Protocol A1281201

A 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)

Statistical Analysis Plan
(SAP)

Version: 1.1 (Amendment)

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Date: 2-MAY-2019

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1. AMENDMENTS FROM PREVIOUS VERSIONS

- Added subgroup analysis section.

2. INTRODUCTION

Note: In this document any text taken directly from the protocol (A121201 protocol amendment 1 dated 19February2019) is italicized.

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.

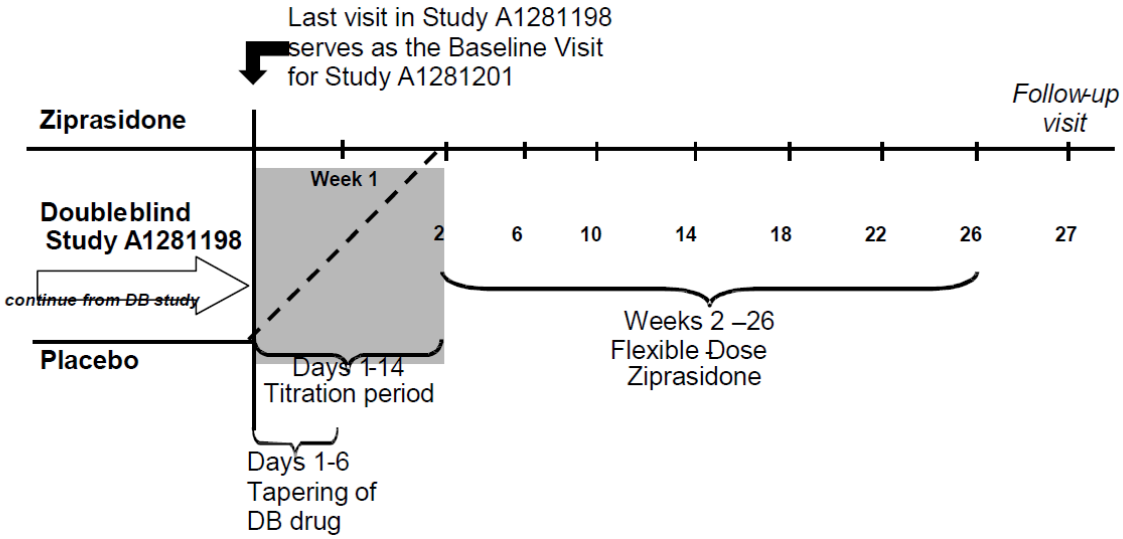
Ziprasidone is an atypical antipsychotic with a high affinity for the dopamine D2 receptor and the 5-Hydroxytryptamine Receptor 2A (5-HT2A) receptors. It blocks re-uptake of serotonin and norepinephrine and exhibits 5-Hydroxytryptamine Receptor 1A (5-HT1A) agonist activity. The indication for this study 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.

2.1. 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 120-160 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 60-80 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.

2.2. Study objective

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.

2.3. 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. All medication will remain blinded until the end of the transition period.

3. ENDPOINTS AND BASELINE VARIABLES AND CONVENTIONS

For collection schedules for all endpoints, please refer to the protocol.

3.1. Efficacy Endpoints

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

3.2. Special Safety Endpoints

- *Child Depression Rating Scale - Revised (CDRS-R).*
- *Columbia Suicide Severity Rating Scale (C-SSRS).*
- *Movement Disorder Scales (SARS, BAS, and AIMS).*

3.3. Safety Endpoints

- *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.

3.4. Baseline Variables

No baseline covariates in the planned analysis.

Baseline visit for the open-label extension study will be the final visit of the double blind trial (Week 4 or early termination visit from A1281198), except for safety ECG parameters. For ECG parameters, baseline values will be the value from the Baseline visit in the double-blind study A1281198.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

4.1. Safety Analysis Set

As the objective of the study is long-term safety and tolerability of ziprasidone, only one analysis set, "Safety Analysis Set" defined below will be used for data summaries.

The Safety Analysis Set (SAS) will include *all subjects who took at least one dose of study medication in this open-label extension study*.

All summaries will be based on the "as reported" visits (as recorded on the Case Report Forms).

For data summary purposes, subjects will be classified into one of the following two groups:

- Ziprasidone/Ziprasidone: randomized to ziprasidone in the preceding double-blind study (and on ziprasidone in the current open-label extension study).
- Placebo/Ziprasidone: randomized to placebo in the preceding double-blind study (and on ziprasidone in the current open-label extension study).

In addition, the above two groups will be combined as:

- Combined: combination of the two groups Ziprasidone/Ziprasidone and Placebo/Ziprasidone. This is essentially the set of all subjects in the current open-label extension study.

Data summaries will be done based on Ziprasidone/Ziprasidone and Placebo/Ziprasidone, as well as Combined.

4.2. Treatment Misallocations

If a subject took incorrect treatment in the preceding double blind study, then the subject will be reported under the treatment they actually received. For example, if a subject randomized to placebo but took Ziprasidone instead in the preceding double-blind study, then the subject will be reported under "Ziprasidone/Ziprasidone" rather then "Placebo/Ziprasidone".

4.3. Protocol Deviations/Violations

A full list of clinically important protocol deviations/violations will be included in the Clinical Study Report. Note that protocol deviations/violations will not exclude subjects from the "Safety Analysis Set" defined in Section 5.1.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

As this is an open-label study with no comparator, no formal statistical hypothesis testing will be conducted.

5.2. General 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.

5.3. Methods to Manage Missing Data

For any efficacy or special assessment rating scale/subscale or special safety variables where there is a missing rating (item), that scale or subscale will be scored as missing. If the whole scale has a missing item but the subscale has no items missing, the total score for the scale will be scored as missing but the subscale score will be computed.

6. ANALYSES AND SUMMARIES

All analyses will be conducted within the SAS population. Analyses will be descriptive in nature. No formal interim analyses are planned.

6.1. Disposition of subjects and Withdrawals

The numbers and percentage of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated, overall and by treatment group.

6.2. Baseline Summaries

All demographic, baseline characteristics and pre-treatment conditions will be summarized using the safety population. Descriptive statistics, including number of patients, mean, standard error, median, and range for continuous variables, and frequency and percent for categorical variables, will be provided for all demographic, baseline characteristics, and pre-treatment conditions.

6.3. Efficacy Analyses

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.

6.4. Special Safety Analyses

No formal analyses for special safety assessments will be performed for this study. However data on the C-SSRS, CDRS-R and Movement disorder scales (SARS, BAS, AIMS) will be summarized using descriptive statistics as described above.

6.5. Safety Analyses

No formal statistical analysis will be conducted on any of the below safety data.

The safety assessments include:

- *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.*

6.5.1. Adverse Events

All randomized subjects who receive at least one dose of antipsychotic treatment will be included in the safety data summarization. All treatment emergent 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 causality discontinuations and treatment emergent discontinuations from the study will be summarized.

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the time of first dosing with open label investigational product until the end of study participation and was not seen prior to the start of treatment in open-label extension (for example, during the baseline or double-blind study), or

- the event was seen prior to the start of treatment but increased in severity during treatment.

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.

6.5.2. Laboratory Data

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.

6.5.3. Physical Exam

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.

6.5.4. Body Weight and Height, BMI, Waist Circumference

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.

6.5.5. Vital Signs

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

6.5.6. Electrocardiograms

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.

6.6. Subgroup analysis

A subgroup analysis of subjects enrolled in Chinese sites will be conducted on the primary, secondary efficacy endpoints, as well as all safety endpoints. The Sponsor plans to utilize the subgroup analysis from both completed pediatric Studies A1281198 and open label study A1281201, to support a submission seeking the indication of the pediatric bipolar disorder for Zeldox in China.

7. INTERIM ANALYSES

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.