26-WEEK OPEN-LABEL EXTENSION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF FLEXIBLE DOSES OF ORAL ZIPRASIDONE IN CHILDREN AND ADOLESCENTS WITH BIPOLAR I DISORDER (MOST RECENT EPISODE MANIC)

Investigational Product Number:	CP-88,059-1
Investigational Product Name:	Ziprasidone Hydrochloride
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable
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Phase:	3

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Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	13 August 2018	
Amendment 1	16 February 2019	Amendment 1 19 February 2019 For this amendment there no substantial changes to the study only non-substantial changes noted below: Corrections have been applied to the text to be consistent with schedule of activities. Clarification on enrollment eligibility, baseline data and transition period provided for subjects from parent study (A1281198). In addition, formatting, clerical and grammar updates have been addressed within this amendment. Non-Substantial: PROTOCOL SUMMARY, Trial Design PROTOCOL SUMMARY, Trial Treatments PROTOCOL SUMMARY, Statistical Methods SCHEDULE OF ACTIVITIES 3. STUDY DESIGN 4.1. Inclusion Criteria 5.4.2. Preparation and Dispensing 5.5. Administration, Open-Label Weeks 3-26 5.9 Concomitant Treatment 6.1. Baseline Visit 6.2. Study Visits During Open-label

		Treatment 6.3 Follow up Visit 7.1.2 Clinical Laboratory Testing 7.1.4. Blood Pressure and Pulse 7.2 Electrocardiograms 7.3.1. Child Depression Rating Scale – Revised (CDRS-R) 7.3.2.4. Columbia Suicide Severity Rating Scale (C-SSRS) 7.4.1. Young Mania Rating Scale (YMRS) 7.4.3. Children's Global Assessment Scale 9.1. Sample Size Determination 9.2. Efficacy Analysis Appendix 2. Criteria for Training Approval without Sponsor

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).

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PROTOCOL SUMMARY

Indication:

Study A1281201 is a 6-month, open label extension study of the ongoing double-blind, randomized, placebo controlled study of ziprasidone in pediatric Bipolar Disorder (Study A1281198). Study A1281201 will enroll adolescents aged 10 to 17 years with Bipolar I Disorder who have participated in double blind Study A1281198. In order to be enrolled in this open label extension trial, subjects must have met the enrollment criteria for Study A1281198, and must meet the inclusion and exclusion criteria for Study A1281201 at the extension study Baseline visit (last visit in the double blind study).

Rationale:

The purpose of adding this extension study to the ongoing Geodon pediatric bipolar program is to obtain additional longer term safety data in children and adolescents with Bipolar I disorder treated with ziprasidone.

Trial Design:

This 26-week open-label extension study is designed to provide information on the safety and tolerability of oral ziprasidone (20-80 mg BID (twice daily) with meals) during long-term administration in children and adolescents with Bipolar I Disorder (current or most recent episode manic). It will enroll subjects who have participated in the 4-week, double-blind, placebo-controlled safety and efficacy trial, Study A1281198, meet study entry criteria, and wish to receive treatment with open-label ziprasidone.

The final visit of the double-blind trial (Week 4 or early termination) will serve as the Baseline Visit for the extension study. During the first 1-14 days of the study, subjects will be transitioned under double-blind conditions to treatment with open label ziprasidone. The dosing of ziprasidone will be flexible in Weeks 3-26 of this study.

Post-Baseline visits will occur at Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26 during treatment, with a follow-up visit at Week 27.

A telephone call must occur 28 to 35 days from administration of the final dose of investigational product to capture any potential adverse events and to confirm appropriate contraception usage.

Endpoints:

Safety Assessments:

- Adverse event reporting;
- Clinical laboratory testing;
- Physical examinations;

- Blood pressure and pulse;
- Height and weight;
- Body Mass Index (BMI), BMI Z-score;
- Waist circumference;
- Electrocardiograms, including QT interval corrected for rate (QTc).

Special Safety Assessments:

- Movement Disorder Scales - Simpson Angus Rating Scale (SARS), Barnes Akathisia Rating Scale (BAS), and Abnormal Involuntary Movement Scale(AIMS);
- Columbia Suicide Severity Rating Scale (C-SSRS);
- Child Depression Rating Scale (CDRS- R).

Efficacy Assessments:

- Young Mania Rating Scale;
- Clinical Global Impression of Severity (CGI-S);
- Children's Global Assessment Scale (CGAS).

Trial Treatments:

All investigational products will be provided by Pfizer and will include oral ziprasidone capsules of 20, 40, 60, and 80 mg strength. Matching placebo capsules will also be supplied for the initial 1-14 day dose transition period. All medication will be packaged in childproof blister cards with columns for AM and for PM capsules.

During the dose transition period (Weeks 1-2, Days 1-14), subjects will receive a study drug blister card for each week of transition dosing. Subjects weighing ≥45 kg will receive 2 weeks of transition medication, while subjects weighing less than <45 kg will receive 1 week of transition medication.

At the baseline visit of the A1281201 study, subjects will transition onto active medication if previously assigned to the placebo group or continue on active study drug. Over the course of the double-blind dose transition period, subjects <45 kg will be transitioned to a total daily dose of 60 mg a day by Day 7 of Week 1 and subjects ≥45 kg will be transitioned to a total daily dose of 120 mg a day by Day 10 of Week 2. (Subjects on 160 mg, 140 mg, 100 mg, and 80 mg active at the end of Study A1281198 will all be transitioned to 120 mg a day at the end of the two-week transition period. Subjects on 120 mg active at the end of Study A1281198 will remain on 120 mg a day through the dose transition period).

During the dose transition period, investigators, subjects, and the study team will be kept blinded to the content of the dose transition cards (which contain both placebo and active ziprasidone capsules) but not to the dose level of study medication.

Dose level for each day of the transition dosing card for subjects who were on placebo or ziprasidone in Study A1281198 are provided in Table 1, Table 2, Table 3 and Table 4.

Any subject who cannot tolerate the transition study medication during Week 1 should be discontinued from the study.

After the Week 2 visit for the ≥45 kg subjects and after the Week 1 visit for the <45 kg subjects, dosing will be open label and flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability. The target dose range for subjects <45 kg is 60 mg to 80 mg/day and for subjects ≥45 kg, 120 mg to 160 mg/day, which are identical to the target dose ranges used in Study A1281198.

The blister cards for Weeks 3-26 will each contain medication for 8 days. Two blister cards will be dispensed at Weeks 2 and 4 and then 4 blister cards will be dispensed at each monthly visit from the Weeks 6 visit through the Week 22 visit. Dose increases should be limited to 20 mg a week during Weeks 6-22 of the flexible dosing weeks of the study. However, subjects ≥45 weight can be increased to 160 mg a day after they have been on a stable dose of 120 mg a day if clinically indicated. Table 1, Table 2, Table 3 and Table 4 provide the dose transition schedule for all possible dose levels for subjects in both weight categories.

Statistical Methods:

Sample Size

The number of subjects entering this open-label trial will be determined by the number of subjects electing to continue treatment after completing or withdrawing from the preceding double blind study, A1281198. We estimate that approximately 55 subjects randomized in the double blind study (based on the increased sample size of N (number) =194 subjects) will be eligible to continue in this open label extension. With an expected dropout rate of approximately 35%, this gives an estimate of approximately 40 subjects to complete this 26 week open label study (if all 55 subjects enter the extension study).

Data Summarization Methods

As this is an open label study with no comparator, no inferential statistics will be performed. Quantitative variables will be described by standard descriptive statistics (n, mean, standard deviation, minimum, and maximum, 95% confidence intervals), and qualitative variables will be summarized by frequency tables. Summaries will include data for all subjects who took at least one dose of investigational product in this open label extension study.

Baseline values for efficacy, outcomes and special safety endpoints will be the last observation made prior to the subject's receiving open label treatment. For safety, for those subjects who were randomized to placebo in the double blind study, baseline values will be

the last observation prior to initiating dosing in the open label extension study (normally, the observation of the last visit in the double blind study); and for those subjects who were randomized to ziprasidone in the double blind study, baseline values will the last observation prior to initiating dosing in the double blind study (normally, the value from the Baseline visit in the double blind study).

Safety data from this trial will be monitored by the independent Data Monitoring Committee (DMC) currently monitoring study A1281198. Details of the board's functions are documented in the DMC Charter.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the 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 table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Activities/ Assessments	**Baseline**[a]	**Open-label Ziprasidone**									**Follow up Visit**	**Follow Up**[l]
Visit Windows[b]		**± 1 Day**				**±3 days**						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Schedule	**Day 1**	**W1**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26/ ET**[a]	**W27**	
Informed Consent, Assent[c]	X											
Inclusion/Exclusion	X											
Physical Exam	X									X		
Body Weight/Height/ BMI/BMI-z score/ waist circumference	X				X					X	X[d]	
ECG*,[e]	X	X	X	X	X		X		X	X	X[d]	
Blood Pressure/Pulse[f]	X	X	X	X	X	X	X	X	X	X	X[d]	
Chem/Hemato/Urinalysis	X				X					X	X[d]	
Hormones (free T4 & TSH, Prolactin)	X				X					X	X[d]	
Fasting glucose, lipids, insulin, HbA1c**	X				X			X		X	X[d]	
Urine drug screen[g]	X				X					X		
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X	X	X	
Verification of contraception	X	X	X	X	X	X	X	X	X	X	X	X[l]
Dispense Double-Blind Transition Card[j,m]	X	X[m,j]										
Dispense Study Drug	X	X	X	X	X	X	X	X	X			
Drug Accountability		X	X	X	X	X	X	X	X	X		
Subject telephone contact[i]		X	X			X	X	X	X	X		X[l]
YMRS	X	X	X		X		X		X	X		
CGI-S	X	X	X	X	X	X	X	X	X	X		
CGAS	X									X		
CDRS-R	X	X	X	X	X	X	X	X	X	X	X[d]	
SARS, BAS, AIMS	X	X	X	X	X	X	X	X	X	X	X[d]	
C-SSRS[k]	X	X	X	X	X	X	X	X	X	X	X	
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X[l]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	

ET = early termination; 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; CGAS =Children's Global Assessment Scale; 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.

* All ECGs will be administered at least 3 hours after food intake.

** Subjects should remain fasting for at least 8 hours prior to the baseline visit, Week 6, Week 18, and Week 26..

a. Baseline Visit is the last visit of the preceding double-blind trial, Study A1281198. In the case of early termination, all procedures specified for Week 26/ET are to be completed.

b. Every effort should be made to bring the subject back to the office on the designated study days; however, monthly office visits will have a ±3 day visit window to allow for slight variations in subject schedules. 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. Only if the subject had clinically significant abnormal findings from a previous visit that require follow-up.

e. 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. The subject should be in the sitting position for approximately 5 minutes and in the standing position for approximately 2 minutes before the measurements are obtained.

g. Following the baseline visit, unscheduled urine drug screens can be performed at additional visits at the investigator's discretion.

h. At all required visits, 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 before the subject may receive investigational product. Unscheduled 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.

i. As double blind study medication will be transitioned during the first two weeks of the study for subjects weighing ≥45 kg and during the first week of the study for subjects <45 kg, the investigator or designated staff must be in contact with the subject and his/her parent(s) and/or guardian(s) in between the Baseline and Week 1 visit and between the Week 1 and Week 2 visit. After the Week 6 visit, the investigator or designated staff must be in contact with the subject and his/her parent(s) and/or guardian(s) in between study visits by telephone to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability and efficacy of the study medication.

j. Double-Blind Transition Card provided only to ≥45 kg weight group subjects.

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 or exhibited suicidal behaviors.

l. Follow up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

m. Any subject who cannot tolerate the transition study medication during Week 1 should be discontinued from the study.

1. INTRODUCTION

This protocol describes a 6-month, open label extension study (A1281201) of the A1281198 study. The purpose of adding this extension study to the ongoing Geodon pediatric bipolar program is to obtain additional longer term safety data in children and adolescents with Bipolar I disorder treated with ziprasidone.

Studies A1281198 and A1281201 are being conducted to fulfill 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 10 to 17 years of age, which was issued by the United States (US) Food and Drug Administration (FDA) to Pfizer in August 2004.

1.1. Mechanism of Action/Indication

Ziprasidone is an atypical antipsychotic with a high affinity for the dopamine D2 receptor and the 5-Hydroxytryptamine Receptor 2A (5-HT2A) receptors. It blocks re-uptake of serotonin and norepinephrine and exhibits 5-Hydroxytryptamine Receptor 1A (5-HT1A) agonist activity. The indication for this study is pediatric Bipolar I Disorder. The study will include out-patient and/or inpatient, male and female subjects aged 10-17 (inclusive) who meet the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM V) diagnostic criteria for Bipolar I Disorder (current or most recent episode manic) and who participated in Study A1281198.

1.2. Background and Rationale

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 Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), as affirmed 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®), 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.

1.2.1. Background on Ziprasidone (CP-88,059-1)

Ziprasidone (CP-88,059-1 oral capsule) is an atypical antipsychotic. It has a high affinity for the dopamine D2 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 a high 5-HT2A/D2 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-HT1A agonist activity may contribute to the alleviation of affective and negative symptoms. Ziprasidone has relatively low affinity for α1 adrenergic and histamine H1 receptors and muscarinic M1 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 P450 3A4 (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. An s-NDA (supplemental New Drug Application) 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 IM (Intramuscular) 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).

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

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To assess the safety and tolerability of oral ziprasidone (20-80 mg BID) during long term, open label administration in children and adolescents with Bipolar I Disorder who participated in Study A1281198.	• Safety Assessments; • Adverse event reporting; • Clinical laboratory testing; • Physical examinations; • Blood pressure and pulse; • Height and weight; • Body Mass Index (BMI) and BMI Z score; • Waist circumference; • Electrocardiograms, including QTc; • Special Safety Assessments; • Movement Disorder Scales (SARS, BAS, and AIMS); • Columbia Suicide Severity Rating Scale (C-SSRS); • Child Depression Rating Scale (CDRS-R); • Efficacy Assessments; • Young Mania Rating Scale; • Clinical Global Impression of Severity (CGI-S); • Children's Global Assessment Scale (CGAS).

3. STUDY DESIGN

This 26 week open label extension study is designed to provide information on the safety and tolerability of oral ziprasidone (20 to 80 mg BID with meals) during long term administration in children and adolescents with Bipolar I Disorder (current or most recent episode manic). It will enroll subjects who have participated in the 4 week, double blind, placebo controlled safety and efficacy trial, Study A1281198, meet study entry criteria, and wish to receive treatment with open label ziprasidone.

The number of subjects entering this open-label trial will be determined by the number of subjects electing to continue treatment after completing or withdrawing from the preceding double blind Study A1281198. We estimate that approximately 55 subjects randomized in the double blind study (based on the increased sample size of N=194 subjects) will be eligible to continue in this open label extension. With an expected dropout rate of approximately 35%, this gives an estimate of approximately 40 subjects to complete this 26 week open label study (if all 55 subjects enter the extension study).

The final visit of the double blind trial (Week 4 or early termination visit from A1281198) will serve as the Baseline Visit for the extension study. The first 1-14 days of Study A1281201 will be considered a transition period during which the study drug will continue to be administered under double-blind conditions. During this double-blind transition period, subjects who were on placebo in Study A1281198 will be provided active medication that will allow them to be titrated up to the appropriate weight-adjusted target dose, following titration schedule that was employed in Study A1281198. Subjects who were on active medication (ziprasidone) at the end of Study A1281198 will continue on that treatment course under double-blind conditions. At the end of the double-blind transition period, all subjects will receive open label ziprasidone.

Any subject who cannot tolerate the transition study medication during Week 1 should be discontinued from the study.

After the Week 2 visit for the ≥45 kg subjects and after the Week 1 visit for the <45 kg subjects, dosing will be open label and flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability. For subjects with a body weight of ≥45 kg, the target dose range is a total daily dose of 120 mg to 160 mg/day given in two divided doses with food. For subjects with a body weight <45 kg, the target dose range is a total daily dose of 60 mg to 80 mg/day given in two divided doses with food.

Subjects who cannot tolerate a dose of 80 mg/day will be allowed to have a dose reduction and to continue study treatment at a lower dose that is tolerable to them. The minimum permitted dose is 40 mg/day (20 mg BID) for all subjects.

Post Baseline visits will occur at Weeks 1, 2, 4, 6, 10, 14, 18, 22 and 26 during treatment, with a follow up visit at Week 27.

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 Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section).

4. SUBJECT ELIGIBILITY CRITERIA

The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

This study will enroll children and adolescents with Bipolar I Disorder, who have participated in double blind Study A1281198. In order to be enrolled in this open label extension trial, subjects must have met the enrollment criteria for Study A1281198, and must meet the following inclusion and exclusion criteria at the A1281201 extension study Baseline visit (last visit in the double blind study). Any questions regarding eligibility must be discussed with a Pfizer clinician prior to the subject's participation in the study.

Subject eligibility should be reviewed and documented by an appropriate 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.

4.1. Inclusion Criteria

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. The subjects must have received investigational product in Study A1281198 and completed at least 3 weeks of double blind treatment before entering this open label extension. However, subjects who have insufficient treatment response and have reached their maximum tolerated dose may enroll in the open label extension as early as 1 week after the end of their titration.

4. In the investigator's opinion, the subject must be likely to benefit from antipsychotic therapy and must have been free from any clinically significant safety concerns during the preceding double blind study (ie, in the opinion of the investigator, the benefits that the subject is likely to derive from continued participation must outweigh the risks).

5. All fertile male subjects and female subjects of childbearing potential who are sexually active and/or their legal guardians, as appropriate, must agree that a highly effective method of contraception be used as outlined in this protocol and for the duration of the study and for 28 days after the last dose of investigational product.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Any subjects from the preceding double blind trail who experienced a serious adverse event which required study medication to be discontinued and the subject to be withdrawn from the study. Subjects who experienced cardiac arrhythmias, conduction abnormalities, or QTc prolongation (confirmed and persistent Fridericia's correction (QTcF) >480 msec or increase from baseline QTcF >60 msec) during the preceding study.

2. Subjects requiring any medications not allowed by the Concomitant Medication Table 12 (see "Concomitant Treatment(s)").

3. Subjects who require treatment with drugs that are known to consistently prolong the QT interval (see Concomitant Medication Table 12).

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

5. Subjects living in the same home as another study participant or having the same caregiver during the same enrollment period (Such subjects can be enrolled in the study at different times but may not be in the study at the same time).

6. 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 the C-SSRS or other information based on the investigator's judgment indicate:

    - Suicide ideation associated with actual intent and a method or plan such that a positive response ('Yes') is made on items 4 or 5 of the suicidal ideation subscale of the C-SSRS; or

    - Any suicide behaviors such that a determination of 'yes' is made to any of the suicide behavior items of the C-SSRS.

7. Pregnant female subjects, breastfeeding female subjects.

8. Participation in other studies other than the preceding Study.

9. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior 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.

4.3. Randomization Criteria

Not applicable.

4.4. Lifestyle Requirements

N/A.

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential, as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s), 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. The investigator or his or her designee will confirm that the subject has selected an appropriate method of contraception from the list of permitted contraception methods (see below). At time points indicated in the Schedule of Activities, the investigator or designee will instruct the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

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 the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject plans to remain 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 separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.5. Sponsor's Qualified Medical Personnel

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 product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is Ziprasidone Hydrochloride.

5.1. Allocation to Treatment

Throughout most of this study, ziprasidone will be administered as open label (OL) investigational product to all subjects.

However, the dose transition from the double-blind study drug administered in Study A1281198 to the open-label dosing in the extension trial A1281201 will be conducted under double-blind conditions.

The double-blind dose transition phase of Study A1281201 will comprise Weeks 1 and 2 for subjects ≥45 kg and Week 1 for subjects <45 kg. The double-blind (DB) medication for this transition period will be assigned according to the subject's randomization number in the preceding study so that the investigator remains blinded during this period.

At the baseline visit of the A1281201 study, subjects will transition onto active medication if previously assigned to the placebo group or continue on active study drug. Over the course of the double-blind dose transition period, subjects <45 kg will be transitioned to a total daily dose of 60 mg a day by Day 7 of Week 1 and subjects ≥45 kg will be transitioned to a total daily dose of 120 mg a day by Day 10 of Week 2. (Subjects on 160 mg, 140 mg, 100 mg, and 80 mg active at the end of Study A1281198 will all be transitioned to 120 mg a day at the

end of the two-week transition period. Subjects on 120 mg active at the end of Study A1281198 will remain on 120 mg a day through the dose transition period).

Any subject who cannot tolerate the transition study medication during Week 1 should be discontinued from the study.

All medication will remain blinded until the end of the transition period. Diagrams of the transition dosing cards for subjects who were on placebo or ziprasidone in Study A1281198 are provided in Table 1, Table 2, Table 3 and Table 4.

At the end of the double-blind transition period, all subjects will start to receive open label ziprasidone. Diagrams of the double-blind dose transition study drug blister cards are provided in Table 1, Table 2, Table 3 and Table 4.

Allocation of subjects to treatment groups will precede through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be signed by two appropriate staff members and stored in the site's file.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Breaking the Blind

As Applicable.

5.3. Subject 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 (case report form) 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 5.8). 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. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

All investigational products will be provided by Pfizer and will include oral ziprasidone capsules of 20, 40, 60, and 80 mg strength. Matching placebo capsules may also be supplied for the initial 1-14 day dose transition period. All medication will be packaged in childproof blister cards with columns for AM and for PM capsules.

Two different types/designs of child resistant blister cards will be provided over the course of the study: a transition card design and a fixed dose card design. Each transition card will contain medication for 7 days plus 3 additional days. Each fixed dose card will contain 7 days of medication per card plus 1 additional day for use in the open label phase. During the transition phase, all blister cards will have 1 to 2 capsules available for the AM and 1 to 2 capsules for the PM administration. During the open label phase (Weeks 2/3-26), the blister cards will have only 1 capsule available for the AM and 1 capsule available for the PM dose of active medication. Each of the AM or PM columns will contain a 20 mg, 40 mg, 60 mg or 80 mg ziprasidone capsules (or matching placebo) during the transition and only active ziprasidone capsules during open-label treatment. The target dose ranges for subjects <45 kg is 60 to 80 mg/day and for subjects ≥45 kg, 120 to 160 mg/day, which are identical to the target dose ranges used in study A1281198.

For more information please refer to the Investigational Product manual for all items related to IP.

Dose Transition Card Container Types	
Double-Blind Dose Transition Card	
Active Ziprasidone or Placebo (separate cards for Day 1/Baseline and Week 2/Visit 2)	≥45 kg body weight
Active Ziprasidone or Placebo (Day 1/Baseline)	<45 kg body weight

In order to accommodate the flexible dosing permitted by the protocol following the dose transition period, 7 types of open label fixed dosing cards, each with a different total daily dose of study drug as described in below tables:

Fixed Dose OL 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

5.4.2. Preparation and Dispensing

On Day 1 (Baseline Visit), one transition card will be dispensed based on the subject's weight (≥45 kg or <45 kg) and previously assigned treatment in Study A1281198 for the first week of dosing. Only subjects ≥45 kg will receive a transition card at Week 2 if needed. After Week 1, subjects from the <45 kg group will be provided a fixed dose card for the second week of the dose transition phase. Medication dose- and weight-based tables illustrate the dosing sequence subjects will be assigned during the transition periods by weight and current assigned dose in A1281198 (Table 1, Table 2, Table 3 and Table 4). Patients <45 kg will be assigned a 60 mg active/placebo titration card at Day 1 of A1281201. Patients ≥45 kg will be assigned one of three dose levels: Patients on the 80 mg or 100 mg dose level in A1281198 will be given a 100 mg active/placebo titration card Day 1 of A1281201, Patients on the 120 mg dose level in A1281198 will be given a 120 mg active/placebo titration card Day 1 of A1281201, and Patients on the 140 mg or 160 mg dose level in A1281198 will be given a 140 mg active/placebo titration card Day 1 of A1281201.

After the baseline visit, the investigator or designed staff must be in contact with the subject and his/her legal guardian(s) on at least one occasion between the baseline visit and the Week 1 visit and between the Week 1 visit and the Week 2 visit, 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 and efficacy of the titration plan.

After the Week 6 visit, the investigator or designated staff must be in contact with the subject and his/her parent(s) and/or guardian(s) in between study visits by telephone to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability and efficacy of the study medication.

Table 1. Double-Blind Dose Transition Blister Cards for ≥45 kg Subjects on 160 mg/day or 140 mg/day of Active Ziprasidone or Placebo at End of Study A1281198, Weeks 1 and 2

140 mg Week 1 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1		80	140/160*
2	60	80	140
3	60	80	140
4	60	80	140
5	60	80	140
6	60	80	140
7	60	80	140
8	60	80	140

140 mg Week 1 Placebo Titration Card			
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

* Subjects on a dose of 160 mg at the end of the A1281198 study will remain at that dose for 1 additional day during the transition period due to the Day 1 card PM dose design. Starting on Day 2 of the transition period these subjects will receive a total daily dose of 140 mg/day.

120 mg Week 2 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1		60	120
2	60	60	120
3	60	60	120
4	60	60	120
5	60	60	120
6	60	60	120
7	60	60	120
8	60	60	120

120 mg Week 2 Placebo Titration Card			
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

Table 2. Double-Blind Dose Transition Blister Cards for ≥45 kg Subjects on 120 mg/day of Active Ziprasidone or Placebo at End of Study A1281198, Weeks 1 and 2

120 mg Week 1 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1		60	120
2	60	60	120
3	60	60	120
4	60	60	120
5	60	60	120
6	60	60	120
7	60	60	120
8	60	60	120

120 mg Week 1 Placebo Titration Card			
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

120 mg Week 2 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1	60	60	120
2	60	60	120
3	60	60	120
4	60	60	120
5	60	60	120
6	60	60	120
7	60	60	120
8	60	60	120

120 mg Week 2 Placebo Titration Card			
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

Table 3. Double-Blind Dose Transition Blister Cards for ≥45 kg Subjects on 80 mg/day or 100 mg of Active Ziprasidone or Placebo at End of Study A1281198, Weeks 1 and 2

100 mg Week 1 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1		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

100 mg Week 1 Placebo Titration Card			
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

* Subjects who were assigned 80 mg at the end of Study A1281198 will have a 20 mg increase in dose starting on Day 1 of the double blind transition period due to the design of the transition dose card.

120 mg Week 2 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1	60	60	120
2	60	60	120
3	60	60	120
4	60	60	120
5	60	60	120
6	60	60	120
7	60	60	120
8	60	60	120

120 mg Week 2 Placebo Titration Card			
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

Table 4. Double Blind Dose Transition Blister Cards for <45 kg Subjects on 40 mg/day, 60 mg/day, or 80 mg of Active Ziprasidone or Placebo at End of Study A1281198, Week 1

60 mg Week 1 Active Titration Card			
Day	**AM Dose (mg)**	**PM Dose (mg)**	**Total Daily Dose (mg)**
1		40	60/80*
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

60 mg Week 1 Placebo Titration Card			
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

* Subjects who were assigned 40 mg at the end of Study A1281198 will have a 20 mg increase in dose starting on Day 1 of the double blind transition period due to the design of the transition dose card. Subjects who were assigned 80 mg at the end of Study A1281198 will receive 80 mg on Day 1 of the dose transition week but from Day 2 onwards will receive a total daily dose of 60 mg/day.

Subjects weighing <45 kg should be issued an open label, fixed dosing card with the desired total daily dose for the second week of the dose transition phase(ie, either 40 mg/day, 60 mg/day, or 80 mg/day; see Table 5, Table 6, or Table 7).

The investigator will decide which fixed dose blister card to provide to the subject for the following week, based on clinical judgment.

Table 5. 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

Table 6. 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

Table 7. 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

Subjects weighing ≥45 kg should be issued an open label fixed dosing card with the desired total daily dose at the start of the third week (Day 15) of the extension study (ie, either 80 mg/day, 100 mg/day, 120 mg/day, 140 mg/day or 160 mg/day total daily dose; see Table 8-Table 11.

Table 8. 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

Table 9. 120 mg Fixed Dose Regimen

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

As a reminder subjects weighing ≥45 kg could be provided the 140 or 160 mg/day fixed dose card (see Table 10 and Table 11) only if they have tolerated 120 mg/day; in addition, the 140 and 160 mg/day fixed dose card should not be issued before Day 15 of the study.

Table 10. 140 mg Fixed Dose Regimen

Day	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
1	60	80	140
2	60	80	140
3	60	80	140
4	60	80	140
5	60	80	140
6	60	80	140
7	60	80	140
8	60	80	140

Table 11. 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

Only site personnel according to their role as determined on the site delegation log may dispense investigational product cards. Subjects will be instructed to take medication with food and to take one capsule in the AM and one capsule in the PM from each assigned blister card during the open label phase.

The investigational product will be dispensed using an IRT drug management system at each visit from baseline to Week 22. A qualified staff member will dispense the investigational product, a unique container numbers on the blister cards provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the blister cards, as provided throughout the course of dosing and return the blister cards, to the site at the next study visit.

5.5. Administration

As study drug administration is complex, the parent or guardian should closely supervise dosing throughout the study, especially during the transition period. Depending on the assigned investigational product, 1 to 2 capsules are taken in the morning and 1 to 2 capsules 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. The missed dose should be skipped if <4 hours remain to the next scheduled dose.

All investigational product is to be taken with food and approximately 12 hours apart. Capsules are to be taken intact. Swallow the capsule whole. Do not crush or chew the capsule.

Transition Period:

The target dose ranges for subjects <45 kg is 60 to 80 mg/day and for subjects ≥45 kg, 120 to 160 mg/day, which are identical to the target dose ranges used in Study A1281198.

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 to 160 mg/day. A dose of 160 or 140 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.

Any subject who cannot tolerate the transition study medication during Week 1 should be discontinued from the study.

Open-Label Weeks 3-26

After the Week 2 visit for the ≥45 kg subjects and after the Week 1 visit for the <45 kg subjects, dosing will be open-label and flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability. Subjects who cannot tolerate a dose of 80 mg/day will be allowed to have a dose reduction and to continue study treatment at a lower dose that is tolerable to them. The minimum permitted dose is 40 mg/day (ie, 20 mg BID) for all subjects. The site will dispense 2 blister cards to the

patient at the Week 2 and Week 4 visit. From the Week 6 visit onwards, there will be 4 weeks between each visit and the site will dispense 4 blister cards to the patient at each visit. Blister cards for Weeks 3-26 will each contain medication for 7 days plus 1 additional day. All investigational products will be provided by Pfizer and will include oral ziprasidone capsules of 20, 40, 60, and 80 mg strength. Matching placebo capsules will also be supplied for the initial tapering period. All medication will be packaged in childproof blister cards with columns for AM and for PM capsules (see Dosage Form and Packaging section).

Dose Reductions

If a subject with a body weight ≥45 kg cannot tolerate the target dose of 120–160 mg/day during the open label phase (Weeks 3-26) the investigator can reduce the dosage. In general, it is recommended dose reductions not exceed 40 mg/day and occur only once a week unless a subject is experiencing an adverse event that necessitates a faster dose reduction.

If a subject weighing <45 kg cannot tolerate the target dose of 60-80 mg/day during the open label phase (Weeks 3-26), the investigator can reduce the total daily dosage to 40 mg/day.

Any subject who cannot tolerate a minimum dose of 40 mg/day will be discontinued from the study.

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 Principal Investigator (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).

5.6. Summary of the Dose Titration Schedule for Study A1281201

1. No dose adjustments are allowed during Week 1 of the Dose Transition period (for either the <45 kg or ≥45 kg dose category); subjects who cannot tolerate the Week 1 dose titration should be withdrawn from the study.

2. Weekly dose adjustments (increases or decreases) are allowed from Week 2 of the Dose Transition period to the end of the study (Week 26). In general, dose adjustments should not occur more frequently than every 7 days to provide an adequate period of time to evaluate the clinical effect of the dose adjustment. Dose adjustments are achieved by issuing an open label fixed dosing card to the subject (ie, with a total daily dose of 40 mg, 60 mg, 80 mg, 100 mg, 120, 140 mg, or 160 mg).

3. The dose may be increased if the subject has been tolerating the current dose level without significant side effects; but, in the clinical judgment of the investigator, has had an insufficient clinical efficacy response. The clinical rationale for the dose increase should be documented in the source documentation for the subject.

4. In general, dose increases should not exceed 20 mg. However, subjects weighing ≥45 kg may be increased to 140 mg or 160 mg total daily dose if they have tolerated the 120 mg dose well, have reached Day 15 of the study, and have had an insufficient clinical efficacy response to the 120 mg total daily dose.

5. The dose may be decreased if, in the clinical judgment of the investigator, the subject is not tolerating the current dose well and is likely to benefit from continued treatment with a lower dose of study drug that may be better tolerated. There is no limit on the number of dose decreases; however, subjects who cannot tolerate a minimum total daily dose of 40 mg should be withdrawn from the study. The clinical rationale for the dose decrease should be documented in the source documentation for the subject. In general, dose decreases should not exceed 40 mg.

6. Subjects who, in the clinical judgment of the investigator, have reached their maximum tolerated dose and still have an insufficient clinical response should be withdrawn from the study.

5.7. Investigational Product Storage

The investigator or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. Investigational product is to be stored at 15-25°C (59-77°F).

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.8. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All blister cards of study drug must be returned to the investigator by the subject at every visit and at the end of the trial.

5.8.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.9. Concomitant Treatment(s)

The Concomitant Medication Table that follows lists common concomitant medications that are permitted or prohibited during the study, however this list may not be fully inclusive. Subjects will 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 investigator must record the use of all concomitant medications in the eCRF (electronic Case Report Form).

The chronic use of certain medications (some hormones, antihypertensives, diuretics, and oral hypoglycemic) is allowed if the subject was using these medications during the preceding double-blind study at a stable dose and the subject's condition is stable.

Lorazepam may be used PRN (as necessary) up to 2 mg/day for anxiety or agitation during the first 4 weeks of dosing but should not be given within 6 hours prior to assessments being performed. If possible, the investigator should start with a low dose of lorazepam to control a subject's symptoms and increase incrementally up to a total of 2 mg, 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.

The frequency and dose of benzodiazepine administration will be recorded on the eCRF. For treatment of insomnia lorazepam may be used as specified above, or alternatively diphenhydramine or zolpidem are permitted.

Urine drug screening (UDS) will be performed at the baseline visit (last visit in the double-blind study) and at visits for Weeks 6 and 26 (or early termination), and at any other visit deemed necessary by the investigator. Subjects with a positive UDS (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, opiates, phencyclidine or propoxyphene) should be counseled against the use of these substances and should be told the implications of drug use for study participation, and his/her parents or guardians should be notified. However, a positive UDS will not automatically result in exclusion or discontinuation from the study. In the case of subjects with a positive UDS (other than for occasional cannabinoid use), investigators should consult with the Sponsor to determine if appropriate to continue the subject in the study.

Table 12. Prohibited/Concomitant Medication Table

The following agents are <u>prohibited</u> during the trial and must be discontinued at least 4½ 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, lisdexamfetaminedimesylates, methamphetamines, and methylphenidates);
Antidepressants (see mono amine 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);
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. Biotin (dose exceeding 100mcg daily) Children multivitamin levels allowed.

The following medications are cited in the Exclusion criteria (A1281198) 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 investigational product:
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 antiinflammatory 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

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

6.1. Baseline Visit

The Baseline visit for this open-label extension study is the same visit as the end of treatment visit in the preceding double-blind study. Procedures to be completed at this visit are detailed in the A1281198 protocol and are indicated on the Schedule of Activities in this protocol. At this visit, the investigator must confirm that the subject meets all inclusion and exclusion criteria for the extension study, and should carefully assess all medical and non-medical conditions in deciding whether the study is appropriate for a particular subject.

Entry into the open-label study requires informed consent in addition to that already obtained for the double-blind study. The subject and the authorized legal representative must understand the nature of the extension study and be able to comply with protocol requirements. The representative must sign an Informed Consent Document and the subject must provide Written Assent prior to any study-specific procedures being performed. The person obtaining the consent must be sufficiently trained on medical issues so that questions can be adequately addressed; therefore, this person must be an M.D., Ph.D. or RN (persons without one of these degrees must be approved by Pfizer). Any subject who turns 18 years of age during the study will need to provide written consent.

Investigational product for the first week of treatment will be dispensed according to the weight-based dose transition scheme described previously (see Section 5.5). Study drug administration will be carefully explained to the subject and legal guardian (see details in Section 5.5, Study Drug Administration). As double-blind investigational product will be transitioned during the first and second weeks (Week 1 only for subjects weighing <45 kg) of the study and open-label medication will be transitioned in, the investigator or designated staff must be in contact with the subject and his/her parent(s) and/or guardian(s) at least once a week during the first two weeks of the study, 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 and efficacy of the transition plan. After the Week 6 visit, the investigator or designated staff must be in contact with the subject and his/her parent(s) and/or guardian(s) in between study visits by telephone to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability and efficacy of the study medication.

6.2. Study Visits During Open-label Treatment

Subjects will attend study visits at Weeks 1, 2, 4, 6, 10, 14, 18, 22, and 26 (or early termination). There will also be a brief follow-up (off treatment) visit at Week 27. The following will be assessed or administered at EVERY on-treatment visit:

- Adverse events;
- Review of concomitant medications;
- Blood pressure and pulse;
- Drug accountability (Document drug returned and record any dosage changes, except Day 1);
- Dispense study drug (except Week 26 or early termination);
- Double-blind transition card provided only for ≥45 kg weight group subjects (Week 1);
- CGI-S;
- C-SSRS;

- CDRS-R;
- Movement disorder scales (SARS, BAS, AIMS);
- A urine pregnancy test will be obtained on all female subjects at all study visits. A positive urine pregnancy test should be confirmed with a serum pregnancy test.
- Verification of contraception.

At week 4 in addition to the above the following will be assessed or administered:

- Electrocardiogram.

At Weeks 1, 2, 6, 14, 22 and 26 (or early termination), in addition to the above, the following will be assessed or administered:

- YMRS;
- Electrocardiogram.

At Weeks 6 and 26 (or early termination), in addition to the above, the following will be assessed or administered:

- Clinical laboratory tests (chemistry, hematology, urinalysis) and urine drug screen;
- Body weight, height, BMI, BMI z score, and waist circumference;
- Hormones (free T4 & TSH (thyroid stimulating hormone), Prolactin).

At Weeks 6, 18, and 26 (or early termination), in addition to the above, the following will be assessed or administered:

- Fasting glucose, lipid profile, insulin and glycated hemoglobin (HbA1c).

The following will be done only at Week 26 (or early termination):

- Physical exam;
- CGAS.

A urine pregnancy test will be obtained on all female subjects at all study visits. A positive urine pregnancy test should be confirmed with a serum pregnancy test.

Following the baseline visit, unscheduled urine drug screens can be performed at additional visits at the investigator's discretion.

Since no investigational product will be available after the Week 26 visit, the physician may initiate appropriate treatment with commercially available medications.

A Telephone Contact is required between the study staff and the subject and his/her parent(s) and/or guardian(s) to ensure that the subject is taking the proper capsules at the proper time and to monitor the tolerability and efficacy of the study drug. The telephone contact will occur as follows:

- Between the Baseline and Week 1 visit;
- Between the Week 1 and Week 2 visit;
- Between the monthly visits starting after the Week 6 visit (contact will occur at approximately Week 8, 12, 16, 20, 24).

6.3. Follow-up Visit

Subjects will attend a brief follow-up visit at Week 27 (or one week after the end-of-treatment visit, in case of early termination). At this visit, adverse events and concomitant medications will be documented. The CSSR-S will be performed, verification of contraception will be assessed, and a urine pregnancy test will be obtained on all female subjects.

The following should be done ONLY IF a subject had abnormal findings at a previous visit that require follow-up: body weight/BMI, height, BMI Z-score, waist circumference; electrocardiogram (ECG); blood pressure/pulse; clinical laboratory values (chem/hemato/urinalysis); hormones (free T4, TSH, Prolactin), fasting glucose, lipid profile, insulin, and HbA1c; movement disorder scales (SARS, BAS, AIMS) and CDRS-R. A urine pregnancy test will be obtained on all female subjects at the follow-up visit.

Follow up Contact

Follow up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

Certain adverse events will result in mandatory withdrawal from the study after appropriate safety follow up.

6.4. Subject Withdrawal

Subjects may withdraw from the trial 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 (see also the Withdrawal From the Study Due to Adverse Events section), 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 the Pfizer clinical monitor or his/her designated representative. 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 8.4.4.

An early termination visit must be scheduled for any subject who discontinues early from the study. At this visit, all assessments scheduled for the Week 26 visit (9) 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.

Certain adverse events will result in mandatory withdrawal from the study after appropriate safety follow-up.

These are as follows:

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.

Event	Criteria
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 (Bazett's correction) prolongation 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.
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. 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 who cannot tolerate a minimum of 40 mg/day of ziprasidone.

Event	Criteria
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 Week 26 according to the Schedule of Activities should be followed.
Rescue Medications	Subject requiring concomitant treatment with mood stabilizers, antidepressants, or stimulants.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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 that he or 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 manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessments

7.1.1. Adverse Events

Adverse events will be assessed and documented on the eCRF at every visit. Detailed instructions for adverse event reporting are found in Section 8 below.

7.1.2. Clinical Laboratory Testing

The results of all laboratory tests required by the protocol will be recorded electronically. A central laboratory will be used for most laboratory tests. Detailed instructions on the handling of laboratory samples will be provided by the Central Laboratory. The instructions will include guidance on cooling of samples following collection, on centrifugation, and on preparation for shipping.

Subjects should remain fasting for at least 8 hours prior to the Baseline, Week 6, 18, and Week 26 lab samples, because of the assessment of a lipid profile and insulin levels. The fasting/non fasting condition will be documented.

The following tests, requiring the drawing of approximately 20 mL of blood, will be completed at the Baseline visit and at Weeks 6 and 26 (or early termination):

- Hematology (complete blood count with differential % and absolute and platelet counts);
- Blood chemistry (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, (BUN), creatinine, glucose, calcium, inorganic phosphorus, magnesium, Serum glutamic oxaloacetic transaminase (SGOT) [aspartate aminotransferase (AST)], Serum glutamic pyruvic transaminase (SGPT) [alanine aminotransferase (ALT)], LDH (lactate dehydrogenase), (total bilirubin, albumin, and total protein);
- Hormones (free T4 and TSH, Prolactin);

- For female subjects, a urine pregnancy test should be performed followed by a serum pregnancy test if the urine test is positive;

- Urinalysis.

The following tests will be done at the Baseline visit (last visit in Study A1281198) and at Weeks 6, 18 and 26 (or early termination):

- Fasting glucose, lipid profile (cholesterol total, high density lipoprotein (HDL), Low-density lipoprotein (LDL)], triglycerides), insulin and HbA1c.

Subjects should remain fasting for at least 8 hours prior to these lab samples. The fasting/non fasting condition will be documented.

The following test will be done in female subjects at the baseline visit and all post-baseline visits (including any ET (Early Term) visit and the Follow Up visit):

- Urine pregnancy test (a positive urine pregnancy test should be confirmed by a serum pregnancy test).

In addition to the scheduled tests, serum pregnancy tests and urine drug screening may also be administered at any other visit that the investigator deems necessary.

No routine laboratory assessments will be performed at the follow-up visit (Week 27) except redraws for laboratory abnormalities present at a previous visit.

Abnormal test findings should be followed up appropriately and reported as an adverse event according to the criteria summarized in Section 8.

7.1.3. Physical Examinations

Physical examinations are to be performed at the Baseline visit (last visit in Study A1281198) and at Week 26 (or early termination). Any significant physical examination finding should be recorded as an adverse event.

7.1.4. Blood Pressure and Pulse

Blood pressure will be measured in the dominant arm (as defined by the subject, parent or legal guardian) and recorded to the nearest whole numbers. Pulse rate will be measured for at least 30 seconds. Two measurements will be obtained at each visit: once while the subject is in a sitting position and then in a standing position to assess orthostatic effects. The subject should be in the sitting position for approximately 5 minutes and in the standing position for approximately 2 minutes before the measurements are obtained.

7.1.5. Body Weight and Height, BMI, Waist Circumference

Body weight, height, and waist circumference will be measured at the Baseline visit and at Week 6 and 26 (or early termination). 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. Investigators will calculate the subject's Body Mass Index (BMI) from height and weight. A BMI and BMI z-score calculator will be provided within the Firecrest site.

BMI z-score 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 in the subject's eCRF. All BMI calculations are to be recorded by the investigator in the source documents and eCRF.

7.2. Electrocardiograms

A 12-lead ECG will be obtained from each subject at Weeks 1, 2, 4, 6, 14, 22 and Week 26 and repeated at the follow-up visit if abnormalities were present at the Week 26 (or early termination) visit. Baseline ECG data will be obtained from A1281198 final study visit. **The subject must fast at least 3 hours before ECGs are obtained.** ECGs must be obtained prior to the collection of any blood sample because drawing blood 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.

All ECGs must be reviewed for safety at the site by a physician qualified to read and interpret the results (ie, a pediatric cardiologist, or an adult cardiologist experienced in the interpretation of pediatric ECGs should be contacted to discuss the ECG). This assessment will include the calculation of QTcF. ECGs must be reviewed on the day of the recording, signed and dated by the reader, and retained in the subject's study records.

ECGs in this study will be collected with an ECG recorder to be supplied to the site. This machine can generate a hard copy tracing, as well as digitally transmit via a modem to a central ECG service (BMS- BioMedical Systems). Standardized site and subject identification information have to be entered into the machine by the ECG technician prior to each recording. The electronic version transmitted to BMS will be the same as the hard copy. BMS will provide clinical interpretation and overread designated parameters (Heart Rate (HR), PR, Respiration Rate (RR), QRS QT, QTcF, QTcB).

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.

7.3. Special Safety Assessments

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

The Child Depression Rating Scale – Revised[11] (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 years of age, it has been widely used with adolescents and its developers recommend it for both children and adolescents.[12] 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 minutes 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 as a safety measure to monitor subjects for the onset of a depressive episode. The CDRS -R will be completed at every visit except baseline (Baseline data will be carried over from Study A1281198).

7.3.2. Movement Disorder Scales

The following scales will be used to assess symptoms and findings related to Parkinsonism, akathisia, and abnormal involuntary movements. The scales will be administered at each visit. 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.

7.3.2.1. Simpson-Angus Rating Scale (SARS)

The Simpson-Angus Rating Scale[13] (SARS) will be administered by investigators 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.

7.3.2.2. Barnes Akathisia Rating Scale (BAS)

The Barnes Akathisia Rating Scale[14] (BAS) will be administered by investigators 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.

7.3.2.3. Abnormal Involuntary Movement Scale (AIMS)

The Abnormal Involuntary Movement Scale[15] (AIMS) will be used to document occurrences of dyskinesias in subjects, specifically tardive dyskinesia. The scale incorporates observation and brief examination of the subject by the investigator 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.

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

The Columbia Suicide Severity Rating Scale (C-SSRS)[16] 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.[17] 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 Central nervous system (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 10-11 at the Screening Visit (A1281198), 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 (A1281198), the Since Last Visit version of the C-SSRS should be utilized (A1281198 study). The Since Last Visit version refers to the subject's experience since their last visit.

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 or exhibited suicidal behaviors.

7.4. Efficacy Assessments

7.4.1. 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 Behavior, 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, and will be administered at Weeks 1, 2, 6, 14, 22 and 26.

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.[18,19]

The YMRS must be administered by an appropriately qualified and experienced individual who has been certified through the Pfizer rater training program. For each subject, the same rater should administer the YMRS at each of the indicated time points.

7.4.2. Clinical Global Impression of Severity Scale (CGI-S)

The Clinical Global Impression of Severity (CGI-S) Scale[20] is a standardized assessment tool used to rate the severity of a subject's illness. The CGI-S assesses the investigator'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-S will be administered at every study visit except the follow-up visit.

7.4.3. Children's Global Assessment Scale

The Children's Global Assessment Scale[21] (CGAS) is a clinician-rated global assessment item for children based on symptoms and social functioning in home, school, and community settings. Scores on this single item range from 1-100 (higher levels indicate greater health), with descriptive anchors for every 10-point interval. Scores above 70 on this scale are considered within the "normal" range. The CGAS will be completed at week 26 or early termination.

7.5. Pregnancy Testing

For female subjects of childbearing potential, 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 confirmed pregnancy test, the subject will be withdrawn from investigational product administration of investigational product but may remain in the study. Pregnancy tests may also be repeated as per request of Institutional Review Board (IRB) / Ethics Committee (EC) s or if required by local regulations.

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

For this study, a central CRO (Contract Research Organization) 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 in Appendix 2 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.

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.

If a rater has been approved to rate in Study A1281198 they will be allowed to rate the same scales for this study.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE 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.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject, parent or legally acceptable representative. In addition, each study subject, parent or legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. 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 on the CRF, and report such an assessment in accordance with the SAE 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. 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 that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

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

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 (outside of any protocol-specified dose adjustments) 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 recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event 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.

Or that is considered to be:

- An important medical event.

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.

8.2.4. 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 is 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 workup of a persistent pretreatment 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;
- Preplanned 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 noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, 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 the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol specified SAEs in this study. All SAEs will be reported to Pfizer safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (Tbili) elevations (>2 × ULN) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and Tbili values will be elevated within the same lab sample). In rare instances, by the time Tbili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to Tbili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and Tbili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a Tbili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST OR ALT OR Tbili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and Tbili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator 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 and Tbili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and Tbili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

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

- 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.
    - 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).
- 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 subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE 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) to Pfizer Safety 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 the 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 Safety 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 to Pfizer Safety 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 SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. 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 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.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors and Lack of Efficacy

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors and lack of efficacy	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4.4.2. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summarization of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the plans outlined in the protocol; however, any major modifications of significant change to the primary endpoint definition and/or its or analysis will also be reflected in a protocol amendment.

As this is an open label study with no comparator, no inferential statistics will be performed. Quantitative variables will be described by standard descriptive statistics (n, mean, standard deviation, minimum, and maximum, 95% confidence intervals), and qualitative variables will be summarized by frequency tables. Summaries will include data for all subjects who took at least one dose of investigational product in this open label extension study.

Baseline values for efficacy, outcomes and special safety endpoints will be the last observation made prior to the subject receiving open label treatment. For safety, for those subjects who were randomized to placebo in the double blind study, baseline values will be the last (pre dose, for ECG and blood pressure/pulse only) observation prior to initiating dosing in the open label extension study normally, the (pre dose, for ECG and blood pressure/pulse only) observation of the last visit in the double-blind study; and for those subjects who were randomized to ziprasidone in the double blind study, baseline values will the last observation prior to initiating dosing in the double blind study (normally, the value from the Baseline visit in the double blind study).

9.1. Sample Size Determination

The number of subjects entering this open-label trial will be determined by the number of subjects electing to continue treatment after completing or withdrawing from the preceding double-blind Study A1281198. We estimate that approximately 55 subjects randomized in the double-blind study (which is proposed to have the sample size increased to N=194 subjects) will be eligible to continue in this open label extension. With an expected dropout rate of approximately 35%, this gives an estimate of approximately 40 subjects to complete this 26 week open label study (if all 55 subjects enter the extension study).

9.2. Efficacy Analysis

No formal efficacy or outcomes analyses will be performed for this study. However, data on the YMRS, CGI-S, and CGAS will be summarized using descriptive statistics as described above.

9.3. Safety Analysis

The safety assessments include:

- Adverse event reporting, [including Possibly Suicide Related Adverse Events (PSRAEs)];
- Clinical laboratory values;
- Physical Exams;
- Vital signs (blood pressure, pulse rate);
- Weight, height, BMI, BMI Z-score, waist circumference;
- Electrocardiograms;
- No formal statistical analysis will be conducted on any of the above safety data.

Data for height, weight, BMI, and waist circumference will be summarized by time point using descriptive statistics. Additionally, height, weight, and BMI will be standardized using CDC (Child Development Chart) 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 antipsychotic treatment will be included in the safety data summarization. All adverse events that are observed from the time of first dosing with open label investigational product until the end of study participation will be included in data summaries.

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

All clinical laboratory data will be displayed in listings grouped by type of laboratory test (eg, hematology, blood chemistry) for each sample collection date. Values outside of the normal range will be noted; the respective normal high or low value will be presented in parentheses, linked to the abnormal laboratory value. Laboratory values will be summarized as median changes from baseline and also by frequency of occurrence of clinically significant abnormal values.

All vital sign measurements will be displayed in listings by subject for each sample collection date and time.

Centrally over read ECG variables will be summarized by mean change from baseline to each measurement time for heart rate, PR interval, RR interval, QRS width, QT interval and QTcB (Bazett's correction) and QTcF (Fridericia's correction) values. Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcF and QTcB are ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcF and QTcB as change from baseline are ≥30 msec increase, ≥60 msec increase and ≥75 msec increase. QTcF is considered the primary QTc value as this correction is more appropriate.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamics (PD) modeling, and/or to support clinical development.

9.5. 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 E-DMC will meet on a regular basis and will operate independently of the sponsor.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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 are 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. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the institutional review boards /ethics committees (IRB/EC), 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.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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 are true. Any corrections to entries made in the CRFs or 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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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 and hospital records), all original signed informed consent and assent 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, 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 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/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

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 staffs 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.

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.

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. 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 regulatory authority in any area of the world, or if the investigator is aware of any new information that 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 a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product 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, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by Pfizer. No longer than 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 supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. 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, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the 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 CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Lish JD, Dime Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic depressive Association (DMDA) survey of bipolar members. J Affective Disord. 1994; 31(4):281 94.

2. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, Soutullo CA. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol. 2000a;10(3):157 64.

3. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. J Amer Acad Child Adolesc Psychiatr. 2000b;3:1543 8.

4. McClellan J, Kowatch R, Findling RL. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2007; 46:107 125.

5. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M, and the Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with Bipolar Disorder. J Am Acad Child Adolesc Psychiatr. 2005;44:213 235.

6. Nandagopal JJ, DelBello MP and Kowatch R. Pharmacologic Treatment of Pediatric Bipolar Disorder. Child Adolesc Psychiatr Clin N Am. 2009: 455 469.

7. Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short term trials. J Am Acad Child Adolesc Psychiatry. 2007; 46:687 700.

8. Patel NC, Keck PE, Jr. Ziprasidone: efficacy and safety in patients with bipolar disorder. Expert Rev Neurother. 2006; 6:1129 1138.

9. Beedham C, Miceli JJ, Obach RS (2003) Ziprasidone metabolism, aldehyde oxidase, and clinical implications. J Clin Psychopharmacol 23:229 232.

10. Investigator's Brochure for Ziprasidone, June 2016.

11. Poznanski EO, Freemen LN, & Mokros HB. (1985). Children's Depression Rating Scale-Revised. Psychopharmacol Bull, 21, 979-989.

12. Poznanski EO & Mokros HB. (1996). Children's Depression Rating Scale, Revised, Manual. LA: Western Psychological Services.

13. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand, 1970;212:11-19.

14. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154: 672-676.

15. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand, 1970;212:11-19.

16. Posner K, Brent D, Lucas C, Gould M, Stanley B, Brown G, Fisher P, Zelazny J, Burke A, Oquendo M, Mann, J. Coloumbia-Suicide Severity Rating Scale, Version 7/19/2008; New York State Psychiatric Institute, 1051 Riverside Drive, NY, NY; for inquiries contact Kelly Posner at posnerk@childpsych.columbia.edu.

17. Posner K, Oquendo M, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;165:1035-43.

18. Fristad MA, Weller RA, Weller EB. The Mania Rating Scale (MRS): further reliability and validity studies with children. Ann Clin Psychiatr. 1995;7:127-32.

19. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2002;41:1216-1223.

20. Guy W. ECDEU Assessment Manual for Psychopharmacology – Revised: United States 1976. Rockville, Maryland: United States Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976; DHEW Publication Number (ADM)76 338. 218 222.

21. Shaffer D, Gould MS, Brasic J, et al. A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatr. 1983; 40(11):1228 31.

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
AST	aspartate aminotransferase
BAS	Barnes Akathisia Rating Scale
BID	Twice daily
BBS	Biospecimen Banking System
BMI	Body Mass Index
BMS	BioMedical Systems
BUN	blood urea nitrogen
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDC	Child Development Chart
CDRS-R	Child Depression Rating Scale – Revised
CGAS	Children's Global Assessment Scale
CGI-S	Clinical Global Impression of Severity
CK	creatine kinase
CNS	Central nervous system
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Clinical Trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DB	Double Blind
DHEA	dehydroepiandrosterone
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
E-DMC	external data monitoring committee

Abbreviation	Term
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HbA1c	glycosylated hemoglobin
HR	Heart rate
HRQL	health-related quality of life
5-HT1A	5-Hydroxytryptamine Receptor 1A
5-HT2A	5-Hydroxytryptamine Receptor 2A
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
ID	identification
IM	Intramuscular
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LDL	Low-density lipoprotein
LDH	Lactate dehydrogenase
LFT	liver function test
LSLV	last subject last visit
MnB	meningitidis serogroup B
MAO	mono amine oxidase
N or n	number
N/A	not applicable
NSAIDs	non-steroidal antiinflammatory drugs
OL	open label
PCD	primary completion date
PD	Pharmacodynamics
PFS	prefilled syringe

Abbreviation	Term
PGx	Pharmacogenomics(s)
PI	principal investigator
PK	pharmacokinetic
PP	Per Protocol
PR	Pulse rate
PREA	Pediatric Research Equity Act
PRN	when necessary
PSRAE	Possibly Suicide Related Adverse Events
PT	prothrombin time
QTcB	Bazett's correction
QTc	QT corrected
QTcF	Fridericia's correction
RCTs	randomized clinical trials
RNA	ribonucleic acid
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS	Simpson Angus Rating Scale
SC	subcutaneous
SGOT -	serum glutamic oxaloacetic transaminase
SGPT -	serum glutamic pyruvic transaminase
s-NDA	Supplemental New Drug Application
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TSH	thyroid-stimulating hormone
UDS	urine Drug Screen
ULN	upper limit of normal
US	United States
YMRS	Young Mania Rating Scale

Appendix 2. 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
YMRS	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 any clinician rated interview based scale such as CGAS, CDRS-R, MADRS, 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 or 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 CGIC
CDRS-R/CGAS	Child and Adolescent or Psychiatrist (or in the case of countries outside the US, the local country equivalent in education and training) or Adult Psychiatrist; 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 YMRS, HAM-D, MADRS, CDRS-R or CGAS
	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
K-SADS	Child and, Adolescent Psychiatrist (or in the	≥1 year clinical experience with pediatric	5 administrations of any diagnostic interview based

Rating Scale	Educational Level*	Prior Clinical and Pediatric Experience	Prior Scale Experience
	case of countries outside the US, the local country equivalent in education and training) or Adult Psychiatrist (PI or SubI) or Doctoral Level Psychologist	population and/or pediatric clinical trial experience	scale such as SCID, MINI, MINI-KID, DIS, 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 ESRS-A, 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.