not enter the open label extension study.

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APPENDICES

1. INTRODUCTION

The present study is designed to assess the efficacy, safety, and tolerability of oral ziprasidone in child and adolescent subjects with Bipolar I Disorder (current or most recent episode manic). It is designed to comply with a Pediatric Research Equity Act (PREA) commitment to assess the safety and effectiveness of Geodon® (ziprasidone) as a treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents), issued by the US Food and Drug Administration (FDA) to Pfizer in August 2004.

1.1. Indication

Ziprasidone is an atypical antipsychotic with a high affinity for the dopamine D_2 receptor and the 5-$HT2_A$ receptors. It blocks re-uptake of serotonin and norepinephrine and exhibits 5-$HT1_A$ agonist activity. The indication for this study is pediatric Bipolar I Disorder. The study will include in-patient and/or out-patient male and female subjects aged 10-17 (inclusive) who meet the DSM-V diagnostic criteria for Bipolar I Disorder (current or most recent episode manic).

1.2. Background and Rationale

1.2.1. Background on Bipolar I Disorder in Children and Adolescents

Bipolar I Disorder is a lifelong disease that is potentially debilitating to the patient and presents serious complications within the patient's family structure. Over half of all bipolar patients report that their symptoms first emerged during childhood or adolescence, and onset before adulthood is associated with greater social morbidity.[1] Children and adolescents with mania often show markedly labile mood, with a mixed or dysphoric picture and intense irritability, as well as severe psychosocial impairment.[2,3] The costs to society and the public health system are immense. Recognizing the onset of these disorders in children or adolescents is a critical health concern, and initiating treatment as early as possible is vital to maximize the probability of a positive outcome for the patient.

Bipolar disorder can be reliably diagnosed in children and adolescents aged 10-17 years, using the same criteria used for adults as outlined in the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-V), and supported by structured diagnostic interviews such as the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), as affirmed recently by the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines.[4] Existing data support the diagnostic and therapeutic continuity between adult and pediatric bipolar disorder. For adults with acute mania in the setting of bipolar disorder, the efficacy and safety of a variety of medications has been established through randomized clinical trials. These agents include lithium, other mood stabilizers from the anticonvulsant class, and atypical antipsychotic medications. For children with bipolar mania, however, there are limited data on the safety and efficacy of these pharmacological agents.[6] Lithium and other mood stabilizers are commonly used for this diagnosis, but the evidence base is not robust for any of these drugs, and except for lithium (for children 12 and older), none of the other mood stabilizers are FDA-approved for this indication.[4,6] Among the class of atypical antipsychotic medications, risperidone (Risperdal®), aripiprazole (Abilify®), and more recently, quetiapine (Seroquel®) and olanzapine (Zyprexa®) have been approved for the treatment of pediatric bipolar mania. Although shown to be effective, several of these

treatments are associated with adverse events such as movement disorders, weight gain, hyperlipidemia and other metabolic effects, which may limit their usefulness in some patients.[7] There remains a great need for additional well-controlled, randomized, double-blind clinical studies to evaluate the efficacy and safety of potential pharmacotherapies in the pediatric population.

1.2.2. Background on Ziprasidone (CP-88,059)

Ziprasidone (CP-88,059-1 oral capsule) is an atypical antipsychotic. It has a high affinity for the dopamine D_2 receptor, potent in vivo activity in rat models of dopamine antagonism (blocking of d-amphetamine-induced locomotor activation and blocking of apomorphine-induced stereotypy), and potent activity in an antipsychotic model in rats that is potentially dopamine-independent (inhibition of conditioned avoidance). Ziprasidone demonstrates high 5-Hydroxytryptamine Receptor 2A ($5\text{-}HT2_A/)D_2$ ratio, which has been associated with a lower risk of extrapyramidal symptoms compared to typical antipsychotics. In addition, blockade of serotonin and norepinephrine re-uptake and 5-Hydroxytryptamine Receptor 1A ($5HT1_A$) agonist activity may contribute to the alleviation of affective and negative symptoms. Ziprasidone has relatively low affinity for α1-adrenergic and histamine H_1 receptors and muscarinic M_1 receptors, which may be associated with modest orthostatic effects and sedation, and low incidence for weight gain and anticholinergic side effects, respectively.[8] Because ziprasidone is metabolized predominantly by the aldehyde oxidase system, in addition to the cytochrome P4503A4 (CYP3A4) system, the likelihood of pharmacokinetic interactions between ziprasidone and other drugs is low.[9]

Ziprasidone has been approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia in adults in the United States (approval, February 2001) and in at least 55 other countries. A Supplemental New Drug Application (sNDA) for the treatment of bipolar disorder in adults with manic symptoms was approved by the FDA in August 2004. The safety and efficacy of ziprasidone monotherapy for the treatment of mania in adults was demonstrated in two double-blind, placebo-controlled trials of 3 weeks duration, and in open-label extension trials of up to 104 weeks duration. These studies demonstrated that ziprasidone was superior to placebo in the treatment of subjects with a manic or mixed bipolar episode, with clinically and statistically significant improvement evident as early as Day 2 of treatment. In November 2009, ziprasidone was also approved by the FDA for adult bipolar maintenance treatment based on a 6 month double-blind study comparing ziprasidone plus a mood stabilizer vs placebo plus a mood stabilizer in subjects who have been treated and responded for at least 4 months to open-label treatment with both agents. The overall profile of adverse events in the adult mania studies is comparable with that seen in schizophrenia studies. Ziprasidone had neutral effects on weight, glucose and lipid profiles in adult patients with mania.[8]

Currently approved and marketed formulations in the US for ziprasidone include the oral capsule (20, 40, 60, and 80 mg) and a rapid onset intramuscular (IM) injectable form (20 mg/ml). As of October 2017, approximately 2,976,798 patients had been exposed to ziprasidone worldwide, cumulatively (based on prescription data and US unique patient count).

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure.[10]

1.2.2.1. Background on Previous Ziprasidone Pediatric Trials

1.2.2.1.1. Study A1281123: Open Label Safety & Tolerability

Study A1281123 was an open-label safety and tolerability study in children and adolescents 10-17 years old, diagnosed with Bipolar I (manic or mixed), schizophrenia or schizoaffective disorder. This Phase 2 study explored the range of tolerated doses of ziprasidone during 3-weeks of low or high fixed dose administration, and characterized the safety and tolerability of flexibly dosed ziprasidone for an additional 24 weeks. Ziprasidone oral suspension was titrated over 10 days to a target dose following a fixed schedule, and then maintained at the target dose until end of Week 3 (Period 1). Two dose ranges were tested: Group 1 subjects (low dose, n=23) started from 10 mg BID to a target dose of 40 mg BID, and Group 2 subjects (high dose, n=40) started from 20 mg BID to a target dose of 80 mg BID. Doses for subjects weighing <45 kg were halved. Subjects could continue flexible dosing in a range of 10-80 mg BID into Period 2 for up to 24 additional weeks. The most common AEs in Groups 1 and 2 were sedation (21.7%, 35.0%), somnolence (34.8%, 27.5%), nausea (21.7%, 27.5%), headache (13.0%, 27.5%), dizziness (13.0%, 25.0%), and vomiting (13.0%, 20%). No unexpected safety or tolerability findings occurred. ECG findings were consistent with those recorded for adult subjects treated with ziprasidone. There were no confirmed QTc intervals over 500 msec and no subject had a QTc increase ≥60 msec from baseline. Most subjects (89%) continued treatment in the 6-month open-label flexible dose extension; and 31 (55%) completed the 6-month treatment. Only sedation (30.4%) and somnolence (30.4%) occurred in more than 20% of the subjects. Weight gain was reported as an adverse event (AE) in 5 of 56 subjects (8.9%). No clinically relevant changes in lipid profile or fasting glucose were observed. Twenty SAEs were reported in 16 subjects. One event (QTc prolongation) was initially reported as related to treatment; this event occurred after termination of therapy, and the causality was subsequently changed to not related to study drug. All other events were unrelated to treatment. Five cases of suicidal ideation and one of self-harm (overdose) were explained by the underlying disorder, pre-existing suicidal ideation, and situational stressors. The higher AE rate in Group 2 (high dose group) in the A1281123 study was attributed partly to the relatively high initial dosing (20 mg BID) and partly to the relatively fast, fixed titration to 80 mg BID, which may not have been tolerated well by some subjects. On the basis of these results, a lower starting dose and a slower, flexible dose titration schedule with lower target dose range were identified for the placebo-controlled Phase 3 studies in pediatric subjects.

1.2.2.1.2. Study A1281132 and Extension Study A1281133: Pediatric Bipolar I Disorder

Study A1281132 was a Phase 3, 4-week, double-blind, placebo-controlled trial to evaluate the safety and efficacy of flexibly dosed ziprasidone in the treatment of pediatric subjects (ages 10-17 years, inclusive) diagnosed with Bipolar I Disorder, manic or mixed episode, as defined by DSM-IV criteria and confirmed by the K-SADS semi-structured diagnostic interview. The inclusion criteria required that subjects have an YMRS score of 17 or greater at screening and baseline. Ziprasidone (oral capsule) was administered twice daily (BID) with meals, titrated over the first 1-2 weeks of treatment and flexibly dosed during

Weeks 3 and 4. Ziprasidone was titrated from a starting dose of 20 mg/day with dose increases of 20 mg/day every 1 or 2 days up to a target dose of 120-160 mg/day for subjects weighing ≥45 kg. The target dose was to be obtained by Day 14. The dose was to increase above 120 mg/day only in subjects who tolerated 120 mg/day. For children weighing <45 kg, the target dose was 60-80 mg/day and a more gradual dose escalation was employed. A total of 149 subjects received ziprasidone and 88 subjects received placebo in a 2:1 randomization, with 65% in the ziprasidone group and 58% in the placebo group completing the study. The mean age of the subjects was 13.6 years in the ziprasidone group and 13.7 years in the placebo group. In this trial, ziprasidone was demonstrated to be superior to placebo based on primary efficacy endpoint (change from baseline to Week 4 YMRS total score), as well as the key secondary assessment (the change from baseline in CGI-S score at Week 4) and the secondary assessment endpoint (the change from baseline in CGI-I score at Week 4). For the exploratory outcome assessments, there was evidence from the Children's Global Assessment Scale (CGAS) that ziprasidone-treated subjects had improved scores compared to placebo and those subjects who were reported to be in school had better responses to ziprasidone treatment. Based on the Neurocognitive Index score of the central nervous system (CNS) Vital Signs Cognitive Battery, there was no change in cognition with treatment. Overall, ziprasidone was safe and generally well tolerated. No new or unexpected AEs were observed in the study. In the ziprasidone group, commonly occurring AEs were attributed to the known pharmacologic effects of ziprasidone in adults. The most common all causality AEs in the ziprasidone group were sedation (32.9%), somnolence (24.8%), headache (22.1%), fatigue (15.4%), nausea (13.4%) and dizziness (12.8%). A total of 13 subjects (6 from the ziprasidone group and 7 from the placebo group) reported 19 SAEs. One subject in the ziprasidone group was administered an overdose of ziprasidone and had an acute dystonic reaction due to the study treatment; the subject was discontinued from the study and recovered without sequelae. All other SAEs were attributed to either disease under study or other illnesses. Ziprasidone was not associated with any change in weight or metabolic parameters in this 4-week study; one subject each in the ziprasidone and placebo group reported AE of weight gain. There were no new or unexpected safety findings in vital signs, or ECGs. No subject had a QT interval, Bazett's correction (QTcB), or QTcF that was 500 msec or higher. One subject in the ziprasidone group (60 mg) had an AE of prolonged (greater than 460 msec) QTcF that resulted in discontinuation. There were no suicides or increase in suicidality during this study.

The A1281133 study was a 26 week open-label extension Phase 3 study, evaluating the safety and tolerability of oral ziprasidone in children and adolescents diagnosed with Bipolar I Disorder, manic or mixed episode. Subjects who participated in Study A1281132, and who met qualification criteria for this study, were allowed to participate in the open-label extension with flexible dose active ziprasidone. Subjects were tapered off their study treatment (double-blind active or placebo, with identical treatment assignment as in the preceding double-blind trial) during the first 6 days and then ziprasidone was titrated up over 2 weeks, in a similar way as in the double-blind study (A1281132). After the Week 2 visit, dosing was flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability. The target dose range was 40-80 mg BID (80-160 mg/day total dose) for subjects weighing ≥45 kg, and 20-40 mg BID (40-80 mg/day

total dose) for those weighing <45 kg. A total of 162 subjects received study treatment, and 67 subjects (41%) completed the study. While no formal efficacy analyses were performed in this study, both efficacy assessments (YMRS and CGI-S scores) showed trends of improved scores with continued ziprasidone treatment. Overall, ziprasidone was safe and generally well tolerated following 26 weeks of continued administration. No new or unexpected AEs were observed in this pediatric population as compared to adult studies with ziprasidone. Commonly occurring AEs were attributed to the known pharmacologic effects of ziprasidone in adults. Most common AEs (all causality) were sedation (26.5%), somnolence (23.5%), headache (22.2%) and insomnia (13.6%). Nineteen subjects had 1 or more treatment-emergent SAEs. Only 2 of these subjects had treatment-related SAEs (aggravated sedation and constipation) that led to discontinuation from the study; both subjects recovered from these events. A total of 26 subjects discontinued the study due to 1 or more AEs that were judged to be related to the study treatment by the investigator. These AEs included sedation (n=9), somnolence (n=5), fatigue (n=4), aggression (n=2), and 1 subject each reported to have insomnia, abdominal pain/duodenitis, akathisia, mania, exacerbation of Bipolar I disorder, prolongation of ECG, depression, rash, and restlessness. The changes in BMI derived Z-scores, which adjust for age and sex, showed little or no change throughout the study. There were no notable changes in metabolic parameters. There were no new or unexpected safety findings in laboratory tests, vital signs, or ECGs. No subject had a QT interval, QTcB, or QTcF that was 460 msec or higher.

One subject receiving 80 mg total daily dose of ziprasidone had an AE of prolonged QTc interval (66 msec prolongation compared to baseline measure) and was discontinued from the study. None of this subject's QTc measures were >460 msec. There was no increase in suicidal ideation or behavior, and there were no suicides during this study.

1.2.2.1.3. Study A1281134 (and Open Label Extension A1281135): Pediatric Schizophrenia

Pfizer conducted 2 Phase 3 studies to evaluate the effects of ziprasidone (oral capsules) in adolescents (age 13-17 years) diagnosed with schizophrenia. The A1281134 study was a 6 week, placebo-controlled double-blind trial to evaluate the efficacy and safety of flexible dose ziprasidone. Eligible subjects could continue in the open-label study A1281135, to evaluate the safety and tolerability of flexible dose ziprasidone over 26 weeks. The weight-based flexible titration regimens and target doses in these two studies were the same as in the pediatric bipolar studies A1281132 and A1281133. A planned interim analysis resulted in a recommendation from the Data Safety and Monitoring Board (DSMB) to terminate the A1281134 study due to futility. Pfizer terminated both studies; as a result participation of 1 subject in the A1281134 study and 92 subjects in the A1281135 study was stopped.

In the A1281134 trial, a total of 193 subjects were treated with ziprasidone and 90 subjects were treated with placebo in a 2:1 randomization. Subject overall mean age was 15.3 years in the ziprasidone group and 15.4 years in the placebo group, and most had a primary diagnosis of schizophrenia, paranoid type. While more subjects in the ziprasidone group completed the study (69.9% vs 57.8% in the placebo group), more subjects in the placebo group discontinued due to insufficient clinical response (20.0% vs 9.3% in the ziprasidone

group). In this study, oral ziprasidone failed to demonstrate superiority in efficacy over placebo in adolescent subjects. Overall, ziprasidone was safe and generally well-tolerated. The higher incidence of AEs in the ziprasidone group was primarily attributed to known, pharmacologic nervous system effects (ie, somnolence, extrapyramidal disorder, tremor, akathisia, insomnia, headache, fatigue, dizziness, nausea, vomiting). The most commonly occurring AEs (all causality) in the ziprasidone group were somnolence (19.2%) and extrapyramidal disorders (11.4%). While the incidence of treatment-emergent AEs (all causality) related to extrapyramidal symptoms was higher in the ziprasidone group (24.9% in ziprasidone group vs 5.6% in the placebo group), evaluation of these symptoms using the Movement Disorder Scales did not reveal statistically significant differences between the treatment groups. The incidence of SAEs in the ziprasidone group compared to placebo was 4.7% vs 1.1%, respectively; none of the SAEs were considered treatment related. The SAEs in the ziprasidone group were suicidal ideation, anxiety, depression, psychotic disorder, schizophrenia, auditory hallucination, hostility, impulsive behavior and overdose. The SAEs in the placebo group were aggression and psychotic disorder. Suicidality was assessed using the Columbia Classification system for Possibly Suicide Related Adverse Events (PSRAEs). Four PSRAEs in the ziprasidone group were considered SAEs (suicidal ideation and self-injurious behavior, intent unknown, in 2 subjects each). Changes in BP and pulse rate were not clinically significant. Two subjects had a QTcF increase of ≥460 msec but <500 msec. Two subjects treated with ziprasidone had AEs of QTcF prolonged (1 mild and 1 moderate) leading to discontinuations from the study. Ziprasidone did not have clinically significant effects on weight and metabolic indices such as fasting glucose and lipids.

A total of 221 adolescent schizophrenia subjects treated in the A1281134 double-blind placebo-controlled study entered the 26 week extension study and were treated with open-label ziprasidone. The study was terminated early for futility by the sponsor; out of 145 subjects (65.6%) who discontinued the study, 92 (41.6%) were discontinued by the sponsor. Overall, ziprasidone was safe and generally well tolerated over 26 weeks of open-label treatment. No new or unexpected AEs were observed during the study. The majority of both all-causality and treatment-related AEs were mild in severity. All causality treatment-emergent AEs occurring at an incidence of ≥5% were somnolence (14.5%), headache (8.6%), tremor (6.3%), schizophrenia (5.0%). The self-rated Tanner Adolescent Pubertal Staging Questionnaire ratings indicated a progression of puberty among subjects. From the special safety evaluations, the decrease in the CDRS-R mean scores throughout the study indicated overall improvement in the level of depression. The Children's Problem Behavior and Aggression Questionnaire (CPBAQ) and CNS Vital Signs scores fluctuated, with no obvious trends. One death, via suicide, occurred during this study. The causality of this event was judged to be related to study medication (poor control of symptoms of schizophrenia). Five other subjects (2.3%) discontinued due to AEs related to the study drug (sedation, somnolence, weight increased, weight decreased, and muscle rigidity) and 1 subject discontinued due to a laboratory abnormality not related to study drug (hepatitis B, causality due to other illness). Only 6 subjects (2.7%) discontinued due to insufficient clinical response. Changes in blood pressure and pulse were small and not clinically significant. One subject had a QTcF interval of ≥460 msec but <500 msec. No subject had an AE of QTc prolonged. There were no clinically significant changes in body weight, and other metabolic indices such as fasting glucose and lipids results.

1.3. Drug Development/Study Rationale

The present protocol has been designed to satisfy a PREA requirement to assess the safety and effectiveness of ziprasidone as a treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents) issued by the FDA to Pfizer in August 2004.

The overall goal of the study is to assess the safety profile and efficacy of ziprasidone in the treatment of pediatric mania in association with bipolar disorder, CCI [redacted] The study population in this protocol will be limited to children and adolescents aged 10 to 17 years (inclusive). In this age range, the same DSM-V criteria for mania are employed for both the pediatric and adult population. While the lower end of the age range for bipolar disorder is not clear, it is both uncommon and difficult to make this diagnosis below the age of 10 years. On the other hand, bipolar disorder in the 10 to 17 year-old population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults.

1.4. Dose Rationale

The dose rationale for this study is based on the results of the open label dose titration study A1281123 and experience in the previous placebo controlled pediatric bipolar study A1281132 (see Section 1.2.2.1 for details of both studies). The target dose ranges for subjects <45 kg is 60-80 mg/day and for subjects ≥45 kg, 120-160 mg/day, which are identical to the target dose ranges used in study A1281132. Subjects weighing <45 kg will be titrated over the first week of the study to a total daily dose in the range of 60 mg to 80 mg a day and subjects weighing ≥45 kg will be titrated over the first 2 weeks of the study to a total daily dose in the range of 120 mg to 160 mg a day. After the target dose range is attained, stable dosing should be maintained for the duration of the study, if possible. However, depending on the clinical judgment of the investigator, the dose may be down titrated at any time in the case of tolerability or safety concerns.

1.5. Risk-Benefit Assessment

Bipolar Disorder I (manic or mixed) is associated with substantial morbidity and mortality, and, to date, few medications have been approved for the treatment of bipolar disorder in the pediatric age group. Although lithium is indicated for the treatment of bipolar disorder in pediatric subjects, significant safety concerns pertain to it. The recently approved atypical antipsychotic medications quetiapine (Seroquel®), aripiprazole (Abilify®), risperidone (Risperdal®), and olanzapine (Zyprexa®) offer additional treatment options, but in some cases can be associated with marked weight gain and metabolic effects (such as hyperlipidemia and diabetes) that pose significant risks for long-term use. There remains a pressing need to establish the safety and efficacy of new treatment options, such as ziprasidone, for bipolar disorder. The information summarized in this protocol, and additional data that are detailed in the Investigator Brochure for ziprasidone, support a favorable risk-benefit assessment for the planned study. Extensive data exist to show that ziprasidone is efficacious and well-tolerated in adults with schizophrenia or bipolar disorder, as summarized in Section 1.2.2. The data on ziprasidone in children and adolescents are more limited, but are sufficient to justify the planned study.

Taking into consideration all the data from previous pediatric ziprasidone studies (reviewed above in Section 1.2.2.1), the proposed study appears to be associated with a favorable risk-benefit ratio. Results of the similarly designed previous pediatric bipolar study A1281132 suggest that ziprasidone is effective and generally well tolerated in this patient population. This study is being conducted to assess and expand the efficacy and safety profile of ziprasidone in children and adolescents with bipolar disorder. Data from previous studies suggest that ziprasidone is both effective and well-tolerated in this patient population and has a safety profile similar to the adult safety profile, with minimal effects on weight gain and metabolic status.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

The primary objectives of the study are:

1. To assess the efficacy of oral ziprasidone compared with placebo in the treatment of children and adolescents aged 10-17 with Bipolar I Disorder (current or most recent episode manic) as measured by the change from baseline to Week 4 in the Young Mania Rating Scale (YMRS) total score.

2. To evaluate the safety and tolerability of oral ziprasidone over 4 weeks in the treatment of children and adolescents with Bipolar I Disorder (current or most recent episode manic).

2.1.2. Secondary Objectives

The key secondary objective of the study is to evaluate the efficacy of oral ziprasidone as compared with placebo in the treatment of children and adolescents with Bipolar I Disorder (current or most recent episode manic) as measured by the change from baseline in the Clinical Global Impression of Severity (CGI-S) score.

Other secondary objectives of the study include:

1. An evaluation of the efficacy of oral ziprasidone as compared with placebo as measured by the Clinical Global Impression of Improvement (CGI-I) score.

CCI [redacted]

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoint of the study is the change from baseline to Week 4 in the YMRS total score.

2.2.2. Secondary Endpoints

The key secondary endpoint of the study is the change from baseline to Week 4 in the CGI-S score.

Other secondary endpoints include the:

- Change from baseline to Weeks 1, 2, and 3 in the YMRS total score;
- Change from baseline to Weeks 1, 2 and 3 in the CGI-S score;
- CGI-I scores at Weeks 1, 2, 3, and 4.

CCI [redacted]

- [redacted]
- [redacted]

2.2.4. Safety Endpoints

Safety and tolerability endpoints will be assessed at scheduled intervals during the study by:

- Adverse event monitoring;
- Suicidality assessment monitoring via the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Concomitant treatment monitoring;
- Clinical laboratory monitoring;
- Physical Examinations;
- Blood Pressure and Pulse;
- Height, weight, BMI, BMI z-score, and waist circumference;
- 12-lead ECG;
- Child Depression Rating Scale - Revised (CDRS-R) monitoring;
- Movement disorder scale (SARS, BAS, and AIMS) monitoring.

3. STUDY DESIGN

This will be a Phase 3, multicenter, 4-week, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and tolerability of flexibly dosed ziprasidone compared with placebo for the treatment of Bipolar I Disorder (current or most recent episode manic) in children and adolescents aged 10 to 17 years (inclusive).

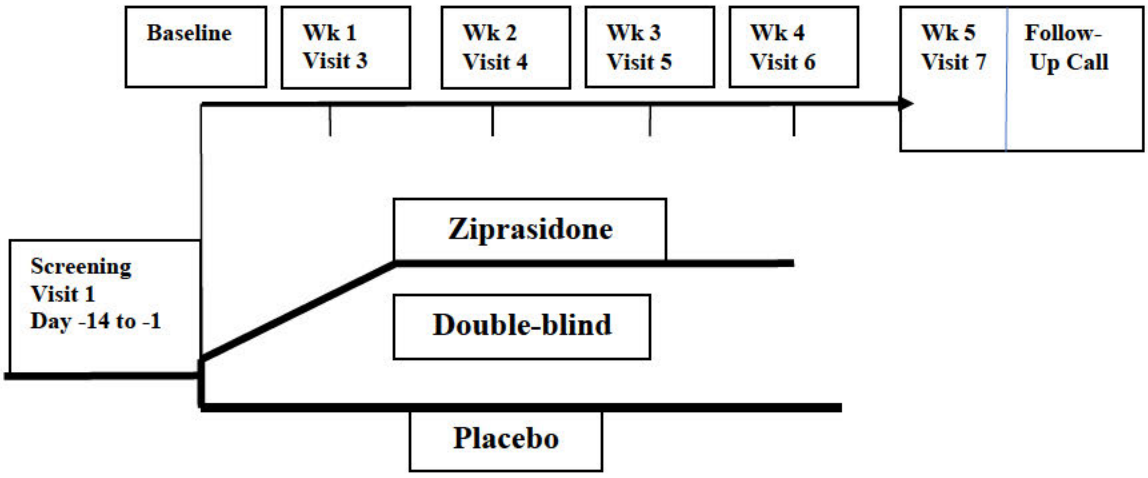
Ziprasidone (or placebo) will be administered as oral capsules given twice daily (BID) with food. Ziprasidone (or placebo) will be titrated over the first 7-14 days of treatment to the target dose range (60-80 mg/day for subjects <45 kg and 120-160 mg/day for subjects ≥45 kg), after which stable dosing will be maintained, if possible, through the end of the double-blind treatment period (end of Week 4, Day 29). However, depending on the clinical judgment of the investigator, the dose may be down titrated at any time in the case of tolerability or safety concerns.

Approximately 194 subjects (97 ziprasidone: 97 placebo) will be recruited from approximately 60 -70 worldwide sites. It is estimated that approximately 300 subjects will be required to be screened to achieve this enrollment target with an anticipated screen failure rate of approximately 40%.

The study will begin with a screening visit to determine subject eligibility, followed by a 1-14 day period to allow for wash-out of exclusionary medications. Subjects who qualify will be randomized at baseline (Day 1) to receive either double-blind oral ziprasidone or placebo (randomization ratio 1:1). The randomization will be stratified by weight group (weight <45 kg, weight ≥45 kg).

Eligible subjects will remain in the treatment period for 4 weeks. After completion of the treatment phase, subjects will either enter the open-label extension study A1281201 or return for a post-treatment follow-up visit at Week 5 if not enrolling into the open label study.

Subjects who are judged to have insufficient treatment response 1 week after completing their dose titration and have reached their maximum tolerated dose should be discontinued from the study and may be eligible to enroll in the open-label extension trial, provided there are no safety concerns and the minimum allowed dose per protocol is achieved.



The end of the study will be the last visit of the last subject for purposes of closing out sites, informing the institutional review board/independent ethics committee (IRB/IEC), and stopping sending Council for International Organizations of Medical Sciences (CIOMS) reports.

3.1. Post Study Care Program

Treatment of Bipolar I Disorder, in both youth and adults, involves stabilization of patients' acute manic symptoms and ongoing or maintenance treatment to prevent relapse.[11] The A1281198 study is a treatment study of youth in the midst of an uncontrolled bipolar I acute manic episode. It is designed to confirm the efficacy of ziprasidone in the treatment and stabilization of acute manic symptoms in youth aged 10-17 years of age.

The purpose of the post study care program is to ensure that medications that are approved for the acute treatment and stabilization of manic symptoms in pediatric subjects will be available to all subjects completing or early terminating from the A1281198 study who are ineligible for or choose not to enter the open- label extension study A1281201. The post study care program will provide financial support for all subjects deemed by the investigator and/or treating physician to be in need of ongoing treatment following their participation in study A1281198. The support may be applied to the cost of treatment with an alternative medication approved and marketed within your country for the acute treatment of pediatric Bipolar I Disorder (for the U.S. including lithium, Risperdal®, Abilify®, Seroquel®, or Zyprexa®). The choice of treatment is to be based on the clinical judgment of the investigator and/or treating physician. [In some cases, subjects may be treated and managed by the investigator following their participation in the study; in other cases, subjects may be referred to another physician for post study care. The post study care program would be available to the subject in either situation.]

The support provided will be limited to the cost of two months of pharmacotherapy with an approved medication within your country. The rationale for limiting support to two months of pharmacotherapy is based on the results of controlled clinical studies of medications approved for acute treatment of pediatric mania, clinical practice, and practice parameters promulgated by the American Academy of Child and Adolescent Psychiatry.[11] Controlled studies of acute treatment of manic episodes in youth have ranged from 2 to 4 weeks in duration.[12-16] After 3-4 weeks of treatment with either Zyprexa®, Seroquel®, Risperdal® or Abilify®, 45% to 64% of subjects on active treatment responded with a ≥50% decrease in severity of their manic symptoms compared to baseline.[13-15]

On the other hand, 36% to 55% of subjects in these clinical studies continued to have substantial symptoms of mania at the end of the study, due either to a less-than-optimal treatment response or to poor toleration. In addition, a proportion of subjects in each study early terminated, in some cases due to side effects. Thus, some subjects exiting from the A1281198 study may require treatment beyond 4 weeks or may need to be switched to an alternative therapy, before their acute symptoms can be controlled.

For all these reasons taken together, it appears both clinically prudent and ethical to offer support for up to two months continued treatment with an approved medication to the participants in study A1281198 who are not eligible for or elect not to participate in the open level extension study A1281201. This level of support for continued treatment of the study subjects is consistent with the available clinical data and standard of care, without -providing inappropriate incentives for eligible patients to participate in the study.

The post-study treatment program is available only in countries where there are marketed approved medications for the treatment of pediatric bipolar disorder. The financial support provided through the post study care program cannot be applied for the use of ziprasidone in the US as it is not approved in this patient population in the US and thus is an investigational agent.

The investigator and/or treating physician who is managing the subject following his/her participation in study A1281198 will be obligated to submit invoices or receipts documenting that the provided funds were applied as required to support the ongoing treatment of the study participants.

Subjects will not be monitored by Pfizer during their participation in the post study care program and no data will be collected on their treatment, clinical response, and safety beyond that required during their participation in the A1281198 study. The active reporting period for Serious Adverse Events (SAEs) as described in Section 8.2 of the protocol (which extends to 28 days following the last dose of study drug) will be observed, however.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

In order to achieve a reasonable distribution of subjects in the different weight categories, an enrollment target of no less than 20% will be set for both weight categories. Since weight and age are generally correlated, it is expected this will also lead to an acceptable distribution of subjects across the age range. Enrollment will be monitored to ensure that an appropriate distribution of age and weight is maintained.

Enrollment is competitive and enrollment at each site will depend on the capabilities of each site. The number of enrolled subjects is not pre-specified for any individual site.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study. A statement that the subject was eligible to enter the clinical trial should be completed by the investigator and included in the subject's source documentation.

There may be instances where siblings, or other subjects living in the same home or having the same caregiver, may both be eligible to enroll in the study.

There is an inherent risk of mis-dosing when more than one subject living in the same home is enrolled at the same time. This also includes subjects from separate households that have the same caregiver. In order to mitigate any risk with dosing, only one subject that shares a household/caregiver should be enrolled during any given timeframe. If another subject meets all inclusion/exclusion criteria for the study, that subject may also be enrolled if the enrollment periods do not overlap.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of personally signed and dated informed consent document by the legal representative and an assent document by the subject indicating that the subject and a legal representative have been informed of all pertinent aspects of the study.

2. Subjects and their legal guardians who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. In-patient and/or out-patient male and female subjects aged 10-17 (inclusive) at screening.

4. Primary diagnosis of Bipolar I Disorder (current or most recent episode manic), as defined by DSM-V criteria and confirmed by the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS). Current symptoms supporting the diagnosis must have been present for at least 7 days prior to screening.

5. YMRS score ≥17 at the screening and baseline visits.

6. In the investigator's opinion, the subject must be likely to benefit from therapy with an atypical antipsychotic drug.

7. Body Mass Index (BMI) z-score between –1.65 and +2.00, inclusive.

8. Subject must be willing and able to discontinue any medications that are prohibited in this study. Any such medications must be discontinued (according to the timeframes in Section 5.5) prior to baseline.

   Subjects who are receiving prohibited medications are to be considered for the protocol only if discontinuation of the medication does not compromise the welfare of the subject and/or alternative medication that is allowed by the protocol is available and appropriate for the subject.

   Psychotropic medications should be tapered down per accepted medical practice and the specific package insert instead of being abruptly discontinued.

If psychotherapy has been ongoing for 3 months prior to the screening visit, it can be continued during the study provided there is no increase in the frequency or duration of the psychotherapy or change in the type of psychotherapy being provided.

9. All male and female subjects who are sexually active and/or their legal guardians, as appropriate, must agree that a highly effective method of contraception be used throughout the study and for 28 days after the last dose of assigned treatment.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

2. Subjects who are clinically stable on treatment regimens that are being well tolerated.

3. Subjects with substance-induced psychotic disorder or whose behavioral disturbance is thought to be due to substance abuse.

4. Subjects with DSM-V defined Substance Use Disorder (including psychoactive substance or alcohol use disorders) within the preceding 1 month of screening (does not apply to nicotine or caffeine).

5. Subjects who are judged by the investigator as being at imminent risk of suicide.

6. Subjects who are judged by the investigator as being at imminent risk of homicide.

7. Subjects should be excluded or a risk assessment should be done to verify that it is safe for the subject to participate in the trial if the subject's responses on any of the screening instruments or other screening information based on the investigator's judgment indicate:

    - A suicide ideation associated with actual intent and a method or plan at any time in their lifetime such that a positive response ('Yes') is made on items 4 or 5 of the suicidal ideation subscale of the C-SSRS;

    - Any lifetime history of suicide behaviors such that a determination of 'yes' is made to any of the suicide behavior items of the C-SSRS.Subjects with significant Intellectual Disability (ie, Intelligence Quotient (IQ) <70) that would interfere with study conduct or with the interpretation of the study assessments.

8. Subjects with significant Intellectual Disability (ie, Intelligence Quotient (IQ) <70) that would interfere with study conduct or with the interpretation of the study assessments.

9. Subjects with Autism Spectrum Disorder (including autistic disorder, Rett syndrome, childhood disintegrative disorder, pervasive developmental disorder – not otherwise specified (PDD-NOS), Asperger syndrome).

10. Subjects with Disruptive Mood Dysregulation Disorder.

11. Subjects with schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder.

12. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

13. Subjects with controlled or uncontrolled Type 1 diabetes.

14. Subjects with Type 2 diabetes unless diagnosed ≥6 months prior to screening and on a stable, well controlled treatment regimen (ie, diet and/or oral hypoglycemic agents; insulin use is considered exclusionary).

15. Subjects with a history of seizure or epilepsy.

    Subjects with a history of febrile seizures are eligible if no seizures have occurred during the last 3 years.

16. Subjects with a history of syncopal episodes (sudden loss of consciousness with loss of postural tone and not preceded by a pre-syncopal phase) or unexplained loss of consciousness.

    Subjects with a history of occasional syncopes of probable vasovagal origin (onset not sudden but preceded by a pre-syncopal phase, presence of predisposing factors such as blood sampling procedure, standing, hot shower, hair curling, etc) are eligible.

17. Subjects with any medical condition or dietary habit that has a significant potential to alter the absorption of the study drug; or subjects taking any medication that may alter drug absorption (eg, anorexia nervosa, bulimia, chronic use of laxatives).

18. Subjects with uncorrected hypothyroidism or hyperthyroidism or whose thyroid function and medication regimen have been stable less than 1 month prior to screening.

19. Alanine aminotransferase (ALT)/Aspartate aminotransferase (AST) values ≥2x and total bilirubin values ≥1.5x the upper limits of normal.

Subjects with an isolated increase of unconjugated bilirubin (Gilbert's syndrome) are eligible.

20. Subjects with a history of chronic hepatitis, known serologic evidence of acute hepatitis or chronic hepatitis (positive hepatitis B virus surface antigen (HbsAg)), or subjects with known hepatitis C antibodies and elevated LFTs.

21. Subjects known to be Human Immunodeficiency Virus (HIV) positive.

22. Subjects with clinically significant hypokalemia or hypomagnesemia not corrected and stabilized by the addition of dietary supplements or some other corrective measure prior to baseline.

23. Subjects with a history of significant cardiovascular disease, including conditions that have previously required treatment or acute evaluation, or significant concurrent cardiovascular disease, including hypotension, congestive heart failure, or congenital heart disease.

    Non-clinically significant sinus bradycardia or sinus tachycardia will not be considered significant medical illnesses and would not exclude a subject from the study.

    Isolated atrial septal defect (ASD), ventricular septal defect (VSD, or patent ductus arteriosus (PDA) will not be considered significant medical illnesses if they are surgically corrected.

24. Subjects with a history of cardiac arrhythmias, conduction abnormalities or known personal history of QT prolongation (including congenital long QT syndrome).

25. Subjects with a known genetic risk for prolonged QT syndrome.

26. Subjects with a clinically significant ECG abnormality at screening or baseline.

27. Subjects with a QTc (Fridericia) ≥450 msec at screening or baseline, which is still prolonged on repeat ECG.

28. Subjects taking any medications that are prohibited (see Section 5.5).

29. Subjects who are taking or have previously received clozapine.

30. Use of a depot antipsychotic within 4 weeks, or a monoamine oxidase inhibitor, Abilify® (aripiprazole) or Prozac® (fluoxetine) within 2 weeks prior to baseline.

31. Subjects known by medical history or hospitalization records to have used phencyclidine within the 30 days prior to screening.

32. Subjects requiring treatment with drugs which have been consistently observed to prolong the QT interval (see Section 5.5).

33. Subjects with history of antipsychotic-induced EPS that does not respond to anti-parkinsonian medication.

34. Subjects with a prior episode of neuroleptic malignant syndrome or prior hypersensitivity to antipsychotic agents.

35. Subjects known to be allergic to ziprasidone.

36. Subjects with a history of non-responsiveness to ziprasidone after an adequate treatment period at a dose between 40-80 mg daily for subjects weighing <45 kg and 120-160 mg daily for subjects weighing ≥45 kg.

37. Subjects currently receiving ziprasidone 30 days prior to screening.

38. Participation in other studies involving investigational drug(s) (Phase 1-4) within 30 days before the current study begins and/or during study participation.

39. Pregnant females; breastfeeding females; males and females who are sexually active who are not using highly effective contraception or not agreeing to continue highly effective contraception for 28 days after last dose of assigned treatment.

40. Subjects that have had unprotected sex within the last 2 weeks prior to screening and do not have 2 negative pregnancy tests two weeks apart are not eligible to receive study drug.

41. Siblings, or other subjects living in the same home or having the same caregiver during the same enrollment period.

4.3. Randomization Criteria

At the baseline visit, subjects must continue to meet all inclusion and exclusion criteria in order to qualify for randomization.

4.4. Life Style Guidelines

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. Subjects who are not sexually active (are abstinent) will not be required to use contraception. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

To improve compliance with contraception, the investigator should, as permitted by local law, provide: (a) confidential contraception counseling and (b) assistance accessing additional reproductive services, if needed.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the subject remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).

4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy.

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the study manual and Study Team on Demand (SToD) system'.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Subjects will be assigned a single subject identification number which will be obtained at the time of screening using the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) and retained throughout the study. A separate randomization number will be assigned to subjects who meet the inclusion/exclusion criteria by the IVRS/IWRS at randomization and will be recorded on the case report form (CRF). Subjects will be centrally randomized to receive 1 of 2 treatment arms (ziprasidone or placebo) in a 1:1 ratio according to a computer generated pseudo-randomization code using the method of permuted blocks.

5.2. Breaking the Blind

The study will be subject, investigator, and sponsor blinded.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process utilizing the IVR/IWR system. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Study medication will be provided by Pfizer and will include oral ziprasidone capsules of 20 mg, 40 mg, 60 mg, and 80 mg strength or matching placebo capsules. All medication will be packaged in child resistant blister cards with columns for AM and PM capsules.

Two different types/designs of blister cards will be provided over the course of the study: a titration card design and a fixed dose card design. Each card will contain medication for 7 days plus 3 additional days. All child resistant blister cards will have 1 capsule available for the AM and 1 capsule for the PM administration of each day. Each AM or PM column will contain either a 20 mg, 40 mg, 60 mg or 80 mg ziprasidone capsule (or matching placebo).

Titration cards will be provided for the first week of treatment for subjects weighing ≥45 kg and those weighing <45 kg. Subjects weighing ≥45 kg will also receive a second titration card at Day 8/Visit 3 for the second week of treatment. Subjects weighing <45 kg will not receive a titration card at Day 8/Visit 3; instead they will receive a fixed dosing card which will allow them either to continue on their current dose or to change to a higher or lower dose, depending on the clinical judgment of the investigator.

Titration Card Container Types	
Active or Placebo (separate cards for Day 1/Visit 2 and Day 8/Visit 3)	≥45 kg body weight
Active or Placebo (for Day 1/Visit 2 only)	<45 kg body weight

In order to accommodate the flexible dosing permitted by the protocol, 7 types of fixed dosing cards, each with a different total daily dose of study drug, will be provided as illustrated below for both active and placebo capsules:

Fixed Dose Card Container Types		
Total Daily Dose	**AM Dose**	**PM Dose**
40 mg	20 mg	20 mg
60 mg	20 mg	40 mg
80 mg	40 mg	40 mg
100 mg	40 mg	60 mg
120 mg	60 mg	60 mg
140 mg	60 mg	80 mg
160 mg	80 mg	80 mg

5.3.2. Preparation and Dispensing

Study medication will first be dispensed at the baseline visit (Day 1) after all baseline assessments have been completed. Treatment assignments will be made in accordance with the randomization sequence. Every blister card supplied to the site will have a unique number. The site will select a weight-based dosing regimen within the IVR/IWR system, and the IVR/IWR system will assign a container number that contains the indicated regimen. The weight-based dosing regimen selected at the start of the trial will continue to be applied throughout the trial; weight fluctuations of the subjects will not be considered to reassign a subject to a different weight based dosing group (ie, ≥45 kg body weight or <45 kg body weight).

At each subsequent medication dispensing visit (Day 8/Visit 3, Day 15/Visit 4, and Day 22/Visit5), subjects will be assigned one blister card for the following study week. The IVR/IWR system will cap the total daily dosage allowed so subjects cannot be prescribed a dose higher than the maximum dose allowed per protocol (ie, subjects <45 kg cannot exceed 80 mg total daily dose and subjects ≥45 kg cannot exceed 160 mg total daily dose). The system will also not allow fixed dosing cards to be dispensed when there is an incremental jump of more than 20 mg/day compared to the last fixed dosing card dispensed (ie, a 120 mg/day fixed dose card could not be dispensed if the last fixed dose card dispensed

was an 80 mg/day card). The only exception to this rule is for subjects ≥45 kg where an increase from 120 mg/day to 160 mg/day will be allowed on Day 14 of the study. In addition, the IVR/IWR system will not allow more than one blister card at a time to be issued to a subject.

On Day 1 (Baseline Visit), a single titration card will be dispensed based on the subject's weight (subject ≥45 kg or <45 kg) for the first week of dosing (see Table 1 and Table 2 below). The titration cards that will be used for the first week of the trial will have a maximum of 80 mg/day for subjects ≥45 kg and a maximum of 60 mg/day for subjects <45 kg.

Table 1. ≥45 kg Titration Regimen for Day 1/Visit 2

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	-	20	20
2	20	20	40
3	20	20	40
4	20	40	60
5	20	40	60
6	40	40	80
7	40	40	80
8	40	40	80
9	40	40	80
10	40	40	80

Table 2. <45 kg Titration Regimen for Day 1/Visit 2

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	-	20	20
2	20	20	40
3	20	20	40
4	20	20	40
5	20	40	60
6	20	40	60
7	20	40	60
8	20	40	60
9	20	40	60
10	20	40	60

At Day 8/Visit 3, subjects weighing ≥45 kg would typically receive a second titration card (see Table 3 below) which will increase their total daily dose to 120 mg/day (reached on Day 10 of the study).

Table 3. ≥45 kg Titration Regimen for Day 8/Visit 3

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	40	60	100
2	40	60	100
3	60	60	120
4	60	60	120
5	60	60	120
6	60	60	120
7	60	60	120
8	60	60	120
9	60	60	120
10	60	60	120

However, the investigator can also choose to provide a fixed dose card with a different daily dose, eg, 100 mg/day or 80 mg/day (see Table 4 and Table 5 below), if in his or her clinical judgment that is the more appropriate choice.

Table 4. 100 mg Fixed Dose Regimen

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	40	60	100
2	40	60	100
3	40	60	100
4	40	60	100
5	40	60	100
6	40	60	100
7	40	60	100
8	40	60	100
9	40	60	100
10	40	60	100

Table 5. 80 mg Fixed Dose Regimen

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	40	40	80
2	40	40	80
3	40	40	80
4	40	40	80
5	40	40	80
6	40	40	80
7	40	40	80
8	40	40	80
9	40	40	80
10	40	40	80

Subjects weighing ≥45 kg should be provided the 160 mg/day fixed dose card (see Table 6) only if they have tolerated 120 mg/day; in addition, the 160 mg/day fixed dose card should not be issued before Day 14 of the study.

Table 6. 160 mg Fixed Dose Regimen

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	80	80	160
2	80	80	160
3	80	80	160
4	80	80	160
5	80	80	160
6	80	80	160
7	80	80	160
8	80	80	160
9	80	80	160
10	80	80	160

At Day 8/Visit 3 , subjects weighing <45 kg can either be maintained on their Day 7 dose (see Table 7) or the dose can be increased to 80 mg/day (see Table 5) or decreased to 40 mg/day (see Table 8). The investigator will decide which fixed dose blister card to provide to the subject for the following week, based on clinical judgment.

Table 7. 60 mg Fixed Dose Regimen

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	20	40	60
2	20	40	60
3	20	40	60
4	20	40	60
5	20	40	60
6	20	40	60
7	20	40	60
8	20	40	60
9	20	40	60
10	20	40	60

Table 8. 40 mg Fixed Dose Regimen

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	20	20	40
2	20	20	40
3	20	20	40
4	20	20	40
5	20	20	40
6	20	20	40
7	20	20	40
8	20	20	40
9	20	20	40
10	20	20	40

Only site personnel according to their role as determined on the site delegation log may dispense study medication cards. Subjects will be instructed to take one capsule in the AM and one capsule in the PM from each assigned blister card.

Subjects are not allowed to leave the clinic with more than one blister card in their possession.

5.3.3. Administration

As study drug administration is complex, the parent or guardian should closely supervise dosing throughout the study, especially during the titration period. One capsule is taken in the morning and one capsule in the evening about 12 hours apart. If a dose is missed, the missed dose should be taken as soon as possible, but the AM and PM doses should be separated by a minimum of 4 hours.

All study medication is to be taken with food. Capsules are to be taken intact. Swallow the capsule whole. Do not crush or chew the capsule.

In general, the target dose should be attained by Days 7-14. For subjects with a body weight ≥45 kg, the target dose range is 120-160 mg/day. A dose of 160 mg/day should not be achieved before Day 14 of treatment.

For subjects with a body weight <45 kg, the target dose range is 60-80 mg/day. A dose of 80 mg/day should not be achieved before Day 8 of treatment.

5.3.3.1. Baseline (Day 1)/Visit 2

At the baseline visit, after all baseline assessments have been completed, each randomized subject will receive one titration blister card for the first week of treatment, which will be assigned based on the subject's body weight (<45 kg or ≥45 kg). The body weight used to determine this assignment will continue to be applied throughout the trial; weight fluctuations of the subject will not be considered to reassign a subject to a different weight based dosing group. The investigator or a staff member will explain the titration card to each subject and his/her parent or guardian, and clearly specify that one capsule must be taken from the AM column with food and one capsule from the PM column with food, sequentially from each row (day) until the next study visit. (See Table 1 and Table 2 for the Day 1/Visit 2 titration blister cards). All subjects will take the first dose of study medication (20 mg or placebo) from the Day 1 row (PM column) in the afternoon or evening of the baseline visit. There will be no AM dose of study medication for Day 1. The subject's first AM dose will be on Day 2.

After the baseline visit, the investigator or designated staff must be in contact with the subject and/or his/her parent(s) and/or guardian(s) at least once during the week, either by telephone or in person, to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability, safety, and efficacy of the study drug.

Only the Principal Investigator (PI) or a designated medically trained sub-investigator can make modifications to the subject's study drug dose. If changes are necessary, an unscheduled visit is recommended so that the subject can be observed and so that changes to the study drug dose can be fully explained to the subject and to his/her parent(s) or guardian(s).

5.3.3.2. Day 8/Visit 3 (end of Week 1)

At Day 8/Visit 3, the investigator should review the clinical response of each subject and determine whether to continue the current study drug dose or to increase or decrease it.

Subjects weighing ≥45 kg should be issued the Day 8/Visit 3 titration card (see Table 3). However, the investigator can also choose to provide a fixed dose card with a different daily dose, eg, 100 mg/day or 80 mg/day (see tables Table 4 and Table 5), if in his or her clinical judgment that is the more appropriate choice.

Subjects weighing <45 kg should be issued a fixed dosing card with the desired total daily dose for the second week of double-blind therapy (ie, either 40 mg/day, 60 mg/day, or 80 mg/day; see Table 5, Table 7, or Table 8).

A dose of 160 mg/day for subjects with a body weight ≥45 kg should not be achieved before Day 14 of treatment, and a dose of 80 mg for subjects with a body weight <45 kg should not be achieved before Day 8 of treatment.

Following the Day 8/Visit 3 clinic visit, the investigator or designated staff must be in contact with the subject and/or his/her parent(s) and/or guardian(s) at least once during the week, either by telephone or in person, to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability, safety, and efficacy of the study drug.

5.3.3.3. Day 15/Visit 4 (end of Week 2)

At the Day 15/Visit 4 (end of Week 2) clinic visit, the investigator should review the clinical response of each subject and determine whether to continue the current study drug dose or in the event of tolerability or safety concerns, to make a downward dose adjustment. Subjects should be issued a single fixed dosing card with the desired total daily dose.

In general, the subject's dose should be kept stable during the remainder of the double-blind treatment period. If clinically necessary due to safety or tolerability concerns, however, downward dose adjustments can be made, in which case the subject should be seen at an unscheduled visit so that the subject can be observed and so that changes to the study drug dose can be fully explained to the subject and to his/her parent(s) or guardian(s).

5.3.3.4. Day 22/Visit 5 (end of Week 3)

At the Day 22/Visit 5 (end of Week 3) clinic visit, the investigator should review the clinical response of each subject and determine whether to continue the current study drug dose or, in the event of tolerability or safety concerns, to make a downward dose adjustment. Subjects should be issued a single fixed dosing card with the desired total daily dose.

5.3.3.5. Day 29/Visit 6 (end of Week 4)

At the Day 29/Visit 6 (end of Week 4) clinic visit, the investigator should review the clinical response of each subject and obtain the end of treatment assessments (see Section 6.4). The Day 29/Visit 6/end of Week 4 visit must be scheduled in the morning hours. Subjects should be instructed to come to the visit fasting, before taking their morning study medication dose, since subjects will be required to take their morning medication under supervision at the site.

5.3.3.6. Dose Reductions

If a subject with a body weight ≥45 kg cannot tolerate a dose of 120 –160 mg/day during the titration weeks, the investigator can reduce the dosage to 100 or 80 mg/day and the subject can remain in the study. Subjects who cannot tolerate a dose of 80 mg/day will discontinue from the double blind study and will not be eligible for continuation of treatment in the open-label extension study. If a subject weighing <45 kg cannot tolerate a dose of 60 mg/day during the Week 1 titration, the investigator can reduce the total daily dosage to 40 mg/day. Subjects who cannot tolerate a dose of 40 mg/day will discontinue from the double blind study and will not be eligible for continuation of treatment in the open-label extension study. In general, dose reductions should not exceed 40 mg/day unless a subject is experiencing adverse events necessitating a faster dose reduction.

Any time there is a post-titration period dose change, it is imperative that the date on which subjects begin taking a different dose is recorded. Only the PI or a designated medically trained sub-investigator can make modifications to the subject's dose. If changes are necessary, unscheduled visits are recommended to be scheduled so that the subject can be observed and so that changes to the dosing plan can be fully explained to the subject and to his/her parent(s) or guardian(s).

5.3.4. Compliance

The investigator must maintain a complete and current dispensing and inventory record that has been supplied by the sponsor.

Study personnel at the site should monitor compliance at each study visit according to the Schedule of Activities by comparing the returned study drug contained within the blister cards keeping in mind the prescribed dose with the dose information reported by the subject on the diary card. Discrepancies between returned capsule counts from the blister cards and subject-reported dose information on the subject diary cards should be reconciled with the subject and/or legal guardian during the office visit. Compliance and any unresolved discrepancies will be documented in the source documents and on the Investigational Product Accountability Log. The study drug CRF page should reflect the reconciled dose information provided by the subject and/or legal guardian.

In addition, photocopies should be made of both sides of the returned blister cards. The photocopies should be dated and signed and kept as part of the source documentation.

The subject diary cards and the photocopies of the blister cards will serve as the source documentation of what medication was taken as the actual blister cards will eventually be destroyed according to drug accountability procedures (see Section 5.4). Information from the subject diary card will be included on the study drug CRF page.

A subject will be considered non-compliant with respect to dosing if the subject misses more than 20% of their scheduled doses over the entire study. Such a condition will be considered a protocol violation and the subject will be excluded from the per protocol (PP) analysis set.

5.4. Drug Storage and Drug Accountability

Upon receipt of the investigational product shipment, the investigator or an appropriate site representative (eg, pharmacist/dispenser) will verify the condition of the study supplies and document per instructions in the pharmacy binder.

The investigator or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Investigational product is to be stored at 15-25°C (59-77°F). Specific details on storage requirements can be found in the pharmacy binder.

Drug should be stored in accordance with the drug label.

Storage conditions stated in the Single Reference Safety Document (SRSD) (ie, Investigator Brochure (IB), Core Data Sheet (CDS), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD)) will be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Investigational product use will be accounted for in the CRF and drug accountability inventory forms as instructed by Pfizer. All drug supplies will be returned to Pfizer or its agent or destroyed on site according to site specific procedures.

5.5. Concomitant Medication(s)

The start and stop date, if applicable, for all concomitant medications received for the disease under study within 1 year before screening and for all other concomitant medications within 90 days before screening until the last scheduled visit will be recorded on the appropriate CRF.

Subject must be willing and able to discontinue any medications that are prohibited in this study (see table below). Any such medications must be discontinued according to the timelines in the table prior to the administration of study medication. Exclusionary medications may have to be tapered instead of being abruptly discontinued if appropriate, in accordance with accepted medical practice.

Lorazepam (oral or intramuscular) may be used pro re nata (PRN) for anxiety or agitation up to a maximum of 2 mg/day but should not be given within 6 hours prior to an efficacy assessment. If possible, the investigator should start with a low dose of lorazepam to control a subject's symptoms, and then increase incrementally up to a total of 2 mg/day, if needed. A comparable benzodiazepine may be used in place of lorazepam with prior permission from Pfizer. The dose administered should be therapeutically comparable to that for lorazepam.

For the treatment of insomnia, lorazepam may be used as specified above, or alternatively, diphenhydramine or zolpidem, as determined by the principal investigator, are permitted on a PRN basis, but should not be given within 6 hours prior to efficacy assessments being performed.

For the treatment of extrapyramidal symptoms that may appear during the trial, benztropine, benzhexol, other anticholinergics, or propranolol may be used based on the discretion of the principal investigator.

Subjects should be instructed not to take any medications, including over-the-counter products, without first consulting the investigator, unless such medications are for emergency use.

The chronic use of certain medications (some hormones, antihypertensives, diuretics, and oral hypoglycemics) are allowed if the subject was prescribed these medications at least 30 days prior to screening, the subject's condition is stable, and the dose is stabilized prior to the first dose of study medication.

Any questions about whether use of a concomitant medication or treatment is prohibited or permitted during a subject's study participation should be discussed with the sponsor. The table below is not all inclusive so contact the sponsor with questions.

Prohibited/Concomitant Medication Table

The following agents are <u>prohibited</u> during the trial and must be discontinued at least 4 ½ half lives (or 10 days, whichever is less) before baseline:
• Antipsychotic agents (see aripiprazole exception below).
• Mood stabilizers (ie, lithium and anticonvulsants, such as lamotrigine and depakote).
• Stimulants (including but not limited to: amphetamines, dexmethylphenidates, dextroamphetamines, lisdexamfetamine dimesylates, methamphetamines, and methylphenidates).
• Antidepressants (see monoamine oxidase (MAO) inhibitors, or fluoxetine exception below).
• Anxiolytics (benzodiazepines and nonbenzodiazepines except those permitted per protocol).
• Sedative/hypnotics (except those permitted per protocol).
• Nootropics (such as hopantenic acid, nikethamide, pyracetam, phenylpyracetam).
• Supplements/herbal agents with CNS effect (ie, Gamma-aminobutyric acid (GABA), glycine, dehydroepiandrosterone (DHEA), St. John's Wort). • Biotin (dose exceeding 100mcg daily) Children multivitamin levels allowed.
• Sympathomimetics (except those permitted per protocol).
• Antiemetics (dopamine antagonists such as prochloperazine and metoclopramide).
• Propranolol as an antihypertensive, reserpine, clonidine, and methyldopa.

• Any medications that have been consistently observed to prolong the QT interval, including:
  • The antiarrhythmic agents: dofetilide (Tikosyn®), sotalol (Betapace®), quinidine (Quinaglute®), Class 1A and III antiarrhythmics;
  • The antipsychotics: mesoridazine (Serentil®), thioridazine (Mellaril®), chlorpromazine (Thorazine®), droperidol (Inapsine®), pimozide (Orap®);
  • The anti-infectives: sparfloxacin (Zagam®), gatifloxacin (Tequin®), moxifloxacin (Avelox®), pentamidine (Pentam®);
  • The anti-malarials: halofantrine (Halfan®); mefloquine (Lariam®), arsenic trioxide (Trisenox™), levomethadyl acetate (Orlaam®), dolasetron mesylate (Anzemet®), probucol (Lorelco®-an antilipemic), tacrolimus (FK 506, Prograf®).

• Recreational drugs.
The following medications are cited in the exclusion criteria section as being prohibited and/or the medications must be discontinued for a longer length of time before baseline:
• Past or present use of clozapine. • Depot antipsychotic within 4 weeks prior to baseline. • Monoamine oxidase inhibitors within 2 weeks prior to baseline. • Abilify® (aripiprazole) within 2 weeks prior to baseline. • Prozac® (fluoxetine) within 2 weeks prior to baseline. • Phencyclidine within 30 days prior to screening. • Commercially available ziprasidone use 30 days prior to screening.
The following types of medications are allowed if taken at least 30 days before screening, the subject's condition is stable, and the dose is stabilized before the first dose of study medication:
• Antihypertensives.
• Antianginal agents.
• Antiarrhythmics (except QTc prolonging).

• Anticoagulants.
• Steroids.
• Theophylline.
• Replacement hormones.
• Oral hypoglycemic.
The following medications are allowed:
• For anxiety or agitation, lorazepam up to 2 mg/day may be used as detailed in the protocol.
• For insomnia, lorazepam, diphenhydramine or zolpidem may be used as detailed in the protocol.
• For the treatment of extrapyramidal symptoms, benztropine, benzhexol, other anticholinergics or propranolol as detailed in the protocol.
• Aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen for mild to moderate pain relief.
• Loratadine, desloratidine, fexofenadine or cetirizine for allergies.
• Common cold preparations are permitted on a PRN basis. Subjects should not take these medications within 6 hours before any visit.
• Laxatives (occasional use).
• Antacids (at least 4 hours before or after study drug administration).
• PRN use or topical or inhaled steroids.

6. STUDY PROCEDURES

The subject and the legal representative must understand the nature of the study and be able to comply with protocol requirements. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's legal representative and a written assent from the subject before any trial specific activity is performed. Subjects who turn 18 years old during the study need to give a written consent unless State law states otherwise, and such State law shall apply.

The subject should be assigned a subject number from the IVR/IWR system after obtaining informed consent. AEs must be recorded from the time that the informed consent is signed.

Every effort should be made to bring the subject back to the office on the designated study days; however, office visits will have a ±3 day visit window to allow for slight variations in subject schedules unless approved on an individual subject basis by the sponsor. When scheduling subsequent visits, the overall treatment period in the protocol should be maintained.

6.1. Screening

Screening procedures are to be performed within 14 days of the baseline visit (Visit 2), unless approved on an individual subject basis by the sponsor. Screening procedures may be completed over 1 or multiple days based on the needs of the site and/or the subject/parent/guardian.

The following information/assessments will be collected/performed during the screening period:

- Subject demography (including date of birth, gender, and race).
- Determine diagnostic eligibility with clinical interview/confirm diagnosis using the K-SADS/prepare diagnostic narrative for external review.

  Determination of a Bipolar I Disorder (current or most recent episode manic) diagnosis will be based on a clinical interview conducted by a child and adolescent psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training) and confirmed by administration of the K-SADS. The K-SADS must be administered by a child and adolescent psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training) who may be the PI or sub-PI or by a PsyD- or PhD-level clinical psychologist trained in child development. See Section 7.4.

  Diagnostic assessments will also be reviewed by an external member of an expert panel. A brief narrative describing the symptoms of the subject which support the diagnosis will be submitted to external experts for verification before the investigator is allowed to randomize the subject composed by the child and adolescent psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training) at the site.

  If the subject meets the DSM-V criteria for Bipolar I Disorder (current or most recent episode manic), the investigator, taking into account the welfare of the subject, will establish whether the subject is willing and/or able to wash-out any exclusionary medications.

- Medical and psychiatric history of subject and family history. Presence of chronic conditions and/or medical history of significance including relevant surgical procedures, including start date will be collected. For conditions identified at screening, the investigator must use medical judgment to determine whether to record the condition as a medical history finding or as an AE. Medical history conditions that worsen after the informed consent is signed are considered AEs.
- Efficacy assessments: YMRS, CGI-S, and CCI See Section 7.3.
- Full physical examination, including body temperature. See Section 7.2.3.
- Height, weight, BMI, BMI z-score, and waist circumference. See Section 7.2.4.
- 12-lead ECG. See Section 7.2.6.
- Blood pressure and pulse. See Section 7.2.5.
- Child Depression Rating Scale – Revised (CDRS-R). See Section 7.2.7.

- Columbia-Suicide Severity Rating Scale (C-SSRS); see Section 7.2.9.

- Laboratory evaluations. Obtain blood and urine samples for blood chemistry, hematology, urinalysis, hormones (free T4 & thyroid-stimulating hormone (TSH), prolactin), and hepatitis serology. See Section 7.2.1.

- Fasting blood samples for glucose, lipid profile, insulin, glycosylated hemoglobin (HbA1c). See Section 7.2.1.

- Urine sample for urine drug screen. See Section 7.2.2.

- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive. (Both the urine and serum pregnancy tests must have a sensitivity for detection of human chorionic gonadotophin (hCG) of at least 25 mIU/mL). In addition, if a subject is not sure whether they might be pregnant at the time of screening, ie, they have had unprotected sex within the last 2 weeks prior to screening, then that subject would be required to have 2 negative pregnancy tests two weeks apart before they could receive study drug. See Section 7.1.

- Prior and concomitant medications.

- Assess and record any reported AEs.

6.1.1. Screen Fail Subject

Screen failure subjects are defined as:

- A subject who does not meet one or more inclusion criteria or meets one or more exclusion criteria will be considered a screen failure.

- If a subject cannot return for the baseline visit within the protocol specified screening period, the subject will be considered a screen failure.

Screen failure subjects may re-screen at a later date. If a subject chooses to re-screen, a second informed consent/assent must be obtained and documented, a new subject number must be assigned, and all screening tests and procedures must be repeated. A subject may not re-screen more than once.

6.2. Visit 2 (Day 1) - Baseline

The baseline visit will occur 1-14 days after the screening visit, allowing time for wash-out of any antipsychotics and/or exclusionary medications and for laboratory results to be received and repeated, if necessary, to confirm eligibility. The following information/assessments will be collected /performed during the baseline visit:

- Confirm all inclusion/exclusion criteria are met.

- 12-lead triplicate ECG. See Section 7.2.6.

- Blood pressure and pulse. See Section 7.2.5.
- Laboratory evaluations only if clinically significant abnormalities are present at screening. Obtain blood and urine samples for blood chemistry, hematology, urinalysis, and hormones (free T4, TSH, and prolactin). See Section 7.2.1.
- Fasting blood samples for glucose, lipid profile, insulin, HbA1c only if clinically significant abnormalities are present at screening. See Section 7.2.1.
- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive. A negative pregnancy test is required (at both the screening and baseline visits) before the subject may receive investigational product. See Section 7.1.
- Urine sample for urine drug screen; see Section 7.2.2.
- Efficacy assessments: YMRS, CGI-S, and CCI See Section 7.3.
- CDRS-R. See Section 7.2.7.
- C-SSRS. See Section 7.2.9.
- Movement disorder scales: SARS, BAS, and AIMS. See Section 7.2.8.
- Record concomitant medications.
- Assess and record any reported AEs.
- Randomization.
- Dispense study drug. Subjects will receive their first capsule in the afternoon/evening (with food) from the blister card PM column for Day 1.
- Contact should be made with the subject by the investigator or designated staff member, either by telephone or in person as an unscheduled visit, after the baseline visit but before Visit 3 to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability, safety, and efficacy of the study drug.

6.3. Treatment Period

See the Schedule of Activities for procedures to be performed at each study visit during the treatment period.

6.3.1. Visit 3 (Day 8/Week 1)

- 12-lead ECG. See Section 7.2.6.
- Blood pressure and pulse. See Section 7.2.5.

- Laboratory evaluations. Obtain blood and urine samples for blood chemistry, hematology, and urinalysis and in females a pregnancy test. See Section 7.2.1.
- Efficacy assessments: YMRS, CGI-S, and Clinical Global Improvement Scale (CGI-I). See Section 7.3.
- CDRS-R. See Section 7.2.7.
- C-SSRS. See Section 7.2.9.
- Movement disorder scales: SARS, BAS, and AIMS. See Section 7.2.8.
- Record concomitant medications.
- Assess and record any reported AEs.
- Perform drug accountability.
- Dispense study drug.
- Contact should be made with the subject by the investigator or designated staff member, either by telephone or in person as an unscheduled visit, after Visit 3 but before Visit 4 to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability, safety, and efficacy of the study drug.

6.3.2. Visit 4 (Day 15/end of Week 2)

- 12-lead ECG. See Section 7.2.6.
- Blood pressure and pulse. See Section 7.2.5.
- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive. See Section 7.1.
- Efficacy assessments: YMRS, CGI-S, and CGI-I. See Section 7.3.
- CDRS-R. See Section 7.2.7.
- C-SSRS. See Section 7.2.9.
- Movement disorder scales: SARS, BAS, and AIMS. See Section 7.2.8.
- Record concomitant medications.
- Assess and record any reported AEs.
- Perform drug accountability.

- Dispense study drug.

6.3.3. Visit 5 (Day 22/end of Week 3)

- 12-lead ECG. See Section 7.2.6.
- Blood pressure and pulse. See Section 7.2.5.
- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive.
- Efficacy assessments: YMRS, CGI-S, and CGI-I. See Section 7.3.
- CDRS-R. See Section 7.2.7.
- C-SSRS. See Section 7.2.9.
- Movement disorder scales: SARS, BAS, and AIMS. See Section 7.2.8.
- Record concomitant medications.
- Assess and record any reported AEs.
- Perform drug accountability.
- Dispense study drug.

6.4. Visit 6 (Day 29/end of Week 4) - End of Treatment (or Early Termination)

The Week 4 visit must be scheduled in the morning hours. Subjects should be instructed to come to the visit fasting, before taking their morning study medication dose, since subjects will be required to take their morning medication under supervision at the site.

- 12-lead triplicate ECG recording, blood pressure and pulse, CCI [redacted] and study medication administration:

  Prior to study medication dosing, all subjects will have a triplicate 12-lead ECG followed by blood pressure and pulse measurements (see below table for timing of procedures).

Event	Time before/after dosing (hours)
Pre-dose	
Triplicate 12-lead ECG*	<-0.1 hours
Blood pressure/pulse	<-0.1 hours
CCI [redacted]	CCI [redacted]

* Triplicate 12-lead ECG taken before blood pressure and pulse.

CCI [redacted]

After the pre-dose ECG and blood pressure/pulse, subjects will have a CCI [redacted] Fasting blood samples for laboratory testing CCI [redacted] drawn. **It is critical that the actual clock time of the Day 28 PM (the evening prior to the Week 4 clinic visit) dose administration CCI [redacted] accurately recorded.**

Subjects will then take breakfast and their morning dose of study medication. One of the extra days (Days 8, 9, and 10) capsules from the week 4 blister card will be used for the dose of study drug provided as the AM dose on Day 29. The weekly assessments (scales, physical exam, height, weight, BMI) can be done at this time.

- Full physical examination, including body temperature. See Section 7.2.3.
- Height and weight, BMI, BMI z-score, waist circumference. See Section 7.2.4.
- Laboratory evaluations. Obtain blood and urine samples for blood chemistry, hematology, urinalysis, and hormones (free T4, TSH, and prolactin). See Section 7.2.1.
- Fasting blood samples for glucose, lipid profile, insulin, and HbA1c. See Section 7.2.1.
- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive. If a subject is not sure whether they might be pregnant at the time of screening, ie, they have had unprotected sex within the last 2 weeks prior to screening, then that subject would be required to have 2 negative pregnancy tests two weeks apart before they could receive study drug. See Section 7.1.
- Urine sample for urine drug screen. See Section 7.2.2.
- Efficacy assessments: YMRS, CGI-S, CGI-I, and CCI [redacted] See Section 7.3.
- CDRS-R. See Section 7.2.7.
- C-SSRS. See Section 7.2.9.
- Movement disorder scales: SARS, BAS, and AIMS. See Section 7.2.8.
- Record concomitant medications.
- Assess and record any reported AEs.
- Perform drug accountability.

In the case of early termination, all procedures specific for Visit 6 (Week 4) are to be completed.

6.5. Visit 7, Follow-up Visit (Day 36/end of Week 5)

Subjects will return for a post-treatment follow-up clinic visit at Week 5, if they are not entering the open-label extension Study A1281201. The following procedures/assessments will be performed at week 5:

- C-SSRS. See Section 7.2.9.
- Record concomitant medications.
- Assess and record any reported AEs.
- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive.

Only if clinically significant abnormalities are present at Visit 6 Week 4, the following will be performed:

- Laboratory evaluations. Obtain blood and urine samples for blood chemistry, hematology, urinalysis, and hormones (free T4, TSH, and prolactin). See Section 7.2.1.
- Fasting blood samples for glucose, lipid profile, insulin, and HbA1c. See Section 7.2.1.
- Blood pressure and pulse. See Section 7.2.5.
- 12-lead ECG. See Section 7.2.6.
- Movement disorder scales (SARS, BAS and AIMS). See Section 7.2.8.

After the Visit 6/Week 4 visit subjects may enter the open label extension study or be switched to one of the alternative approved therapies for treatment of pediatric bipolar disorder within your country (for the U.S. including lithium, Abilify®, Risperdal®, Zyprexa®, and Seroquel®) if in the judgment of the investigator or treating physician, continued pharmacotherapy is warranted.

Contact may occur via telephone and must occur 28 to 35 days from administration of the final dose of investigational product to capture any potential adverse events (see the Adverse Events Information section) and to confirm appropriate contraception usage (see the Life Style Guidelines section) for subjects who do not enter the open label extension study.

Based on accumulated safety data from the pre-marketing clinical trials with ziprasidone, short term treatment with ziprasidone does not appear to be associated with a marked withdrawal syndrome and it should be feasible and well tolerated to immediately switch the subjects from ziprasidone treatment to an alternative treatment. Following the last dose of study drug, ziprasidone plasma concentrations should self-taper over 2 to 3 days, during

which time the alternative medication can be titrated up to ensure that treatment of the subject is not interrupted.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or to follow-up on adverse events at the subject's request or as deemed necessary by the investigator.

6.7. Subject Withdrawal

The investigator is responsible for the clinical management of the subject throughout his or her participation in the study. A subject should be discontinued from the study if, based on the investigator's clinical judgment, it is no longer in the subject's interest to continue. If a subject is discontinued, the investigator will ensure that the subject receives appropriate clinical care and follow-up. Subjects who are discontinued from the study may be eligible to participate in a post study care program (see Section 3.1).

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. The investigator must determine the primary reason for discontinuation. If a discontinuation is due to a serious adverse event, the serious adverse event must be reported immediately to Pfizer. Withdrawal due to an adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted in Section 8.

Because of the placebo control being used in this trial, it is important to provide guidelines to investigators who, during the study, may need to determine whether a subject should be removed from the study as a result of insufficient clinical response (or due to safety considerations arising from it) or whether that subject would benefit from alternative therapies. These guidelines are summarized in the table below in Section 6.7.1. The table also identifies those adverse events that require special action.

An end of treatment visit must be scheduled for any subject who discontinues early from the study. At this visit, all assessments scheduled for the Week 4 visit should be performed. The investigator will record the reason for study discontinuation in the eCRF, provide or arrange for appropriate follow-up (if required), and document the course of the subject's condition.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Efforts to contact the subject should be fully documented in the subject's record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who were randomly assigned and withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

6.7.1. Specific Withdrawal Criteria

Specific adverse events and dosing response events, as shown in the table below, mandate withdrawal from this study.

Event	Criteria
Syncope	All syncopal episodes suggestive of cardiac arrhythmia (sudden loss of consciousness, loss of postural tone, and no pre-syncopal phase), except vasovagal syncope will be considered adverse events and the subject will be discontinued from the study. Every effort should be made to obtain vital signs and an electrocardiogram at the time of the event. Further evaluation, eg, Holter monitoring, may also be useful. Subjects experiencing syncope of probable vasovagal origin (onset not sudden but preceded by a pre-syncopal phase, presence of predisposing factors such as blood sampling procedure, standing, hot shower, hair curling, etc) will also be considered adverse events but subjects may continue study participation after sponsor approval.
Prolonged QT	Electrocardiograms are to be reviewed and compared to baseline to assess potential changes. ECGs showing a QTcF of ≥480 msec or a suspected increase from baseline of 60 msec or greater must be repeated within the same visit. If the QTcF value persists at ≥480 msec and/or the change from baseline persists at ≥60 msec, the study drug must be discontinued immediately and a pediatric cardiologist or an adult cardiologist experienced in the interpretation of pediatric ECGs should be contacted to discuss the ECG result. A verified increase in QTcF of ≥60 msec or a verified occurrence of QTcF ≥480 msec will be considered as an adverse event of QTc prolongation. QTcB prolongation (Bazett's correction) will not be used to define adverse events; QTcB will be measured only to enable historical comparisons.
Ventricular arrhythmia	An ECG showing ventricular arrhythmia (except single ventricular extrasystoles) should be followed up with a rhythm strip ECG and Pfizer must be notified. In addition, a stat over read from the central vendor should be requested, a pediatric cardiologist or adult cardiologist experienced in the diagnosis and treatment of pediatric arrhythmias should be consulted, and the subject monitored, as necessary. If the ventricular arrhythmia is confirmed, the subject must be discontinued from the study.

Event	Criteria
Imminent Risk of suicide	It is expected that investigators will be assessing the risk of suicidality with every subject at every visit. A subject must be discontinued from the trial due to imminent risk of suicide and appropriate actions should be undertaken whenever: (1) A subject is judged by the investigator as being at imminent risk of suicide at any time during the study, or (2) A subject has answered "yes" on items 4 or 5 of the suicidal ideation subscale of the C-SSRS or any behavioral questions on the C-SSRS on more than one occasion (ie, subject had a positive response on the C-SSRS, underwent a risk assessment and was allowed to continue on study, but then had a second positive response on the C-SSRS at a later visit).
Pregnancy	If a pregnancy occurs during the course of this trial, ziprasidone must be discontinued and the subject will not be eligible for the open-label study. *Study drug must be discontinued as soon as pregnancy is suspected or a positive urine pregnancy test is reported. The subject must be discontinued from the trial if the pregnancy is confirmed via a positive serum pregnancy test.*
Minimum Total Daily dose	Subjects with body weight <45 kg with who cannot tolerate a dose of 40 mg/day or greater. Subjects with body weight ≥45 kg who cannot tolerate a dose of 80 mg/day or greater.
Insufficient clinical response	Subjects who have insufficient treatment response and have reached their maximum allowed or maximum tolerated dose should be discontinued from the study and should return for a follow-up clinic visit as soon as possible. The procedures listed at Visit 6/Week 4 according to the Schedule of Activities should be followed.
Rescue Medications Open Label Study	Subject requiring concomitant treatment with mood stabilizers, antidepressants, or stimulants. Subjects who have insufficient treatment response at 1 week after the end of their titration, despite having reached their maximum tolerated dose should discontinue from the study and may enroll in the open-label extension trial.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pregnancy Testing

For female subjects, a urine dipstick pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at all visits as specified in the Schedule of Activities. If the urine dipstick test is positive, a serum pregnancy test should also be performed. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and at the end of the study to confirm the subject has not become pregnant during the study. In the case of a positive hCG test, the subject will be withdrawn from study medication but may remain in the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

In addition, if a subject is not sure whether they might be pregnant at the time of screening, ie, they have had unprotected sex within the last 2 weeks prior to screening, then that subject would be required to have 2 negative pregnancy tests two weeks apart before they could receive study drug.

7.2. Safety Assessments

7.2.1. Laboratory Assessments

A central laboratory will be used for all clinical laboratory determinations unless a special test is required or a special circumstance is encountered such that timely results from a central laboratory are not possible. In both these cases, an additional clinical laboratory may be designated by the investigator. The investigator or other appropriate staff member should notify the sponsor that a local clinical laboratory is being used. Laboratory certification and laboratory normal range documentation must be provided to the sponsor for all laboratories used other than the central laboratory.

Sample collection, storage, and shipping information can be found in the laboratory manual.

No routine laboratory assessments will be performed at Week 5 (for those subjects who complete the study but do not enter the extension study) except redraws for laboratory abnormalities present at Week 4 and urine pregnancy tests in female subjects. The laboratory determinations listed below will be obtained according to the visit schedule listed in the Schedule of Activities:

Blood Chemistry

- Sodium;
- Potassium;
- Calcium;
- Chloride;
- Glucose (fasting);*

- Bicarbonate or carbon dioxide;
- Blood urea nitrogen or Urea;
- Creatinine;
- Creatine phosphokinase (CPK);
- Phosphorus;
- Magnesium;
- Uric acid;
- Bilirubin, total;
- Bilirubin, direct;
- Bilirubin, indirect;
- Total protein;
- Albumin;
- Aspartate aminotransferase (AST);
- Alanine aminotransferase (ALT);
- lactate dehydrogenase (LDH);
- Gamma-glutamyl transpeptidase (γGT);
- Alkaline phosphatase.

Hematology

- Hemoglobin;
- Hematocrit;
- Red blood cell count;
- White blood cell count with differential [% and absolute];
- Platelet count.

Urinalysis (Routine)

- Specific gravity;

- pH;
- Dipstick Protein, qualitative;
- Glucose/sugar, qualitative;
- Ketones/acetone, qualitative;
- Hemoglobin/blood, qualitative;
- Microscopic if blood or protein results are trace, +1, +2, +3, or +4.

Hormones

- Free T4;
- TSH;
- Prolactin.

Lipid Profile

- Triglycerides (fasting);*
- Total cholesterol (fasting);*
- High-density lipoprotein and low-density lipoprotein cholesterol (fasting);*
- Insulin (fasting);*
- HbA1c (fasting);*
- Hepatitis serology.

*Subjects should remain fasting for at least 8 hours prior to these lab samples (glucose, lipid profile, insulin and HbA1c) being drawn.

Urine Pregnancy Test

- For female subjects, a urine pregnancy test should be performed at all study visits, followed by a serum pregnancy test if the urine test is positive.

Out-of-range values will be interpreted by the investigator with a comment of "not clinically significant" (NCS) or "clinically significant" (CS) on the final laboratory reports. All laboratory tests with values that become abnormal to a clinically significant degree after investigational product administration must be repeated and the investigator must continue to follow-up as medically indicated until values have returned to baseline or until the condition stabilizes. If laboratory values do not return to normal or baseline within a reasonable period, the etiology must be identified and the sponsor notified. All clinically significant laboratory tests will be recorded on the AE CRF.

7.2.1.1. Total Volume of Blood Collected

The total volume of blood collected from each subject over the entire duration of the study will be approximately 70 mL.

7.2.2. Urine Drug Screen

A urine drug screen (UDS) will be obtained according to the visit schedule listed in the Schedule of Activities. In addition to the scheduled tests, a UDS may also be administered at any other visit that the investigator deems necessary.

Subjects with a positive test result for amphetamines, barbiturates, benzodiazepines, cannabinoids, opiates, and propoxyphene, at the discretion of the investigator and after discussion with the sponsor, may be eligible for admission if there is an acceptable medical explanation for the subject's positive test result (ie, prior legitimate prescription of a benzodiazepine for anxiety or opiate for pain) or evidence of isolated abuse rather than a pattern of established drug use.

A positive urine drug screen after randomization should be discussed between the investigator and the sponsor as to the potential impact and continued participation of the subject in the study.

The following analytes will be tested:

- Amphetamines;
- Barbiturates;
- Benzodiazepines;
- Cannabinoids;
- Cocaine;
- Methadone;
- Methaqualone;
- Opiates;
- Phencyclidine;
- Propoxyphene.

7.2.3. Full Physical Examination

A full physical examination including oral/tympanic body temperature (°C) will be conducted according to the Schedule of Activities. The full physical examination will evaluate clinically important abnormalities within a body system (eg, general appearance, skin, head/ears/eyes/nose/throat, heart, lungs, breasts (if medically indicated), abdomen, external genitalia (if medically indicated), extremities, back/spinal system, lymph nodes) or worsening of medical history conditions.

Clinically important physical examination abnormalities detected at the screening visit should be noted on source documents and the medical history. Thereafter, any new clinically important abnormalities or worsening of conditions noted at the screening visit must be recorded on source documents and recorded on the AE record as appropriate.

7.2.4. Body Weight, Height, BMI, BMI z-score, and Waist Circumference

Body weight (lbs/kg), height (inches/cm) and waist circumference (inches or cm) will be measured according to the Schedule of Activities. All measurements should be taken with the subject wearing only light indoor clothing and without shoes. Height will be measured with a stadiometer; weight will be measured with a standard physician's scale. Body Mass Index (BMI) and BMI z-score will be calculated from height and weight. At screening, BMI z-score is used to determine eligibility.

BMI z-scores will be used to evaluate changes in body weight. An increase in the BMI z-score (adjusted for age) of 1 or more is to be documented as an adverse event. All BMI and BMI z-scores are to be recorded in the source documents.

7.2.5. Blood Pressure/Pulse (Sitting and Standing)

Blood pressure (mm Hg) should be measured using a manual aneroid or mercury sphygmomanometer with a cuff appropriate to the subject's arm girth placed over the bare skin. Subjects should rest sitting with feet flat on the floor at least 5 minutes before sitting blood pressure readings are taken. The sitting pulse rate (beats/minute) should be measured after the blood pressure. Pulse rate should be measured for at least 30 seconds.

After standing for approximately 2 minutes, another blood pressure reading will be taken followed by a standing pulse reading.

Whenever possible, the subject should refrain from products containing nicotine or caffeine 2 hours before taking blood pressure measurements. Also, whenever possible, blood pressure measurements should be taken on the same arm throughout the study.

Blood pressure and pulse will be measured according to the Schedule of Activities. At Visit 6/Week 4, subjects will take their morning study medication during the visit. Blood pressure and pulse will be measured before study medication dosing (trough).

7.2.6. 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be conducted at various time points according to the Schedule of Activities.

Readings and interpretations of ECG tracings will be performed centrally. Information to be reported by the central scoring site will include the subject's demographic information; beats per minute (bpm); overall interpretation; rhythm type; respiratory rate; heart rate intervals PR, QRS, QT, QTcF (ms), and QTcB (ms); and any comments. The values of QTcF will be used for clinical decision making and interpretative assessment of changes in QTc. QTcB will be measured to enable comparisons with historical data but not used for clinical decisions due to inaccuracies of the Bazett's formula in correcting for heart rate.

All ECGs must be obtained before or at least 3 hours after food intake. ECGs must be obtained **prior to blood pressure/pulse measurements and prior to collection of any blood sample** CCI because these assessments can affect the ECG. To standardize the collection procedure, the ECG should be collected in a comfortable and quiet place after the subject has been allowed to rest in a supine position for approximately 5 minutes.

Baseline and Visit 6 (end of treatment/early termination) ECGs must be administered in triplicate, tracings should be collected approximately 2 minutes apart.

At the Day 29/Week 4 visit, subjects will take their morning medication with food at the visit. An ECG will be done before dosing.

All ECGs must be reviewed for safety (including a review of the QTcF value) at the site by a physician within a reasonable time from the day of the recording [48 hours is recommended], signed and dated by the reviewing physician and retained in the subject's study records.

Participation in the study is contingent on the subject having both screening and baseline ECGs without clinically significant abnormalities.

ECGs showing a QTcF of ≥480 msec or a suspected increase of QTcF from baseline of 60 msec or greater must be repeated within the same visit. If the QTcF value persists at ≥480 msec and/or the change from baseline persists at ≥60 msec, the study drug must be discontinued immediately and a pediatric cardiologist or an adult cardiologist experienced in the interpretation of pediatric ECGs should be contacted to discuss the ECG result (see Section 6.7.1).

If discontinued, the subject will not be eligible to enter the open-label extension trial.

7.2.7. Child Depression Rating Scale – Revised (CDRS-R)

The Child Depression Rating Scale – Revised[17] (CDRS-R) is a clinician-rated scale that assesses 17 distinct symptom areas to derive an index of depression severity. Though originally developed for children 6-12 yrs, it has been widely used with adolescents and its developers recommend it for both children and adolescents.[18] Clinicians' ratings are based on information obtained from interviews with both child and parent (or guardian) informants;

interview guides have been developed to structure the interview to ensure all 17 symptom areas are assessed. For this trial, the manual's recommendations on resolving discrepancies between informants will be used (ie, most impaired rating given by valid informant will be assigned). It takes about 20-30 min to administer and rate the CDRS-R. Ratings are assigned on a 7-point scale (ranging from 1-7, with higher values indicating greater impairment). A total scale score is calculated by summing the 17 items. The total score on the CDRS-R will be used to assess changes in depression severity over time between treatment groups.

7.2.8. Movement Disorder Scales

The following scales will be used to assess symptoms and findings related to Parkinsonism, akathisia, and abnormal involuntary movements. Investigators will be instructed to record movement disorders as adverse events (AEs) only if they are clinically meaningful. Specifically, investigators will be asked to record the disorder as an adverse event only if (1) clinically meaningful movement disorder side effects are observed or are volunteered by the subject, (2) a clinically meaningful movement disorder is present at baseline and increases in severity, or (3) concomitant therapy (benztropine, benzhexol, or other anticholinergics or propranolol) is initiated or reinstated for movement disorders while the subject is participating in the study. All dystonic movements are to be recorded as AEs unless present at the same severity at baseline.

7.2.8.1. Simpson-Angus Rating Scale (SARS)

The Simpson-Angus Rating Scale[19] (SARS) will be administered to assess parkinsonian symptoms and related extrapyramidal side effects through observation of the subject. The scale contains 10 items, including gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, glabellar tap, tremor, and salivation. The head rotation item (from the modified Simpson-Angus Rating Scale) will be substituted for the original #7 item, head dropping**.** Seven of the ten items measure parkinsonian rigidity. Each item is rated on an anchored 5-point scale, with 0 = the absence of the condition or normal and 4 = the most extreme form of the condition. A total score is obtained by adding all of the scores of the individual items. The SARS takes approximately 10 minutes to administer.

7.2.8.2. Barnes Akathisia Rating Scale (BAS)

The Barnes Akathisia Rating Scale[20] (BAS) will be administered to assess akathisia. The scale is designed to rate akathisia through observation of restless behavior and questioning of the subject to determine the degree of subjective restlessness and distress associated with restlessness. A global clinical rating completes the assessment.

The first 3 items of the BAS (Objective, Subjective, and Distress related to restlessness) are rated on a 4-point scale (0-3). The fourth item, the global clinical assessment of akathisia, uses a 6-point scale (0-5). Only the global clinical assessment measure from this scale will be analyzed. Higher scores indicate increased severity. All ratings are anchored. The BAS takes approximately 10 minutes to administer.

7.2.8.3. Abnormal Involuntary Movement Scale (AIMS)

The Abnormal Involuntary Movement Scale[21] (AIMS) will be used to document occurrences of dyskinesias in subjects, specifically tardive dyskinesia. The scale incorporates observation and brief examination of the subject and consists of 12 items. Items 1-4 assess the severity of orofacial movements. Items 5-7 assess extremity and truncal dyskinesias. Items 8-10 rate global severity of movements as indicated by the examiner's judgment of the severity of abnormal movements (item 8), the examiner's judgment of the subject's incapacitation due to the movements (item 9), and the subject's awareness of the movements and associated distress (item 10). Items 11-12 concern the subject's dental status.

Items 1-10 are rated on a 5 point (0-4) anchored severity scale with 0 = none, 1 = minimal, may be normal, 2 = mild, 3 = moderate, and 4 = severe. Items 11 and 12 are questions with yes/no answers. Only the sum of the first 7 items will be analyzed. The AIMS can be completed in 5-10 minutes.

7.2.9. Suicidality Assessments

7.2.9.1. Suicidality Assessments at Screening

A risk assessment should be done if the subject's responses on any of the screening instruments or other screening information indicate that:

- The subject has had suicide ideation associated with actual intent and/or plan at any time in their lifetime such that a positive response ('Yes') is made on items 4 or 5 of the suicidal ideation subscale of the C-SSRS; or
- The subject has any lifetime history of suicide behaviors such that a determination of 'yes' is made to any of the suicide behavior items of the C-SSRS; or
- In the investigator's judgment a risk assessment is required.

A written copy of the risk assessment should be included in the subject's clinical record (source documentation).

7.2.9.2. Suicidality Assessments at Baseline and Post-baseline Visits

At the baseline visit (visit 2) and post-baseline visits, the C-SSRS will be administered. If there are 'yes' answers on items 4 or 5 of the suicidal ideation subscale of the C-SSRS or any behavioral questions of the C-SSRS, a risk assessment should be done to determine whether it is safe for the subject to continue to participate in the trial. If there are any 'yes' answers on items 4 or 5 of the suicidal ideation subscale of the C-SSRS or any behavioral questions of the C-SSRS at the post-baseline visits, supplemental information should be collected and the appropriate CRFs completed for the purpose of constructing a narrative that allows a detailed description of the adverse event(s) and outcome(s). Supplemental information will also be collected for a completed suicide.

A written copy of the risk assessment should be included in the subject's clinical record (source documentation).

7.2.9.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS)[22] will be used to evaluate suicide ideation and severity at screening, baseline, and each post-baseline visit. The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS is the prospective counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization system.[23] Responses to individual C-SSRS items can be mapped directly to the C-CASA categories (ie, completed suicide, attempted suicide, preparatory acts, suicidal ideation, non-suicidal self-injurious behavior) for summary and analysis purposes. The C-SSRS has been broadly used in numerous industry sponsored randomized clinical trials (RCTs) in both CNS and non-CNS indications.

The C-SSRS is available in a Baseline version and a "Since Last Visit" version. The baseline version assesses suicidal behavior over the lifetime and suicidal ideation at the time the subject was most suicidal. The "Since Last Visit" version assesses suicidal ideation and behavior between visits in a clinical trial. The clinician administering the interview should use information provided by the subject as well as other sources of information (eg, from parent(s) or guardian(s)) to determine if suicidal ideation or behavior occurred.

The C-SSRS contains 2 required items pertaining to suicidal ideation, 4 required items pertaining to suicidal behavior, and 1 required item pertaining to non-suicidal self-injurious behavior. There are 8 additional suicidal ideation items and 2 additional suicidal behavior items which are completed in cases of positive responses for other items, as well as 2 items for completed suicide and suicide behavior present during the interview. Thus, there is a maximum of 19 completed items.

The Suicidal Ideation items are rated on a dichotomous scale (yes or no). There is also an Intensity of Ideation subscale, which assesses the Frequency, Duration, Controllability, Deterrents, and Reasons for Ideation associated with the Most Severe suicide ideation reported by the patient, using 5-point Likert scales. The Suicidal Behavior items and the Non-Suicidal Self-Injurious Behavior items are also scored dichotomously yes or no. In addition, the total number of attempts (including interrupted and aborted attempts) is recorded. This is followed by a Lethality subscale which rates the Actual Lethality/Medical Damage and Potential Lethality of the attempt on 5- and 3-point Likert scales, respectively. A total score can be generated for the Intensity of Ideation portion of the interview. Otherwise, no other total scores are generated. In the event of a positive categorical response the interviewer can provide text or narrative that further describes the thought or behavior.

For subjects who are ages 7-11 at the Screening Visit, the Children's Since Last Visit version of the C-SSRS should be utilized, even if the child has his/her 12th birthday during participation in this study. The Since Last Visit version refers to the subject's experience since their last visit.

For subjects who are ages 12-17 at the Screening Visit, the Since Last Visit version of the C-SSRS should be utilized. The Since Last Visit version refers to the subject's experience since their last visit.

7.2.10. Subject Contact

Contact should be made with the subject by the investigator or designated staff member, either by telephone or in person as an unscheduled visit, after the baseline visit but before Visit 3 and after Visit 3 but before Visit 4 to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability, safety, and efficacy of the titration plan/study drug.

7.3. Efficacy Assessments

7.3.1. 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. It has operationally-defined anchors, and is based on patient self-report combined with clinician observations. The YMRS will be administered using the Kowatch interview guide, which adapts the scale for pediatric populations. It requires 15-30 minutes to complete. The YMRS was developed for the assessment of mania severity in hospitalized adults, but its validity in pre-pubertal patients has been demonstrated, and it is now widely accepted and used as a primary measure of mania severity in outpatient studies of children and adolescents with bipolar disorder.[24,25]

The YMRS must be administered by an appropriately qualified and experienced individual who has completed the Pfizer rater training program. For each subject, the same rater should administer the YMRS at each of the indicated timepoints. A co-rater who has successfully completed the Pfizer rater training program may administer the YMRS in lieu of the primary rater, on rare occasions when the primary rater is unavailable due to illness or other unavoidable circumstances.

7.3.2. Clinical Global Impression Scales (CGI-S and CGI-I)

The Clinical Global Impression (CGI) Scale[26] is a standardized assessment tool used to rate the severity of a subject's illness and improvement over time. The CGI using two subscales: Severity of Illness (CGI-S) and Global Improvement (CGI-I). The CGI-S assesses the rater's impression of the subject's current illness state. Scores range from 1 (not ill at all) to 7 (among the most extremely ill). The CGI-I subscale rates the subject's improvement or worsening from baseline. Scores range from 1 (very much improved) to 7 (very much worse).

CCI

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[redacted]

7.4. Rater Qualifications/Training/Certification for Diagnostic, Efficacy, and Safety Rating Scales

For this study, a central contract research organization (CRO) will work with the Sponsor to verify that raters meet the rating scale qualification criteria for the study and are trained on administration of the scales. This will apply to raters identified at the start of the study as well as those raters that may need to be added during the life of the study.

Potential raters who fully meet the education and clinical experience described below will be allowed to continue with rater training without Sponsor review. Potential raters who do not fully meet these criteria will require individual review by the central CRO and the Sponsor for potential inclusion in rater training. A final determination will be made by the Sponsor as to whether the potential rater can or cannot proceed to training. Once evaluated and documented an individual rater may receive the approval to rate on a specific scale based on their education level and prior clinical experience. When a rater has been approved based upon their education and experience as described above, they will be granted access to the study specific training materials. Once all scale specific training is satisfactorily completed, documentation of training completion by the central CRO will occur. Upon receipt of the documentation by the central CRO, a rater can begin administration of the specific scale(s) for the study.

Criteria for Training Approval without Sponsor Review

Rating Scale	Educational Level*	Prior Clinical and Pediatric Experience	Prior Scale Experience
C-SSRS	MD or DO; PhD in Clinical or Counseling Psychology; RN or Master's level degree in a medical, social work, or mental health field.	≥1 year clinical experience with pediatric population and/or pediatric clinical trial experience.	Prior training with C-SSRS within the past two years with valid documented certification will exempt rater from having to retake C-SSRS training.**

Rating Scale	Educational Level*	Prior Clinical and Pediatric Experience	Prior Scale Experience
YMRS	Child andAdolescent Psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training); or Adult Psychiatrist (PI or Sub Investigator (SubI)) or Doctoral Level Psychologist.	≥1 year clinical experience with pediatric population and/or pediatric clinical trial experience.	5 administrations of any clinician rated interview based scale such as CCI CDRS-R, Montgomery and Asberg Depression Rating Scale (MADRS), Hamilton Depression Scale (HAM-D).
	MD, MA, MS, MSW, RN, BS, BA	≥1 year clinical experience with pediatric population and/or pediatric clinical trial experience.	5 administrations of any clinician rated interview based scale.
CGI	Child and Adolescent Psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training) or Adult Psychiatrist; (PI or SubI) or Doctoral Level Psychologist.	≥1 year clinical experience with pediatric population and/or pediatric clinical trial experience.	5 administrations of the CGI or similar type global rating scale such as Clinical Global Impression of Change Scale (CGIC).
CCI [redacted]	CCI [redacted]	C C I [redacted]	CCI [redacted]

Rating Scale	Educational Level*	Prior Clinical and Pediatric Experience	Prior Scale Experience
	CCI [redacted]		
	CCI [redacted]	CCI [redacted]	CCI [redacted]
K-SADS	Child andAdolescent Psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training); or Adult Psychiatrist (PI or SubI) or Doctoral Level Psychologist.	≥1 year clinical experience with pediatric population and/or pediatric clinical trial experience.	5 administrations of any diagnostic interview based scale such as Structured Clinical Interview for DSM-IV (SCID), Mini-international neuropsychiatric interview (MINI), Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), Diagnostic Interview Schedule (DIS), Composite International Diagnostic Interview (CIDI).
AIMS/BARS/SAS	Child and, Adolescent Psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training); or Adult Psychiatrist or other physician.	≥1 year clinical experience with pediatric population and/or pediatric clinical trial experience.	5 administrations of any movement scale such as AIMS/BARS/SAS or Extrapyramidal Symptom Rating Scale-A (ESRS-A), Unified Parkinson's disease rating scale (UPDRS) or the Global Dystonia Scale.

* International equivalencies will be accepted. Doctoral level psychologist (PhD or PsyD) must be trained in child development.

** Upon 2 year expiration of documented certification, raters will be required either to retake C-SSRS training or resubmit valid, current documented certification. Should the two years lapse during the course of the study, retraining updated training and a renewed certificate will be required.

CCI [redacted]

CCI [redacted]

7.6. Triggered Requirements

The following specific cardiac safety parameters of concern for the compound require the following action to be taken (see also Section 6.7.1):

Condition	Action
QT Prolongation	ECGs are to be reviewed and compared to baseline to assess potential changes. ECGs showing a QTcF of ≥480 msec or a suspected increase from baseline of 60 msec or greater must be repeated within the same visit. If the QTcF value persists at ≥480 msec and/or the change from baseline persists at ≥60 msec, the study drug must be discontinued immediately and a pediatric cardiologist or an adult cardiologist experienced in the interpretation of pediatric ECGs should be contacted to discuss the ECG result. Verified increase in QTcF of ≥60 msec or verified occurrence of QTcF ≥480 msec will be considered as an adverse event of QTc prolongation. QTcB prolongation (Bazett's correction) will not be used to define adverse events; QTcB will be measured only to enable historical comparisons.
Ventricular Arrhythmia	An ECG showing ventricular arrhythmia (except occasional ventricular extrasystoles) should be followed up with a rhythm strip ECG and Pfizer must be notified. In addition, a stat over read from the central vendor should be requested, a pediatric cardiologist or adult cardiologist experienced in the diagnosis and treatment of pediatric arrhythmias should be consulted, and the subject monitored, as necessary. If the ventricular arrhythmia is confirmed, the subject must be discontinued from the study.

Condition	Action
Syncope	All syncopal episodes suggestive of cardiac arrhythmia (sudden loss of consciousness, loss of postural tone, and no pre-syncopal phase), except vasovagal syncope will be considered adverse events and the subject will be discontinued from the study. Every effort should be made to obtain vital signs and an electrocardiogram at the time of the event. Further evaluation, eg, Holter monitoring, may also be useful. Subjects experiencing syncope of probable vasovagal origin (onset not sudden but preceded by a pre-syncopal phase, presence of predisposing factors such as blood sampling procedure, standing, hot shower, hair curling, etc) will also be considered adverse events but subjects may continue study participation after sponsor approval.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For AE's and SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

- AEs (serious and non serious) should be recorded on the CRF from the time the subject has provided informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on SAE Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- Concurrent with:

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for Liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy -occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also Section 6.7 Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent/legal guardian. In addition, each study subject/parent/legal guardian will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

This study has been designed to have 85% statistical power to show a difference between drug and placebo at conventional levels (ie, 5% level, 2-sided) of statistical significance. Based on the previous Pfizer pediatric study A1281132, the estimated difference in change from baseline of the YMRS total score for ziprasidone versus placebo is –4.55 points (from descriptive and LSMEANs at week 4) with an approximate within-group standard deviation of 8.0.

The effect size used in the design of this study is 0.57, and is consistent with the weighted estimate of the effect size (0.65) of second generation antipsychotics in pediatric bipolar patients published in the recent meta-analysis of Correll et al,[28] which was based on the results of multiple placebo-controlled trials.

Using EAST (version 5.4) for a two-sample t-test, the sample size needed to detect this difference with 85% power at a two-sided significance level of 5% was determined to be 111 randomized subjects. Adjusting for dropouts (approximately 38% at week 4) and including the additional 14 subjects being enrolled to mitigate the impact of the rater training issue, the total sample necessary is 194 subjects (1:1 enrollment with 97 on ziprasidone and 97 on placebo). The power for this study has now increased to 88%.

The randomization will be stratified by weight group (weight <45 kg, weight ≥45 kg) to ensure treatment balance within each of the two weight groups.

Shortly after enrollment into this study commenced, Pfizer was informed by the rater training vendor (on 29 September 2014) that an internal audit had revealed an error in their internal processes. This error resulted in some sites being notified that they could start screening subjects before all raters at the sites had completed all of the required rater training activities. The primary endpoint assessments (YMRS) and/or the diagnostic interviews (KSADS) of 14 subjects were impacted by the rater training issue.

In agreement with the FDA to ensure the robustness of the inferential analysis, Pfizer will recruit an additional 14 subjects into the study and conduct a sensitivity analysis excluding these 14 patients to mitigate the possible effect of the rater training issue that was identified. The original sample size for this study was 180 subjects. For the revised sample size, a total of 194 subjects (97 ziprasidone: 97 placebo) will be recruited from approximately 60-70 worldwide sites. The power of the study including the additional subjects is 88%. It is estimated that approximately 300 subjects will be required to be screened to achieve this enrollment target with an anticipated screen failure rate of approximately 40%.

9.2. Statistical Summary and Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be finalized and dated prior to enrolling the first subject, and subsequently maintained by the sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications or significant change to the primary endpoint definition and/or its or analysis will also be reflected in a protocol amendment.

9.3. Definition of Study Populations

For this protocol, an intent-to-treat (ITT) analysis set will be defined as the set of all subjects who were randomized, had baseline measurements, took at least 1 dose of study medication (ziprasidone or placebo), and with at least 1 post-baseline visit.

The per-protocol (PP) analysis set will include all patients in the ITT set without major protocol violations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations will be reviewed to generate the list of subjects with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria will be finalized prior to breaking the blind.

Both the ITT and PP analysis sets will be used in the analyses of all efficacy endpoints, with the ITT being primary. The Safety Analysis Set which includes all subjects who were randomized and took at least 1 dose of study medication (ziprasidone or placebo) will be used in the analyses of the safety data. Only the ITT analysis set will be used in the analyses of the outcome CCI and special safety assessments (CSSRS data, CDRS, and movement disorder scales).

9.4. Study Conduct and Subject Disposition

The number of subjects screened, randomized to the double-blind treatment phase, and completing the study will be summarized. The reason for all discontinuations will be summarized by treatment group.

9.5. Baseline Characteristics and Treatment Group Comparability

Baseline demographic and other characteristics will be tabulated for all treated subjects. Quantitative variables will be described by standard descriptive statistics (mean, standard deviation, minimum, and maximum), and qualitative variables will be summarized by frequency tables.

9.6. Efficacy Analysis

Early termination (ET) visit efficacy data will be “windowed” (ie, “slotted” to a regular study visit time using an algorithm specified in the SAP.

Descriptive statistics for all efficacy endpoints by treatment group and visit will be provided.

9.6.1. Analysis of Primary Endpoint

The primary efficacy endpoint is change from baseline in the YMRS score. The primary time point is Week 4. All other collection time points will be considered secondary.

Analysis of change from baseline in the YMRS score will be conducted using Statistical Analysis System (SAS) PROC MIXED to fit a mixed model repeated measures analysis of covariance (ANCOVA) with treatment, visit and visit-by-treatment interaction, and weight category as fixed effects and baseline score as a covariate. Subject effect will enter the MMRM model as a random effect. The estimation method used will be restricted maximum likelihood. An unstructured covariance matrix will be used in the REPEATED statement. In case SAS PROC MIXED fails to converge, other covariance matrix structures will be considered in the sequence of Toeplitz, First-Order Autoregressive, and Variance Components. The EMPIRICAL option will be specified to compute the estimated variance-covariance matrix of the fixed-effects parameters. Type III sums of squares will be used to test both main effects and interactions. The primary comparison will be between ziprasidone and placebo at Week 4, conducted as a two-sided test at 5% level of significance. Based on the specified model, the point estimate and 95% confidence interval (CI) for the difference in means between the two treatments will be constructed using the least squares means and appropriate standard errors.

If the test result is significant and in favor of ziprasidone, then efficacy of flexibly-dosed oral ziprasidone in the treatment of children and adolescents with Bipolar I Disorder (current or most recent episode manic) will be established.

A sensitivity analysis will be done by adding an interaction term of treatment and weight category to the primary analysis model specified above. Supplemental analyses of the primary variable will be performed to support the robustness of the conclusions drawn from the primary mixed models repeated measures analysis described above. These supplemental analyses will include the following:

- Summaries of reasons for discontinuations by treatment group;
- Pattern-mixture ANCOVA analysis of change from baseline YMRS scores.

For the pattern-mixture analysis, grouping of the subjects on the basis of their dropout or missing-data patterns will be explored. Two appropriate grouping variables will be defined in the SAP. The percentage of subjects showing a ≥50% reduction in YMRS scores from baseline to Week 4 will be presented descriptively for each group.

9.6.2. Analysis of Secondary Endpoints

The secondary efficacy endpoints include:

- Change from baseline to week 4 in the CGI-S score (key secondary endpoint);
- Change from baseline to weeks 1, 2, and 3 in YMRS and CGI-S;

- Raw CGI-I score at weeks 1, 2, 3, and 4 (as opposed to change from baseline).

For change from baseline in the CGI-S score, analyses will be conducted using SAS PROC MIXED to fit a mixed model repeated measures ANCOVA with treatment, visit and visit-by-treatment interaction and weight category as fixed effects and baseline score as a covariate. Subject effect will enter the MMRM model as a random effect.

For the raw CGI-I score, analyses will be conducted using SAS PROC MIXED to fit a mixed model repeated measures analysis of variance (ANOVA) with treatment, visit and visit-by-treatment interaction and weight category as fixed effects. Subject effect will enter the MMRM model as a random effect.

For all the above analyses, the estimation method used will be restricted maximum likelihood. An unstructured covariance matrix will be used in the REPEATED statement. In case SAS PROC MIXED fails to converge, other covariance matrix structures will be considered in the sequence of Toeplitz, First-Order Autoregressive and Variance Components. The EMPIRICAL option will be specified to compute the estimated variance-covariance matrix of the fixed-effects parameters. Type III sums of squares will be used to test both main effects and interactions. The point estimates and 95% CIs for the difference in means between the two treatments will be constructed using the least squares means and appropriate standard errors.

For all the above analyses, the point estimates and 95% CIs for the difference in means between the two treatments will be provided using the least squares means and appropriate standard errors.

Descriptive statistics for raw CGI-I scores and for change from baseline CGI-S scores will be provided by treatment group and visit classification.

CCI [redacted]

9.8. Analysis of Safety Assessments

The safety assessments include:

- Adverse Event Reporting;
- Clinical Laboratory Testing;
- Physical Examinations;

- Blood Pressure and Pulse;
- Height and Weight, BMI, waist circumference;
- Electrocardiogram.

CCI [redacted] No formal statistical analysis will be conducted on any of the other safety data listed above.

Data for height, weight, BMI, and waist circumference will be summarized by timepoint using descriptive statistics. Additionally, height, weight, and BMI will be standardized using Centers for disease control (CDC) growth charts and the resulting z-scores presented in listings and frequency tables in 1-unit intervals. In addition, frequency tables of above/below a 1-point increase in the z-scores for BMI will be presented.

All randomized subjects who receive at least one dose of study drug will be included in the safety analysis. All adverse events that are observed from the time of first dosing with study medication (at randomization) until the end of study participation will be included in the safety analysis. Adverse events that occurred during treatment with the antipsychotic medication will be reported separately if the event occurred prior to randomization.

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities and will be summarized by treatment group. The incidence of treatment-emergent adverse events will be tabulated by treatment group and by system organ class. In addition, the incidence of serious adverse events and adverse events that cause withdrawal will be tabulated. All adverse events will be listed.

CCI [redacted]

All clinical laboratory data will be subjected to clinical review, summarized by frequency of events and mean changes from baseline.

All vital sign measurements will be displayed in listings by subject for each sample collection date and time. The measurement taken immediately prior to randomization will be used as the baseline for calculating changes in vital signs.

Centrally over-read ECG variables will be summarized by mean change from baseline to each measurement time for heart rate, PR interval, QRS width, QT interval and QTcF (Fridericia correction) values. Baseline will be defined as the mean of the pre-dose triplicates at the Baseline Visit. Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcF are ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcF as change from baseline are ≥30 msec increase and ≥60 msec increase. QTcF is considered the primary QTc value for measurements of change and for clinical decision making as this correction is more accurate with changes in heart rate. To enable historical comparisons, categorical changes in QTcB (Bazett's correction) also will be tabulated but clinical decisions and interpretation of data will be based on QTcF values.

9.9. Analysis of Special Safety Assessments

The special safety assessments include:

- CDRS-R;
- C-SSRS;
- Movement Disorder Scales (SARS, BAS, and AIMS).

For special safety assessments, descriptive statistics (n, mean, standard deviation, min, max, 95% CI) by treatment group and visit for the change from baseline will be provided.

For all of the Movement Disorder Scales, descriptive statistics by treatment group and visit for change from baseline will be provided. For the SARS, the total score from the sum of all 10 sub-items will be summarized. For the BAS, only the global clinical assessment item will be summarized. For the AIMS, only the sum of the first seven items (ie, movement cluster) will be summarized. In addition, the same change from baseline MMRM model used for the primary and secondary endpoints will be applied to the Movement Disorder Scales.

The prospectively collected C-SSRS item responses will be mapped to the C-CASA suicidality event codes. No formal statistical hypothesis testing will be undertaken. Listings of both the C-CASA categories as well as the underlying C-SSRS scale data will be prepared. In addition a summary table of C-CASA category frequencies at screening, baseline, and all post-baseline visits without regard to baseline will be compiled. Additional tables displaying post-baseline worsening and new-onset of suicidality within reporting categories (suicidal ideation) will also be prepared.

CCI [redacted]

CCI [redacted]

9.11. Interim Analysis

No interim analysis is planned for this study.

9.12. Data Monitoring Committee

This study will utilize an External Data Monitoring Committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. The E-DMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of such conflicts may be financial, scientific, or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor regulatory agencies are to be members of the E-DMC. Membership is to be for the duration of the clinical trial including the post study generation of final reports.

The EDMC will meet on a regular basis and will operate independently of the sponsor.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be [password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs data collection tools ([/DCTs)] and hospital records), all original signed informed consent[/assent] documents, copies of all CRFs[/DCTs], safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting

minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be [password protected or secured in a locked room] to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent[/assent] documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, [or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, [or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

If the study permits consent from a legally acceptable representative, include the following paragraph:

Whenever consent is obtained from a subject's [legally acceptable representative/parent(s) or legal guardian], the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the

person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject [or the subject's legally acceptable representative, parent(s), or legal guardian and the subject's assent, when applicable, before any study specific activity is performed [unless a waiver of informed consent has been granted by an IRB/EC]. The investigator will retain the original of each subject's signed consent[/assent] document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and/investigator databases may be used as recruitment procedures. All advertisements, however, should be reviewed by the Sponsor before seeking ethics or IRB approval.

As part of the study recruitment plan, the following strategies may also be initiated (where necessary, the appropriate ethics committee and/or IRB approvals must be obtained before implementing): specialist site referrals; indication area support group visits; web-based links; community postings; and hospital newsletters.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as the time when the last subject completes the last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of ziprasidone at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AACAP	American Academy of Child and Adolescent Psychiatry
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASD	Isolated atrial septal defect
AST	aspartate aminotransferase
BA(R)S	Behavioural Activity Rating Scale
BID	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
bpm	beats per minute
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDC	Centers for disease control
CDRS-R	Child Depression Rating Scale - Revised
CDS	Core Data Sheet
CCI	CCI
CGIC	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CPBAQ	Children's Problem Behavior and Aggression Questionnaire
CPK	Creatine phosphokinase
CRF	case report form
CRO	Contract Research Organization
CS	clinically significant
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P4503A4
DCTs	data collection tools
DHEA	dehydroepiandrosterone
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee

Abbreviation	Term
ECG	electrocardiogram
E-DMC	External Data Monitoring Committee
EDP	Exposure during pregnancy
EPS	extrapyramidal symptoms
ESRS-A	Extrapyramidal Symptom Rating Scale-A
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Scale
HbA1c	glycosylated hemoglobin
HbsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotophin
HIV	Human Immunodeficiency Virus
5-$HT1_A$	5-Hydroxytryptamine Receptor 1A
5-$HT2_A$	5-Hydroxytryptamine Receptor 2A
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
INR	international normalized ratio
IQ	Intelligence Quotient
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	intrauterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LDH	lactate dehydrogenase
LFT	Liver function test
LPD	Local Product Document
LSMEANs	Least-Squares Means
MADRS	Montgomery and Asberg Depression Rating Scale
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHP	mental health provider
MINI	Mini-international neuropsychiatric interview
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MMRM	mixed model repeated measures
MSW	Clinical Social Worker
NCS	not clinically significant

Abbreviation	Term
NSAIDs	non-steroidal anti-inflammatory drugs
PCD	primary completion date
PDA	patent ductus arteriosus
PDD-NOS	pervasive developmental disorder – not otherwise specified
PI	principal investigator
CCI	CCI
PNP	psychiatric nurse practitioner
PP	Per-Protocol
PR	Pulse rate
PREA	Pediatric Research Equity Act
PRN	pro re nata
PSRAEs	Possibly Suicide Related Adverse Events
PT	prothrombin time
QTc	QT corrected
QTcB	Bazett's correction
QTcF	Fridericia correction
RCTs	randomized clinical trials
SAE	serious adverse event
SAP	statistical analysis plan
SA(R)S	Simpson-Angus Rating Scale
SAS	Statistical Analysis System
SCID	Structured Clinical Interview for DSM-IV
sNDA	Supplemental New Drug Application
SPC	Summary of Product Characteristics
SRSD	single reference safety document
SubI	Sub Investigator
TSH	thyroid-stimulating hormone
UDS	urine Drug Screen
ULN	upper limit of normal
UPDRS	Unified Parkinson's disease rating scale
US	United States
USPI	United States Package Insert
VSD	ventricular septal defect
YMRS	Young Mania Rating Scale