NDA/BLA Multidisciplinary Review and Evaluation

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Established/Proper Name	Ziprasidone HCl
(Proposed) Trade Name	Geodon
Pharmacologic Class	Atypical antipsychotic
Code name	N/A
Applicant	Viatris Specialty LLC
Doseage form	Capsule
Applicant proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of bipolar I disorder in pediatric patients ages 10-17 years
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	371596008 Bipolar I disorder (disorder)
Recommendation on Regulatory Action	Approval/PREA PMR Fulfilled
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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Reviewers of Multidisciplinary Review and Evaluation

Regulatory Project Manager	Sarah Seung, PharmD, MS
Nonclinical Reviewer	Sonia Tabacova, PhD
Nonclinical Team Leader	Aisar Atrakchi, PhD
Office of Clinical Pharmacology Reviewer(s)	Kofi Kumi, PhD, Jie Liu, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Luning (Ada) Zhuang, PhD Atul Bhattaram, PhD
Clinical Reviewer	Roberta Glass, MD
Clinical Team Leader	Martine Solages, MD
Statistical Reviewer	Semhar Ogbagaber, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Martine Solages, MD
Division Director (OCP)	Mehul Mehta, PhD
Division Director (OB)	Hsien Ming J Hung, PhD
Division Director (DP)	Tiffany R. Farchione, MD

Additional Reviewers of Application

OPQ	Lin Qi, PhD, CMC reviewer Gurpreet Gill Sangha, PhD, Branch Chief
Microbiology	NA
OPDP	Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer Aline Moukhtara, RN, MPH, Team Leader
OSI	Jenn Sellers, MD, PhD, Medical Officer
OSE/DEPI	NA
OSE/DMEPA	NA
OSE/DRISK	NA
Other	NA

Abbreviations: DEPI Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DP, Division of Psychiatry; DRISK, Division of Risk Management; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Glossary

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BD	bipolar I disorder
BID	twice daily
BLA	biologics license application
BMI	body mass index
CBC	complete blood count
CDER	Center for Drug Evaluation and Research
CDRS-R	Children's Depression Rating Scale–Revised
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
CI	confidence interval
CR	Complete Response
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DP	Division of Psychiatry
DPMH	Division of Pediatrics and Maternal Health
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDA	U.S. Food and Drug Administration
HbA1c	glycosylated hemoglobin
IND	Investigational New Drug
IRT	Interdisciplinary Review Team
ITT	intent-to-treat
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NDA	new drug application
OCP	Office of Clinical Pharmacology
OSI	Office of Scientific Investigation
PK	pharmacokinetics
popPK	population pharmacokinetic
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event

SAP	statistical analysis plan
SARS	Simpson-Angus Rating Scale
TSH	thyroid stimulating hormone
WR	Written Request
YMRS	Young Mania Rating Scale

1. Executive Summary

1.1. Product Introduction

Ziprasidone HCl (trade name: Geodon) is an atypical antipsychotic that is indicated for the treatment of schizophrenia and bipolar I disorder (BD) in adults (NDA 20825; approval dates: February 5, 2001 and August 19, 2004). Ziprasidone is available in oral capsules. An intramuscular form is available for the treatment of acute agitation associated with schizophrenia. The Applicant has proposed broadening the indicated population to include pediatric patients ages 10 to 17 years with acute manic or mixed episodes associated with BD (with or without psychotic features). (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy results are based on improvement of the primary endpoint, the Young Mania Rating Scale (YMRS), in which a reduction in the YMRS total score is evidence of improvement in BD symptoms. In the 4-week Study A1281198, (b) (4) Major protocol violations in Study A1281198 prompted the Agency to conduct site inspections and conduct a sensitivity analysis to explore the impact of the violations on the study results. Ultimately, site inspections did not uncover additional concerns about conduct of the study and the sensitivity analysis indicated that the violations did not impact the overall efficacy results. However, there are insufficient long-term safety data in this submission to support a labeling claim for ziprasidone use in pediatric patients diagnosed with BD.

The Agency determined that Study A1281198 did fulfill the terms of the Applicant's outstanding postmarketing requirement (PMR-682-1) as outlined when the requirement was issued. Study A1281198 will be described in section 8 of labeling (Pediatric Use). However, because of the lack of long-term safety data, the indicated population will not be broadened to include pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ziprasidone is an atypical antipsychotic that is indicated in adults for the treatment of schizophrenia, the acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder, and maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. Ziprasidone's efficacy in schizophrenia may be mediated through antagonism at dopamine type 2 (D2) and serotonin type 2 (5HT2) receptors. Its mechanism of action in bipolar disorder is unknown.

In this supplemental new drug application, the Applicant has proposed broadening ziprasidone's indicated population to include pediatric patients ages 10 to 17 years with acute manic or mixed episodes associated with bipolar I disorder. This application is also intended to meet the Applicant's requirement to submit pediatric assessments under the Pediatric Research Equity Act (PREA). The Applicant has an outstanding PREA postmarketing requirement to assess the safety and effectiveness of ziprasidone in pediatric patients ages 10 to 17 years with bipolar disorder. (b) (4)

The Applicant has submitted the results of a 4-week, double-blind, placebo-controlled efficacy and safety study (Study A1281198), data from a small number of patients from a discontinued long-term safety extension (A1281201), and information about antipsychotic use in the pediatric population from a literature review.

In 2013, the Agency advised that Study A1281198 had the potential to fulfill the outstanding PREA requirement. In January 2020, the Division of Psychiatry (the Division) notified sponsors of atypical antipsychotic medications, including this Applicant, that extrapolation of effectiveness to pediatric patients with bipolar disorder would be acceptable if the drug is indicated for adults, the adult and pediatric pharmacokinetic profiles are similar, and the long-term clinical safety data and relevant juvenile animal studies support the use of the drug in pediatric patients. Ziprasidone is indicated for bipolar disorder in adults, the pharmacokinetic profiles are similar in adults and pediatric patients, and the Division has agreed to waive the requirement for a juvenile animal study in this case. (b) (4) Although the Division advised the Applicant to continue collecting long-term safety data, the Applicant nevertheless notified the Division of the termination of Study A1281201 in June 2020. In October 2020, the Division cautioned the Applicant that their proposal to satisfy the PREA postmarketing requirement relied on outdated advice and did not meet the current standard that requires long-term clinical studies to demonstrate safe chronic use. In the February 2021 Filing Issues Identified Letter issued in response to this application, the Division indicated that it would review the application to assess if the Applicant has fulfilled the outstanding PREA requirement.

However, the Division noted that, in the absence of long-term pediatric safety data, it is unlikely that this submission would support a pediatric indication for bipolar disorder.

As noted above, a short-term efficacy and safety study is no longer required for a pediatric bipolar indication provided the other criteria outlined in the January 2020 advice letter are met, but the Applicant initiated Study A1281198 prior to the dissemination of this guidance and submitted results with this application. The primary endpoint in Study A1281198 was the change from Baseline to Week 4 on the YMRS, a validated, 11-item instrument that assesses manic symptoms in pediatric patients. The maximum score on the YMRS is 60; decreases in scores indicate clinical improvement. (b) (4)

The Applicant has acknowledged that raters who had not completed all the required training performed assessments for some patients in Study A1281198. The statistical analysis plan was revised (with agreement from the Division) to increase the sample size and to include a sensitivity analysis excluding patients whose diagnostic and primary efficacy endpoint assessments were impacted by these protocol violations. The sensitivity analyses performed by the Applicant and confirmed by the Division did not find an impact on the study results. Nonetheless, the protocol violations raised concerns about the overall conduct of the study and prompted clinical site inspections. The Office of Scientific Investigations (OSI) conducted inspections of three sites and concluded that the study appears to have been conducted adequately.

The data submitted with this application did not point to a unique safety profile in pediatric patients, but the overall safety data are limited. Safety findings in the short-term study generally mirrored those in the adult program, but too few patients were exposed to ziprasidone in the long-term safety study to fully assess ziprasidone's impacts on weight, metabolic parameters, QT interval, suicidal ideation and behavior, and extrapyramidal symptoms in pediatric patients. The review of published literature did not provide robust information about the long-term use of ziprasidone in pediatric patients; data regarding diagnosis, dosage, and duration of exposure could not be systematically assessed using the cited literature. Given the limited long-term safety information included with this application, the data are insufficient to conclude that the benefits of ziprasidone outweigh the risks in pediatric patients with bipolar disorder. No change to the indicated population is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric bipolar I disorder is characterized by the occurrence of manic episodes, which are almost always interspersed with major depressive episodes. Patients may also experience mixed episodes, during which symptoms of mania and depression are present concurrently. Bipolar disorder is associated with impaired academic and social functioning and increases the risks of adverse outcomes such as suicidal ideation and behavior and substance use. Onset of bipolar disorder typically occurs in adolescence or young adulthood. Bipolar disorder is a chronic condition for which ongoing psychopharmacologic treatment is recommended.	Pediatric bipolar disorder is a serious, chronic, and impairing condition that often begins in adolescence and generally requires treatment with medication over the lifespan. Patients with bipolar disorder are at risk for potentially life-threatening sequalae, including suicidal behavior and substance use disorders.
Current Treatment Options	• Multiple atypical antipsychotics are approved for the treatment of mania and mixed episodes in pediatric patients with bipolar disorder; lithium is also indicated in this population.	Ziprasidone is approved for the treatment of bipolar disorder in adults and has been used off-label in pediatric patients. Therefore, although multiple other medications are available for the treatment of pediatric bipolar disorder, efficacy and safety data on the use of ziprasidone in this population are needed.
Benefit	• In a 4-week, randomized, double-blind, placebo-controlled study (Study A1281198), (b) (4) The maximum score on the YMRS is 60; a lower score indicates less severe symptoms. • The placebo subtracted difference in least squares mean change from baseline was (b) (4) • Of note, the Applicant reported major protocol violations in this acute efficacy and safety study. The violations raised concerns about the overall conduct of the study, but sensitivity analyses indicated that these violations did not appear to impact the efficacy result.	(b) (4) .

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Exposures following the proposed dosing regimen in pediatric patients ages 10 to 17 years are expected to be generally comparable to those achieved in adult patients.	
Risk and Risk Management	• The most commonly reported adverse events in Study A1281198 were somnolence/sedation, fatigue, nausea, decreased appetite, headache, vomiting, musculoskeletal and connective tissue disorders, and akathisia. This pattern of adverse events is generally consistent with that observed in adults. • Approved labeling for ziprasidone includes a warning about the risk of QT prolongation. No new QT-related safety signals were identified in a review of the pediatric electrocardiogram data. • Approved labeling also includes warnings regarding the risks of dyslipidemia, weight gain, hyperglycemia, suicide, and tardive dyskinesia. The risk of these adverse reactions, which may become more apparent with chronic use, could not be fully evaluated with the limited long-term safety data in this application.	In the submitted clinical studies, the safety profile in pediatric patients with bipolar disorder was similar to the profile in adult patients. However, the application included insufficient long-term safety data to permit a full assessment of the risks of chronic use of ziprasidone. Therefore, there is not enough information to conclude that the benefits of ziprasidone outweigh its risks in the pediatric population. No changes to the indicated population are recommended. The Division ultimately concluded that Study A121198 did fulfill the Applicant's postmarketing requirement to perform an assessment of efficacy and safety in pediatric patients with bipolar disorder as the terms of the requirement were described at the time it was issued. Section 8 of labeling will be updated to note that a 4-week pediatric study has been conducted but will indicate that the safety and effectiveness of ziprasidone in pediatric patients have not been established.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	Section 8.1.2., Section 8.2.4
		☐	Observer-reported outcome (ObsRO)	
		X	Clinician-reported outcome (ClinRO)	Section 8.1.2, Section 8.2.4
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Bipolar I disorder (BD) is characterized by the occurrence of manic episodes. Typically, patients experience major depressive episodes as well. Individuals may also have mixed episodes, during which they experience symptoms of mania and depression concurrently. The symptoms of mania include a decreased need for sleep, increased energy, euphoria, irritability, grandiose delusions, impulsivity, risky behavior, and hypersexuality. Patients generally receive this lifelong diagnosis during adolescence or young adulthood, but some individuals may exhibit symptoms earlier in childhood. Pediatric BD can disrupt school, social interactions, and family life. Although there may be significant overlap in the symptomatology of mania in adults and children, pediatric patients may present very differently, because children may have difficulty verbalizing symptoms and emotions, have a high rate of comorbidity, and require a determination if their behavior is within a normal variation of their developmental stage. Because of the unique diagnostic challenge of BD in the pediatric population, a specialist (e.g., a child and adolescent psychiatrist) usually makes the diagnosis. Estimates of the prevalence of pediatric BD vary, but one meta-analysis estimates that pediatric BD has a lifetime prevalence of 1.8% (Van Meter et al. 2011). For adults, the prevalence of BD in the United States in adults aged 18 years and older is approximately 1% (Rowland and Marwaha 2018). BD is a chronic illness, and, without treatment, a manic episode can be life-threatening when a patient experiences disinhibition and poor judgment resulting in risky behavior.

2.2. Analysis of Current Treatment Options

Table 1, below, summarizes the six medications currently approved for the treatment of mania in bipolar I disorder in the pediatric population. Risperidone, quetiapine, aripiprazole, and asenapine have approval for use in pediatric patients ages 10 to 17 years. Olanzapine has approval for patients ages 13 and older and is second-line because of the increased risk of dyslipidemia and weight gain in adolescents as compared to adults. Lithium has approval for treatment of manic and mixed episodes in pediatric patients ages 7 and older.

The following anticonvulsant medications have an indication to treat manic episodes in adult BD and are used off-label to treat pediatric patients with BD: sodium valproate, valproic acid, and carbamazepine extended-release. Pediatric patients may receive off-label treatment with lamotrigine (Lamictal), which is indicated for the maintenance treatment of BD in adults but is not intended for use in acute manic or mixed episodes.

Table 1. Summary of FDA-Approved Treatments for BD in the Pediatric Population

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Risperidone (Risperdal)	BD: Mania in pediatric patients ages 10 to 17 years -acute treatment only	2007	1 to 6 mg daily	3-week, placebo-controlled, flexible dose trial in 169 patients ages 10 to 17 years with manic or mixed episode of BD. Dose 0.5 to 2.5 mg/day (N=50), 3 to 6 mg/day (N=61), or placebo (N=58) Primary endpoint: Mean change from baseline of YMRS: Both dose groups were superior to placebo	Tardive dyskinesia, weight gain, somnolence, hyperprolactinemia
Aripiprazole (Abilify)	BD: Acute treatment of manic and mixed episodes in pediatric patients ages 10 to 17 years -monotherapy or adjunctive therapy with lithium or valproate -maintenance treatment extrapolated from adults	2008	2 to 10 mg daily	4-week, placebo-controlled, fixed dose (10 or 30 mg) trial in 296 patients ages 10 to 17 years with BD, manic or mixed episodes with or without psychotic features. Primary endpoint: Mean change from baseline of YMRS: 10 mg group: -14.2 (N=59); 30 mg group: -16.5 (N=53); placebo: -8.8 (N=49)	Somnolence, headache, vomiting, EPS, fatigue, increased appetite, insomnia, nausea, and weight gain.
Quetiapine (Seroquel)	BD: Mania in pediatric patients ages 10 to 17 years -monotherapy	2009	400 to 600 mg daily	3-week, placebo- controlled, fixed dose (400 or 600 mg daily) in 284 patients ages 10 to 17 years with BD, manic episode Primary endpoint: Mean change from baseline of YMRS: 400 mg group (N=95): -14.3; 600 mg daily (N=98):-15.6; placebo (N=91): -9.0	EPS, akathisia, somnolence, dizziness increased weight

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Olanzapine (Zyprexa)	BD: Acute manic or mixed episodes in pediatric patients ages 13 to 17 years. -monotherapy 2nd line because of weight gain and dyslipidemia	2009	2.5 to 20 mg/day	3-week, placebo-controlled, flexible-dose (2.5 to 20 mg/day) in 161 patients ages 13 to 17years with manic or mixed episodes associated with BD Primary endpoint: Mean change from baseline of YMRS: Olanzapine groups had statistically significant greater mean reduction of YMRS score versus placebo group	Weight gain, dyslipidemia, sedation, tardive dyskinesia
Asenapine maleate (Saphris)	BD: Acute monotherapy treatment of manic or mixed episodes in pediatric patients ages 10 to 17 years	2015	2.5 to 10 mg/day twice daily, sublingually	3-week, placebo-controlled, fixed dose (2.5 mg, 5 mg, and 10 mg twice daily) in 403 patients with acute mania associated with BD. Primary endpoint: Mean change from baseline of total YMRS: 2.5 mg daily (N=88): -12.3; 5.0 mg daily (N=98):-15.6; 10.0 mg daily (N=81) -15.9: Placebo (N=79) -9.6	Neuroleptic Malignant Syndrome, tardive dyskinesia, hyperglycemia, diabetes, dyslipidemia, weight gain, leukopenia, neutropenia, agranulocytosis, QT prolongation, and seizures
Lithium (Lithobid)	BD: Manic and mixed episodes in pediatric patients ages 7 years and older	2018	Serum concentration between 1.0 and 1.5. Dosage is individualized based on serum concentrations and clinical response.	8-week, placebo-controlled in 81 patients ages 7 to 17 years with acute manic or mixed episodes of BD. Dose ranges 300 to 3600 (mean dose 1483 mg ±584) with serum levels ranging from 0 to 0.2 (mean level 0.98 mEq/L ±0.47)	Sedation, diarrhea, weight gain, increased thirst, and urination

Source: Product Label for: Abilify, Lithobid, Risperdal, Seroquel, Zyprexa, Asenapine
Abbreviations: BD, bipolar I disorder; EPS, extrapyramidal symptoms; YMRS, Young Mania Rating Scale

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

In February 2001, ziprasidone HCl (marketed as Geodon) was approved in the United States for the treatment of adults with schizophrenia (NDA 20825) and, subsequently, in August 2004 for the treatment of manic or mixed episodes associated with bipolar I disorder in adults (NDA 20825/S-009). At the time of approval for BD in adults (August 19, 2004), the Agency issued the following postmarketing requirement (PMR) for a deferred pediatric study under the Pediatric Research Equity Act (PREA):

PMR 682-1: You are required to assess the safety and effectiveness of Geodon as a treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents).

The original deadline for the Final Report Submission was June 30, 2008.

(b) (4)

On October 12, 2012, the Applicant notified the Division that, in order to fulfill PREA requirement PMR 682-1, they intended to conduct a new randomized, double-blind, placebo-controlled study of ziprasidone in pediatric patients with acute mania associated with BD. At the request of the Applicant, the Agency granted a deferral extension (on October 26, 2017) for PMR 682-1 with a final due date of December 31, 2020. The Applicant submitted this current supplement to fulfill PMR 682-1. Section 3.2, below, lists further details of the regulatory

history. The supplement was originally received on December 28, 2020. A major amendment was filed on March 24, 2021.

3.2. Summary of Presubmission/Submission Regulatory Activity

The pediatric development program for ziprasidone has an extensive regulatory history spanning over two decades. The following summarizes meetings and communications between the Applicant and the Agency and lays out the sequence of events under each major regulatory topic.

- Regulatory Summary of the Pediatric Written Request (WR) for ziprasidone:
  - February 11, 2003: The Agency issued a WR for pediatric studies (b) (4)
  - (b) (4)
  -
- Regulatory history of PMR 682-1:
  - August 19, 2004: As part of the approval for the indication of BD in adults, the Agency issued PMR 682-1 for a deferred pediatric study under the PREA with a final report submission date of June 30, 2008.
  - (b) (4)
  -
  -
  -
  - On October 12, 2012, the Applicant notified the Division of Psychiatry that, in order to fulfill PREA requirement PMR 682-1, they intended to conduct a new randomized,

double-blind, placebo-controlled study of ziprasidone in pediatric patients with acute mania associated with BD.

- December 19, 2012 and September 29, 2017: The Applicant requested a first and second extension of the PMR 682-1 due date. The Agency extended the final due date to December 31, 2020. The Agency denied a third deferral extension request (submitted October 30, 2020).
- September 3, 2013: In a Type C guidance meeting, the Agency advised the Applicant that their proposed short-term safety and efficacy study, A1281198, should be extended to a 4-week study and that, otherwise, the overall design and statistical plan in the submitted draft protocol had potential to fulfill the outstanding PREA requirement. The Division encouraged the Applicant to obtain longer-term pediatric safety data. The Applicant submitted their own summary of the meeting; according to this summary, the Applicant concluded from the meeting discussion that if PREA were satisfied, the results of the study would go into labeling.
- October 28, 2013: The Applicant submitted (to IND 54297) Protocol A1281198, a 4-week, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety trial of flexible doses of oral ziprasidone in children and adolescents with BD (current or most recent episode manic).
- May 23, 2014: The Applicant reported initiating Studies A1281198 and A1281201.
- April 26, 2017: The Division issued a Written Response (b) (4) The Division emphasized the complexity and uniqueness of accurately diagnosing BD in pediatric patients, and the need for a child and adolescent psychiatrist, who specializes in psychiatric diagnoses in the pediatric population.
- December 6, 2017: Preliminary meeting comments document the Applicant's plan to initiate a 6-month, open-label, extension trial (Study A1281201) to enhance subject recruitment and obtain additional long-term safety data in the pediatric population. Also, the Division agreed with the Applicant's proposal to increase the sample size of Study A1281198 by 14 patients to replace 14 patients who had assessments done by untrained personnel and would be excluded from the final analysis. The Applicant cancelled the scheduled meeting after receiving the preliminary comments.
- July 26, 2018: Written responses from the Division addressed questions regarding the Applicant's proposed amendments to the protocols for Study A1281198, the 4-week, placebo-controlled study, and Study A1281201, the 6-month extension study. The Division recommended an emphasis on safety findings, a titration schedule for patients who were on placebo in Study A1281198 and who entered the safety extension, and an increased frequency of visits and telephone check-ins throughout the study.
- January 13, 2020: FDA issued a General Advice letter to the Applicant (and other sponsors of atypical antipsychotics) outlining the updated nonclinical and clinical requirements to support the extrapolation of adult schizophrenia and BD data to the pediatric population (patients ages 13 years and older for schizophrenia and 10 years and older for BD). The letter explained that short-term pediatric efficacy

studies for antipsychotics with a mechanism similar to ziprasidone are no longer necessary. However, clinical long-term studies with sufficient exposure are crucial to demonstrate safe chronic use and to support labeling for the pediatric population.

- March 31, 2020: The Applicant submitted a proposal to fulfill PMR 682-1 by extrapolation of adult data.
- On May 29, 2020: The Agency informed the Applicant that they did not have sufficient long-term safety data to fulfill the requirements to extrapolate adult data for pediatric labeling. (b) (4) (b) (4) This letter also encouraged the Applicant to collect long-term safety data in Study A1281201 and consider permanently halting the short-term study A1281198 because long-term safety data had become the main focus for the demonstration of safety in the pediatric population.
- June 2020: The Applicant terminated both Studies A1281198 and A1281201.
- October 5, 2020: In a teleconference, the Applicant discussed plans to submit a pediatric supplement to fulfill PMR 682-1 (b) (4) The Agency agreed to evaluate whether the Sponsor's proposed pediatric supplement would fulfill the PREA PMR. However, the Agency cautioned the Applicant that their proposal to satisfy the PREA PMR relied on outdated advice and did not meet the current standard that requires long-term clinical studies to demonstrate safe chronic use to support labeling for the pediatric population. The Agency also restated concerns regarding the integrity of data collected in the extension studies, (b) (4)
- December 28, 2020: The Applicant submitted the pediatric supplement NDA 20825/S-063.
- February 26, 2021: In the Filing Issues Identified Letter, the Division indicated that it would review this submission to assess if the Applicant has fulfilled the outstanding PREA requirement. However, the Division noted that, in the absence of long-term pediatric safety data, it is unlikely that this submission would support a pediatric indication for bipolar disorder.
- March 24, 2021: The Applicant submitted a major amendment to NDA 20825/S-063 which included data from Study A1281201.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The Division of Psychiatry (DP) requested that OSI conduct site inspections; the three sites chosen for inspection contained either large numbers of enrolled patients or numerous reported protocol violations. The final OSI report (DARRTS: Sellers: 12/15/2021) concluded that the data generated from the three inspected sites appeared to be acceptable, and Study A1281198 appeared to have been conducted adequately.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This submission does not contain a pharmacology/toxicology section. As per Division's letter dated August 24, 2016, a juvenile animal toxicity study was not required to support clinical trials in pediatric patients with bipolar ages 10 to 17 years, based on an acceptable justification provided by the Applicant.

6. Clinical Pharmacology

6.1. Executive Summary

Geodon (ziprasidone) capsule was approved in 2004 for the acute treatment as monotherapy of manic or mixed episodes associated with BD. The available strengths include 20, 40, 60, and 80 mg.

A PMR was issued (PMR 682-1) for the Applicant to assess the safety and effectiveness of ziprasidone in pediatric patients ages 10 to 17 years with BD. The current efficacy supplement containing study A1281198 is intended to fulfill PMR 682-1.

Pharmacokinetic (PK) similarity between pediatric patients ages 10 to 17 years and adults was previously evaluated in four other PK studies (refer to the clinical pharmacology review filed in DARRTS on Apr 8, 2019). In that review, the conclusion was that there was no difference in PK between pediatric patients ages 10 to 17 years and adults after dose adjustment based on body weight.

In Study 1281198, one serum sample was collected from each subject during the Week 4 visit immediately prior to the morning dose on the day of visit. The descriptive statistics for serum ziprasidone trough concentration and a retrospective pooled population pharmacokinetic analysis were included in this submission.

6.2. Summary of Clinical Pharmacology Assessment

The PK information from Study 1281198 suggests that the observed median and mean serum ziprasidone trough concentration at Week 4 seems to be similar between the <45 kg and ≥45 kg body weight subgroups. The concentrations from Study 1281198 are in similar range as observed in adults at approved doses of 40, 60 and 80 mg twice daily (BID).

6.2.1. Pharmacology and Clinical Pharmacokinetics

Refer to approved the label for Geodon (ziprasidone)

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose regimen [redacted] (b) (4)

Therapeutic Individualization

No new information on drug interactions or effects of organ (renal and hepatic) impairment was included in this efficacy supplement. Refer to the approved label for Geodon (ziprasidone) capsules for recommendations on drug interactions and use in specific populations.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

No new pharmacokinetic and pharmacodynamic information describing the characteristics of ziprasidone were included in this efficacy supplement. Refer to the approved label for Geodon (ziprasidone) capsules for information on the characteristics of ziprasidone.

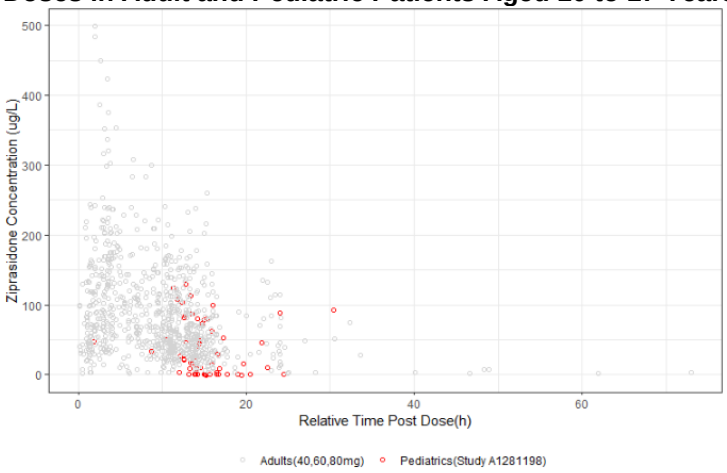
6.3.2. Clinical Pharmacology Questions

Are the pharmacokinetics of ziprasidone similar in pediatric patients ages 10 to 17 years and adults?

Yes. PK similarity between pediatric patients ages 10 to 17 years and adults was previously evaluated in four PK studies (refer to the clinical pharmacology review filed in DARRTS on Apr 8, 2009). In that review, the conclusion was that there was no difference in PK between pediatric patients ages 10 to 17 years and adults after dose adjustment based on body weight.

Figure 1 presents a comparison of PK profiles for adults from Studies 128-109 (80 mg BID), 128-303 (40 or 80 mg BID), 128-114 (40 or 80 mg BID) and 128-115 (60 mg BID) versus for pediatric patients from Study A1281198 (20, 40, 60 or 80 mg BID). Overall, ziprasidone concentrations in the pediatric data from Study A1281198 (only one trough concentration was assessed per patient) appear to be in the same range as approved doses in adults.

Figure 1. Observed Ziprasidone Concentration Versus Relative Time Post Dose for 40/60/80 mg Doses in Adult and Pediatric Patients Aged 10 to 17 Years in Study A1281198



Source: Clinical Pharmacology Reviewer's analysis

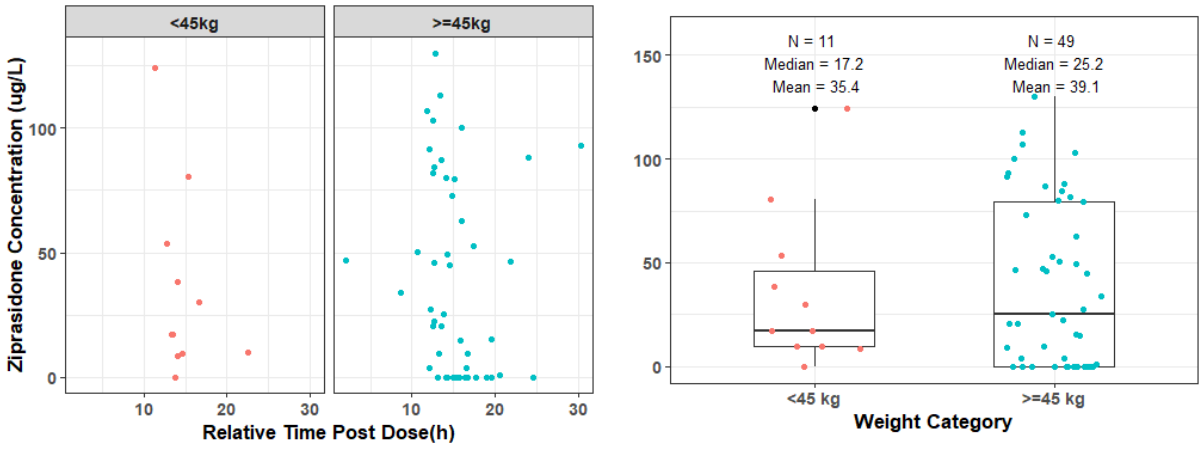
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

(b) (4)

The proposed dose regimen for pediatric patients is (b) (4)

The number of samples in patients <45 kg was smaller compared with those ≥45 kg. The plots and summary of descriptive statistics of trough concentrations are provided in the following figures and table. The observed median and mean serum ziprasidone trough concentration at Week 4 are similar between the <45 kg and ≥45 kg body weight subgroups (Figure 2 and Table 2) in Study A1281198.

Figure 2. Comparison of Observed Ziprasidone Trough Concentration in Pediatric Patients With Body Weight <45 kg vs. ≥45 kg in Study A1281198 After Week 4



Source: Clinical Pharmacology Reviewer's Analysis

Table 2. Descriptive Statistics for Serum Ziprasidone Trough Concentration (ng/mL) by Weight Category at Week 4 in Study A1281198

	Weight <45 kg n = 11	Weight ≥45 kg n = 48
NALQ	10	34
Mean	36.8	38.0
SD	36.82	39.29
CV (%)	100	103
Median	24.9	23.7
Min	0.0	0.0
Max	124.0	130.0

n = Number of observations (non-missing concentrations)
NALQ = Number of observations Above Lower Limit of Quantitation. Summary statistics are not presented if NALQ = 0.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.5 ng/mL.

Source: Applicant's Clinical Overview, page 19
Abbreviations: CV, coefficient of variation; SD, standard deviation

The total exposures of ziprasidone following the proposed dosing regimen in pediatric patients ages 10 to 17 years are expected to be generally comparable to those achieved in adult patients. (b) (4)

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. No new information on the effect of organ (renal and hepatic) impairment was included in this efficacy supplement. Refer to approved label for Geodon (ziprasidone) for recommendations on use in specific populations.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. Geodon capsule is to be administered with food. No new information on drug-drug interactions was included in this efficacy supplement. Refer to the approved label for Geodon (ziprasidone) for additional information.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 3 lists the efficacy and safety studies that were considered in this review. Table 4 lists previously completed studies in pediatric patients with BD and schizophrenia who were exposed to ziprasidone. However, the data from these studies were not considered in this review because of data integrity concerns. Please see Section 3 (Regulatory Background) for details.

Table 3. Clinical Studies for Bipolar Disorder (Current or Most Recent Episode Manic) in Pediatric Patients in NDA 20825/S-063

Study Name	Trial Design/Duration	Primary Endpoint	No. of Patients (n) in Treatment Groups/Disposition	Study Population
Study A1281198	Randomized, 4-week, placebo-controlled, flexible dose (weight-based), multicenter	YMRS total score	Total treated: N=171 <45 kg: N=30 ≥45 kg: N=141 Completed: N=132 (77%) Discontinued: N=39 (23%)	10 to 17 years
Study A1281201	Open-label, flexible-dose (weight-based), 26-week extension study of A1281198	Safety	Total treated N=23 <45 kg: N=6 ≥45 kg: N=17 Completed: N=10 (43%) Discontinued: N=13 (56%) Extension study of A1281198	10 to 17 years

Source: Study Reports for Studies A1281198 and A1281201
Abbreviations: YMRS, Young Mania Rating Scale

(b) (4)

7.2. Review Strategy

The efficacy review focused on Study A1281198, a randomized, 4-week, placebo-controlled, flexible-dose study in pediatric patients ages 10 to 17 years diagnosed with bipolar disorder (current or most recent episode manic).

The safety review focused primarily on Study A1281198 and includes a discussion of observed trends in Study A1281201, the longer-term, 26-week, open-label safety extension.

In an effort to provide additional data about the safety profile of ziprasidone, the Applicant included 71 published articles that mention ziprasidone or provide information regarding antipsychotic effects in the pediatric population. The clinical reviewer evaluated whether these articles provide data pertinent to the safety assessment in pediatric patients with bipolar disorder.

(b) (4)

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. A1281198

Trial Design

Study A1281198 was a 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose (weight-based) study evaluating the safety and efficacy of ziprasidone for the treatment of BD (current or most recent episode manic) in pediatric patients ages 10 to 17 years. The study also incorporated sparse PK sampling. There were a total of 58 sites, which included five in Ukraine and 52 in the United States. The Applicant terminated 22 sites; the reasons for termination were unclear in the study report.

To be eligible for inclusion, patients had to meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) criteria for a primary diagnosis of BD (current or most recent episode manic) with diagnostic confirmation via the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL), a semistructured diagnostic interview. Inclusion criteria also included a Young Mania Rating Scale (YMRS) score of ≥17 at the Screening and Baseline visits and a body mass index (BMI) z-score between -1.65 and +2.00. Other requirements included a normal physical exam and laboratory findings, a negative serum beta-hCG test for females, and a QTc (Fridericia) ≤450 msec at Screening or Baseline with no history of QT interval prolongation. Notable exclusion criteria included:

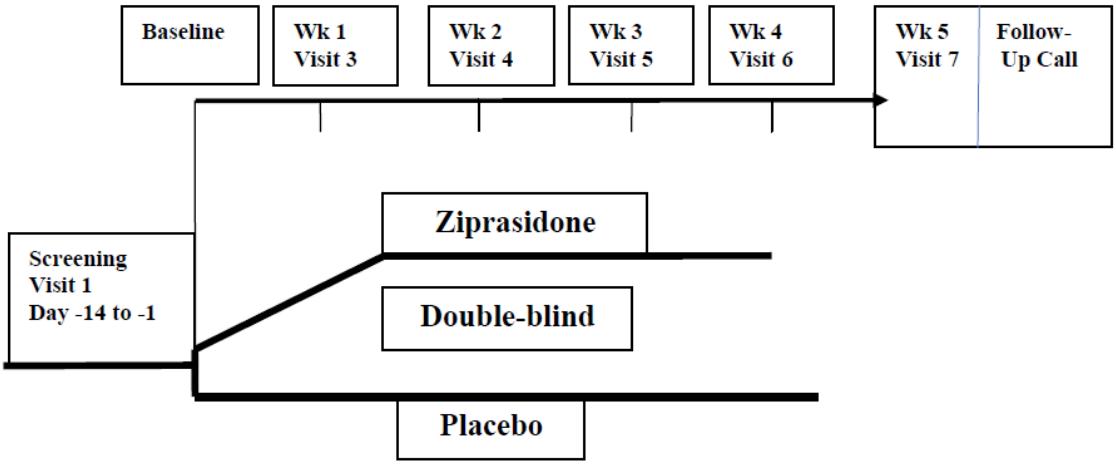
- Patients with DSM-5 defined Substance Use Disorder (including psychoactive substance or alcohol use disorders) within the preceding 1 month of screening.
- Patients at risk of hurting themselves or others as judged by the Investigator.
- Patients at risk for suicide based on any lifetime history of suicidal behavior according to the Columbia Suicide Severity Rating Scale (C-SSRS) score.
- An Intelligence Quotient (IQ) <70 that would interfere with study conduct or with the interpretation of the study assessments.
- Patients with autism spectrum disorder, disruptive mood dysregulation disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder

Prohibited concomitant medications included anxiolytics (except lorazepam up to 2 mg per day), monoamine oxidase inhibitors, antidepressants, antipsychotics, stimulants, anticonvulsant mood stabilizers, and any medication that prolongs the QT interval. Prohibited medications had a wash-out period of 2 weeks prior to baseline (depot antipsychotics 4 weeks prior to baseline).

Randomization to either the placebo group or the ziprasidone treatment group occurred at baseline. Flexible dosing for the ziprasidone group was based on the patient's weight (<45 kg or ≥45). After a 1- to 2-week titration period, the target dose range for patients <45 kg was 60 to 80 mg ziprasidone daily, while patients ≥45 kg had a target dose range of 120 to 160 mg

ziprasidone daily. Participation in the study required a minimum tolerated dose of 60 mg ziprasidone for patients <45 kg and 80 mg for patients ≥45 kg. At the end of the study, patients could enter into the open-label ziprasidone extension study (A1281201) or were offered alternative therapies for treatment of their BD.

Figure 3. A1281198 Study Design



Source: Study A1281198 protocol, p. 29

Study Endpoints

The primary efficacy endpoint was change from Baseline to Week 4 in the YMRS score. The key secondary efficacy endpoint in this trial was change from Baseline to Week 4 in the Clinical Global Impression–Severity (CGI-S) score.

Statistical Analysis Plan

The statistical plan as described below was prespecified before data unblinding.

Multiplicity Adjustment

No adjustments were made for multiple comparisons. Multiplicity adjustment is not relevant in this case because there was only one treatment group compared to placebo, with only one primary efficacy endpoint and one key secondary endpoint.

Analysis Method

The prespecified primary efficacy analysis was mixed model repeated measures (MMRM) analysis without imputing missing data. The MMRM model assesses the change from baseline in YMRS and is adjusted for treatment, visit and visit-by-treatment interaction, and weight category as fixed effects and baseline score as a covariate. The model parameters were to be estimated using the restricted maximum-likelihood method (REML), with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. The analysis population was the intent-to-treat (ITT) analysis set, which

was defined as the set of all patients who were randomized, had baseline measurements, took at least one dose of study medication (ziprasidone or placebo), and had at least one postbaseline visit.

Sample Size and Power

Original Sample Size: The statistical analysis plan (SAP) stated that 111 subjects would yield 85% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumed a treatment effect of -4.55 (relative to placebo) and a within-group standard deviation of 8, (b) (4) , which was the estimated difference in change from Baseline to Week 4 in the YMRS total score for ziprasidone versus placebo. Adjusting for a dropout rate of 38% at Week 3, a total sample size of 180 subjects (90 subjects per treatment groups) were to be randomized.

Re-estimation of Sample Size: The original sample size was adjusted because the Data Monitoring Committee revealed that the assumed dropout rate was substantially less than 38% based on blinded data during the trial. Assuming a dropout rate of approximately 20% (at Week 4) and keeping other assumptions the same results in a total sample size of approximately 138 (69 per arm).

Protocol Amendments

The Applicant submitted the first and second protocol amendments on August 31, 2018 and April 19, 2019.

The first amendment rescinded the requirement of two pregnancy tests within the 14-day screening period and stated that pregnancy tests would be conducted at each visit.

The second protocol amendment described an increase in the sample size to replace 14 patients who had protocol violations attributed to unqualified personnel conducting the primary endpoint assessments (YMRS) or the diagnostic interview instrument (K-SADS); the Written Response Only Meeting Minutes of December 6, 2017, include the Division's agreement to the Applicant's proposal to increase the sample size by 14 patients and conduct a sensitivity analysis to mitigate the effect of the incomplete rater trainings.

The original SAP had a submission date of October 28, 2013. There were two amendments to the SAP (dated March 8, 2019 and July 21, 2020). The second SAP amendment was submitted to the Division on December 24, 2020. The first SAP amendment increased the sample size by 14 patients to replace the 14 patients with protocol violations due to unqualified personnel conducting the primary endpoint or the diagnostic interview instrument. To assess the impact of this protocol violation, the Applicant would conduct a sensitivity analysis excluding these 14 patients impacted by the rating training issue. The second SAP amendment proposed replacing a higher number of identified patients with protocol violations to 18 (with a final sample size of 156). This amendment made re-adjustments based on a new dropout rate assumption as revealed from blinded data during the trial. In the A1281198 Study Report (p. 39), the Applicant

states that after finalization of the SAP amendment Version 1.2, a total of 19 participants were excluded from the analysis.

Reviewer's comment: It is concerning that the Applicant identified 14 patients with protocol violations due to unqualified personnel conducting both the diagnostic instrument for inclusion criteria and the primary efficacy instrument (i.e., instrument crucial to the integrity of the study) and, 16 months later, reported that they identified an increased total of 18 patients. Even after the SAP amendment, the Applicant identified one more patient subject to this violation, increasing the number of affected patients to 19. Also, the increasing number of patients with this violation raised questions about whether unidentified patients could have been subject to this protocol violation. As noted above, the Division requested clinical site inspections to assess the conduct of the study.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant provided the following attestation:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice Guidelines and International Guidelines for Biomedical Research Involving Human Subjects. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Data Quality and Integrity

There were a significant number of protocol violations including informed consent violations, medication errors, and nonqualified raters conducting eligibility determinations.

As noted above, the amended SAP indicated that 18 patients were impacted by protocol violations related to the use of unqualified raters. The study report indicated that an additional impacted patient was later identified. In an information request dated September 14, 2021, the Division asked the Sponsor to clarify the number of patients that the Applicant had excluded from the sensitivity analysis that evaluated the impact of the rater training issue. This information was requested from the Applicant to allow the Division to confirm the results of the sensitivity analysis.

Also, the Applicant did not report that there were two sites (1007 and 1036) with Principal Investigators who do not appear to have specialty training in child and adolescent psychiatry, which was a protocol requirement (refer to FDA Written Response of April 26, 2017).

Because of the seriousness and quantity of the protocol violations, the DP requested that OSI conduct site inspections; the sites chosen for inspection contained either large numbers of enrolled patients or numerous reported protocol violations.

Financial Disclosure

The Applicant adequately disclosed a certification of financial interests and arrangements stating that none of the 231 investigators participating in Study A1281198 had financial interests or arrangements described in 21 CFR Part 54.

Patient Disposition

Of the 280 patients screened, 171 patients were randomized (86 ziprasidone, 85 placebo). There were 132 patients who completed the study, including 60 (69.8%) in the ziprasidone group and 72 (84.7%) patients in the placebo group. The withdrawal rate was higher in the ziprasidone group (27%) compared to the placebo group (12%) primarily due to adverse events. Table 5, below, is a summary of how the Applicant attributed reasons for discontinuations.

Table 5. Patient Disposition Summary, Study A1281198

Number (%) of Subjects	Ziprasidone (N=86) n (%)	Placebo (N=85) n (%)
Disposition Phase: Treatment		
Discontinued	23 (26.7)	10 (11.8)
Insufficient Clinical Response	2 (2.3)	2 (2.4)
Adverse Event	14 (16.3)	4 (4.7)
Medication Error Without Associated Adverse Event	1 (1.2)	0
Death	0	0
Protocol Deviation	0	0
Lost to Follow-Up	0	1 (1.2)
Withdrawal By Parent/Guardian	4 (4.7)	2 (2.4)
Screen Failure	1 (1.2)	0
Other	1 (1.2)	1 (1.2)
Completed	63 (73.3)	75 (88.2)
Disposition Phase: Follow-Up		
Discontinued	26 (30.2)	13 (15.3)
Insufficient Clinical Response	2 (2.3)	2 (2.4)
Adverse Event	14 (16.3)	4 (4.7)
Medication Error Without Associated Adverse Event	1 (1.2)	0
Death	0	0
Protocol Deviation	0	0
Lost to Follow-Up	0	1 (1.2)
Withdrawal By Parent/Guardian	7 (8.1)	4 (4.7)
Screen Failure	1 (1.2)	0
Other	1 (1.2)	2 (2.4)
Completed	60 (69.8)	72 (84.7)

Source: A1281198 Clinical Study Report Table 5, p. 41

Protocol Violations/Deviations

Table 6, below, categorizes the 189 protocol violations and deviations listed in the Applicant's submission for the placebo-controlled, randomized, 4-week study A1281198. These protocol violations occurred in 66 (76.7%) patients in the ziprasidone and 66 (77.6%) patients in the placebo group or 132 (78.6%) of the total study population. For further discussion, please refer to the Data Integrity and Quality Section, above.

Table 6. Protocol Violations in the Intent-To-Treat Population, Study A1281198

Protocol Violations	Ziprasidone (N=85) n (%)	Placebo (N=83) n (%)
Inclusion/exclusion criteria violation	5 (5.9)	3 (3.6)
Enrolled patient in the study with suicidal risk without getting a risk assessment by PI	1 (1.2)	0
Enrolled patients taking prohibited medications	3 (3.5)	2 (2.4)
Included patients outside the BMI inclusion criteria	2 (2.4)	1 (1.2)
Informed consent violation	8 (9.4)	3 (3.6)
Investigator did not sign or date on the same day as patient, parent, or guardian	1 (1.2)	0
Obsolete version of consent or assent signed	3 (3.5)	2 (2.4)
Correct version of consent or assent not signed by guardian, patient, or administrator	4 (4.7)	1 (1.2)
Medication errors	15 (17.6)	9 (10.8))
Patient missed 20% of all doses in study	2 (2.4)	1 (1.2)
Patient missed 20% of doses between study visits	5 (5.9)	2 (2.4)
Patient took incorrect dose	2 (2.4)	2 (2.4)
Patient took prohibited concomitant medication during study	1 (1.2)	2 (2.4)
Medication stored outside required temperature range	7 (8.2)	3 (3.6)
Laboratory violation	9 (10.6)	9 (10.8)
Required labs not done during screening	0	4 (4.8)
Labs not done during the course of the study	9 (10.6)	1 (1.2)
Samples not labeled properly	0	1 (1.2)
Lab sample unable to be analyzed	2 (2.4)	1 (1.2)
Procedure or test violations	55 (64)	58 (69.9)
Rating done by rater not qualified to complete assessment	13 (15.3)	14 (16.9)
Performed improperly per protocol	46 (54.1)	58 (69.9)
Performed improperly and required for eligibility determination	2 (2.4)	4 (4.8)
Not reviewed by investigator	0	1 (1.2)
Performed outside protocol window	0	1 (1.2)
Not performed during the study	0	3 (1.2)
Other	7 (8.2)	8 (9.6)
Protocol discontinuation criteria not followed	2 (2.4)	1 (1.2)
Randomized out of protocol-defined window	1 (2.4)	0
Visit outside time specified in protocol	3 (3.5)	7 (8.4)
Delayed report of serious adverse event to the Applicant	1 (1.2)	0
Total violations =189	N=99	N=90

Source: A1281198 Study Report: Appendix Table 14.1.1.3, p. 122
Abbreviations: BMI, body mass index; PI, principal investigator

Table of Demographic Characteristics

As summarized in Table 7, there were no major differences in the demographic characteristics of the ziprasidone group and the placebo group. The majority of patients in the study were Caucasian females.

Table 7. Demographic Characteristics, Study A1281198

	Ziprasidone (N=86)			Placebo (N=85)		
Parameter	**Male (N=38)**	**Female (N=48)**	**Total (N=86)**	**Male (N=38)**	**Female (N=47)**	**Total (N=85)**
Age (years)						
<10, n (%)	0	0	0	0	0	0
10-13, n (%)	27 (71.1)	19 (39.6)	46 (53.5)	21 (55.3)	23 (48.9)	44 (51.8)
14-17, n (%)	11 (28.9)	29 (60.4)	40 (46.5)	17 (44.7)	24 (51.1)	41 (48.2)
>17, n (%)	0	0	0	0	0	0
Median	12.0	14.0	13.0	13.0	14.0	13.0
Mean (SD)	12.6 (2.14)	13.9 (2.11)	13.3 (2.21)	13.7 (2.01)	13.5 (2.14)	13.6 (2.07)
Range(min,max)	(10, 17)	(10, 17)	(10, 17)	(11, 17)	(10, 17)	(10, 17)
Race, n (%)						
White	23 (60.5)	36 (75.0)	59 (68.6)	25 (65.8)	30 (63.8)	55 (64.7)
Black or African American	13 (34.2)	10 (20.8)	23 (26.7)	11 (28.9)	13 (27.7)	24 (28.2)
Asian	0	1 (2.1)	1 (1.2)	0	1 (2.1)	1 (1.2)
Other	2 (5.3)	1 (2.1)	3 (3.5)	2 (5.3)	3 (6.4)	5 (5.9)
Ethnicity, n (%)						
Hispanic or Latino	5 (13.2)	7 (14.6)	12 (14.0)	7 (18.4)	7 (14.9)	14 (16.5)
Not Hispanic or Latino	33 (86.8)	41 (85.4)	74 (86.0)	31 (81.6)	40 (85.1)	71 (83.5)
Racial designation, n (%)						
Southeast Asian	1 (2.6)	0	1 (1.2)	0	0	0
Far East Asian	0	1 (2.1)	1 (1.2)	0	1 (2.1)	1 (1.2)
North American Indian	0	1 (2.1)	1 (1.2)	2 (5.3)	0	2 (2.4)
Pacific Islander	0	0	0	0	0	0
Alaskan Native	0	0	0	0	0	0

Source: A1281198 Study Report Table 8 p. 4
Abbreviations: SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The ziprasidone and placebo groups did not differ in mean baseline weight, height, or BMI (Table 8).

Table 8. Baseline Growth Parameters, Study A1281198

Measurement	**Ziprasidone (N=86)[a]**	**Placebo (N=85)[a]**
Weight (kg)		
n[b]	86	85
Mean	57.54	58.01
SD	14.518	14.541
Median	56.10	58.50
Min	26.444	31.400
Max	92.079	104.500

Measurement	Ziprasidone (N=86)[a]	Placebo (N=85)[a]
Weight (kg) <45		
n[b]	15	15
Mean	37.04	38.31
SD	4.620	4.124
Median	36.47	38.10
Min	26.444	31.400
Max	44.906	43.300
Weight (kg) ≥45		
n[b]	71	70
Mean	61.87	62.23
SD	11.941	12.311
Median	58.97	60.70
Min	45.100	45.100
Max	92.079	104.500
Height (cm)		
n[b]	86	85
Mean	157.88	159.69
SD	10.627	11.410
Median	156.55	160.02
Min	129.000	137.000
Max	185.400	187.960
BMI (kg/m²)		
n[b]	86	85
Mean	22.79	22.45
SD	4.152	3.761
Median	22.25	22.40
Min	15.900	15.300
Max	33.800	32.700
BMI Z-Score		
n[b]	86	85
Mean	0.83	0.75
SD	0.869	0.816
Median	1.10	0.90
Min	-1.600	-1.640
Max	2.240	2.040

Source: A1281198 Study Report Table 9 p. 46-47
BMI (kg/m²) = weight (kg)/[height (cm)]²
BMI Z-score is derived using the Children's Hospital of Philadelphia z-score calculator based upon the CDC growth chart.
[a] N = number of subjects in the specified group.
[b] n = Number of subjects with the specified characteristic.
PFIZER
Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; SD, standard deviation

The mean baseline YMRS score for the ziprasidone (30.7±6.6) and placebo (29.2±6.5) groups were comparable; the mean baseline CGI-S scores were also similar in the ziprasidone group (4.6±0.6) and placebo group (4.6±0.7). Eight patients (9%) in the ziprasidone group and 11 patients (13%) in the placebo group had received prior treatment with an antipsychotic. Attention deficit hyperactivity disorder (ADHD), the most prevalent comorbid illness in both treatment groups, was reported in 32 patients (37%) in the ziprasidone group and 27 patients in the placebo group (31.8%). Five patients (5.8%) in the ziprasidone group and seven patients (8.2%) in the placebo group took the permitted concomitant medications of clonazepam, lorazepam, or propranolol.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

According to clinical study report for Study 1281198 (Clinical Study Report Appendix Table 14.1.1.3), 14% of the patients in the database had recorded medication errors, which included 15 patients (17.6%) in the ziprasidone group and 9 patients (10.8%) in the placebo group. The A1281198 study report states that four patients in the ziprasidone treatment group and three patients in the placebo group who had protocol deviations related to the investigational product were excluded from the per protocol (PP) analysis. See the Applicant's table (Table 9) that lists exclusions from the PP population due to compliance issues.

Table 9. Exclusions From Per Protocol Population and Important Protocol Deviations in the Intent-To-Treat Population

Protocol Deviation Category/Subcategory	Ziprasidone (N=85) n (%)	Placebo (N=83) n (%)
Concomitant medications	0	1 (1.2)
Subject took prohibited medication during study treatment.	0	1 (1.2)
Investigational product	4 (4.7)	3 (3.6)
Dosing was not compliant cumulatively over the entire study, defined as 20% of all doses were missed	2 (2.4)	1 (1.2)
Subject took incorrect dose	2 (2.4)	2 (2.4)
Procedures/tests[a]	10 (11.8)	9 (10.8)
Rating done by a rater who was not qualified to complete assessment	10 (11.8)	9 (10.8)

Source: A1281128 Study Report, p. 43, Table 6
[a] These subjects were excluded from the per protocol analysis because their YMRS or KSADS ratings were performed by unqualified raters.

Efficacy Results – Primary Endpoint

This study evaluated the efficacy of flexible doses of ziprasidone, compared to placebo, in pediatric patients (ages 10 to 17 years) with bipolar I disorder. The target dose ranged from 60 mg/day to 80 mg/day for patients <45 kg and 120 mg/day to 160 mg/day for patients ≥45 kg. The primary efficacy endpoint was change from Baseline to Week 4 in YMRS total score. The YMRS is an 11-item instrument that assess the severity of mania in patients with BD. 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 is based on patient self-report combined with clinician observations. (b) (4)

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(b) (4)

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8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review focuses primarily on data from Study A1281198, a 4-week, placebo-controlled, flexible-dose study in 171 pediatric patients ages 10 to 17 years diagnosed with bipolar disorder or BD (current or most recent episode manic). The Applicant also submitted data from Study A1281201, a 26-week extension study of Study A1281198; 23 patients entered but only 10 patients completed the study. The database from Study A1281201 is too limited to make long-term safety conclusions based on this study for the purposes of labeling. However, whenever possible, this review includes observed trends from the long-term study.

The Applicant submitted 71 published articles in an effort to provide additional information about the long-term safety of ziprasidone in the pediatric population. The articles discussed the effects of antipsychotic medications in the pediatric population, and some articles covered issues specific to ziprasidone use. An in-depth review revealed that none of these articles provided sufficiently controlled or complete data to support safety conclusions appropriate for labeling purposes (See Section 8.2.9 Additional Safety Explorations).

(b) (4)

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8.2.2. Review of the Safety Database

Overall Exposure

Table 18, below, summarizes the safety population from the 4-week study A1281198; the majority of patients were white with a mean age of 13.6 years and a relatively equal gender distribution across the treatment groups. Table 19 summarizes the safety population for the 26-week extension Study A1281201; the majority of patients were white with a mean age of 14.1 years and an equal gender distribution across the treatment groups. Table 20 shows that the mean exposure for A1281201 was 124 days (18 weeks) with a range of 4 to 186 days in which 10 of 23 patients (43%) were enrolled for ≥181 days.

Table 18. Demographic Characteristics of Safety Population in Study A1281198

	Ziprasidone (N=86)			Placebo (N=85)		
	Male (N=38)	Female (N=48)	Total (N=86)	Male (N=38)	Female (N=47)	Total (N=85)
Age (Years):						
<10	0	0	0	0	0	0
10-13	27 (71.1%)	19 (39.6%)	46 (53.5%)	21 (55.3%)	23 (48.9%)	44 (51.8%)
14-17	11 (28.9%)	29 (60.4%)	40 (46.5%)	17 (44.7%)	24 (51.1%)	41 (48.2%)
>17	0	0	0	0	0	0
Median	12.0	14.0	13.0	13.0	14.0	13.0
Mean (SD)	12.6 (2.14)	13.9 (2.11)	13.3 (2.21)	13.7 (2.01)	13.5 (2.14)	13.6 (2.07)
Range(min,max)	(10, 17)	(10, 17)	(10, 17)	(11, 17)	(10, 17)	(10, 17)
Race						
White	23 (60.5%)	36 (75.0%)	59 (68.6%)	25 (65.8%)	30 (63.8%)	55 (64.7%)
Black or African American	13 (34.2%)	10 (20.8%)	23 (26.7%)	11 (28.9%)	13 (27.7%)	24 (28.2%)
Asian	0	1 (2.1%)	1 (1.2%)	0	1 (2.1%)	1 (1.2%)
Other	2 (5.3%)	1 (2.1%)	3 (3.5%)	2 (5.3%)	3 (6.4%)	5 (5.9%)
Ethnicity						
Hispanic or Latino	5 (13.2%)	7 (14.6%)	12 (14.0%)	7 (18.4%)	7 (14.9%)	14 (16.5%)
Not Hispanic or Latino	33 (86.8%)	41 (85.4%)	74 (86.0%)	31 (81.6%)	40 (85.1%)	71 (83.5%)
Racial Designation						
Southeast Asian	1 (2.6%)	0	1 (1.2%)	0	0	0
Far East Asian	0	1 (2.1%)	1 (1.2%)	0	1 (2.1%)	1 (1.2%)
Noth American Indian	0	1 (2.1%)	1 (1.2%)	2 (5.3%)	0	2 (2.4%)
Pacific Islander	0	0	0	0	0	0
Alaskan Native	0	0	0	0	0	0

Source: A1281198 Study Report: Table 8, p. 45 and Summary of Clinical Safety: Table 2 p. 19
Abbreviations: SD, standard deviation

Table 19. Demographic Characteristics of Safety Population in Study A1281201

	Ziprasidone/Ziprasidone (N=10)			Placebo/Ziprasidone (N=13)			Combined (N=23)		
	Male (N=5)	Female (N=5)	Total (N=10)	Male (N=6)	Female (N=7)	Total (N=13)	Male (N=11)	Female (N=12)	Total (N=23)
Age (Years):									
<10	0	0	0	0	0	0	0	0	0
10-13	3 (60.0%)	2 (40.0%)	5 (50.0%)	3 (50.0%)	1 (14.3%)	4 (30.8%)	6 (54.5%)	3 (25.0%)	9 (39.1%)
14-17	2 (40.0%)	3 (60.0%)	5 (50.0%)	3 (50.0%)	6 (85.7%)	9 (69.2%)	5 (45.5%)	9 (75.0%)	14 (60.9%)
18	0	0	0	0	0	0	0	0	0
Median	13.00	15.00	13.50	13.50	15.00	15.00	13.00	15.00	15.00
Mean (Std. Dev.)	13.2 (2.17)	14.8 (2.28)	14.0 (2.26)	13.5 (2.43)	14.7 (1.50)	14.2 (1.99)	13.4 (2.20)	14.8 (1.76)	14.1 (2.07)
Range(min,max)	(10, 16)	(12, 17)	(10, 17)	(11, 16)	(12, 17)	(11, 17)	(10, 16)	(12, 17)	(10, 17)
Gender									
Male	5 (100.0%)	0	5 (50.0%)	6 (100.0%)	0	6 (46.2%)	11 (100.0%)	0	11 (47.8%)
Female	0	5 (100.0%)	5 (50.0%)	0	7 (100.0%)	7 (53.8%)	0	12 (100.0%)	12 (52.2%)
Race									
White	4 (80.0%)	4 (80.0%)	8 (80.0%)	4 (66.7%)	6 (85.7%)	10 (76.9%)	8 (72.7%)	10 (83.3%)	18 (78.3%)
Black or African American	0	1 (20.0%)	1 (10.0%)	1 (16.7%)	0	1 (7.7%)	1 (9.1%)	1 (8.3%)	2 (8.7%)
Asian	0	0	0	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	1 (16.7%)	0	1 (7.7%)	1 (9.1%)	0	1 (4.3%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0
Multiracial	1 (20.0%)	0	1 (10.0%)	0	1 (14.3%)	1 (7.7%)	1 (9.1%)	1 (8.3%)	2 (8.7%)

Source: A1281201 Study Report: Table 6, p. 33

Table 20. Duration of Treatment for Safety Population in Study A1281201

	Ziprasidone/Ziprasidone (N=10)	Placebo/Ziprasidone (N=13)	Combined (N=23)
Duration of Treatment (Days)[a]			
n	10	13	23
Mean (Std. Dev.)	83.70 (69.455)	154.92 (60.003)	123.96 (72.392)
Median	72.00	181.00	179.00
Range(min,max)	(7.00, 183.00)	(4.00, 186.00)	(4.00, 186.00)
Category (Days)[a]			
<=1	0	0	0
2-7	1 (10.0)	1 (7.7)	2 (8.7)
8-14	1 (10.0)	0	1 (4.3)
15-28	1 (10.0)	0	1 (4.3)
29-60	2 (20.0)	1 (7.7)	3 (13.0)
61-90	0	0	0
91-120	1 (10.0)	0	1 (4.3)
121-150	2 (20.0)	1 (7.7)	3 (13.0)
151-180	0	2 (15.4)	2 (8.7)
>=181	2 (20.0)	8 (61.5)	10 (43.5)

Source: A1281201 Study Report: Table 8, p. 38
Ziprasidone/Ziprasidone = ziprasidone group in Study A1281198
Placebo/Ziprasidone = placebo group in Study A1281198

Adequacy of the Safety Database

The Applicant has not provided sufficient long-term exposure data to support the safe chronic use of ziprasidone in the pediatric population. (b) (4) (b) (4) n this supplement, Study A1281201, a 26-week study and the only long-term study in this database, had exposure data for 10 patients exposed for at least 181 days; this is insufficient exposure to evaluate the safety profile for ziprasidone in the pediatric population diagnosed with BD, who usually requires long-term treatment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Although the Division had previously advised the Applicant that long-term safety data would be needed to expand the bipolar disorder indication to the pediatric population, the original submission (received December 28, 2020) did not include long-term safety data from Study A1281201. In the Filing Review Issues Identified Letter, the Division reiterated to the Applicant that, in the absence of long-term pediatric safety data, it was unlikely that the submission would support the pediatric indication. The Applicant submitted a major amendment with this data, resulting in a 3-month extension of the review clock.

The clinical reviewer noted that the review of the submitted materials was challenging because the Applicant did not update clinical safety summary documents with the major amendment and the data were generally not summarized in tabular form. Some of the summary tables that were included were difficult to interpret; for example, the Applicant's summary tables for the final visit measurement of vital signs and electrocardiograms (ECGs) included end of treatment values of all patients rather than values of only patients who completed the study. The Applicant did not include any subgroup analyses for efficacy. The Applicant submitted an analysis of adverse events by age group but did not provide subgroup safety analyses for other demographic groups. The clinical and statistical review teams issued information requests and conducted additional dataset queries to evaluate the subgroup data. Also, the clinical reviewer noted that the sequence of events as outlined in the submitted narratives for serious adverse events (SAEs) were difficult to follow. In addition, the Applicant identified only SAEs of chest pain, anxiety, and sunburn in a participant (Patient (b) (6)) who was hospitalized for evaluation of a suspected pulmonary embolism (of note, pulmonary embolism is on the list of rare postmarketing events in the ziprasidone label).

As discussed in the Section 8.1.2, there were concerns regarding the quality and integrity of the data in this supplement, including the use of raters who had not completed training activities before administering diagnostic and primary endpoint assessments. Therefore, the Division of Psychiatry consulted the Office of Scientific Investigation to conduct site inspections. OSI

inspected three clinical sites and concluded that the Study A1281198 appears to have been conducted adequately.

Categorization of Adverse Events

The study reports for Studies A1281198 and A1281201 state that the Applicant used the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 to record and code adverse events (AEs). The following is the Applicant's 3-tiered approach to summarize AEs for Study A1281198:

- Tier-1 events were prespecified events of clinical importance and were maintained in a list in the product's Safety Surveillance Review Plan. QT prolongation, suicide/self-injury, extrapyramidal disorder and hyperprolactinemia were designated as Tier-1 events.
- Tier-2 events were "common" events other than Tier-1 events. A MedDRA preferred term met the definition of a Tier-2 event if there were at least four events in any treatment group.
- Tier-3 events were events that were neither Tier-1 nor Tier-2 events. Tier 3 adverse events were summarized using standard Pfizer data standards tables, where all adverse events are included (i.e., Tier 3 adverse events are not shown separately).

Routine Clinical Tests

Clinical laboratory tests for both Studies A1281198 and A1281201 included complete blood count (CBC), serum chemistry tests, liver function tests, urinalysis, urine drug screen, free T4, thyroid-stimulating hormone (TSH), prolactin, ECGs, fasting glucose, lipid profile, insulin, glycosylated hemoglobin (HbA1c), and urine pregnancy tests. The Applicant administered the following outcome measures to assess safety: The Children's Depression Rating Scale (CDRS-R), the Simpson-Angus Rating Scale (SARS, an assessment of drug-induced parkinsonism), the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the C-SSRS. See Table 21 below for the schedule of events for both studies.

Each visit in Studies A128198 and A128201 included monitoring of predose sitting and standing blood pressure and pulse; ECG monitoring occurred after recording vital signs. Recording of weight, height and waist circumference occurred at Baseline and Week 4 for Study A128198 and at Baseline, Week 6, and Week 27 for Study A1281201. BMI z-scores were also recorded during both studies.

See Table 21, below, for the frequency of assessment monitoring.

Reviewer's comment: The safety assessments in these studies were adequate to address relevant safety concerns and are standard for clinical studies in a population of patients with bipolar I disorder.

Table 21. Schedule of Safety Evaluations (by Week) in Studies A1281198 and A1281201

Safety Assessment	A1281198	A1281201
Clinical laboratory tests	S; 0, 1, 4	0, 6, 26
Vitals	S; 0, 1, 2, 3, 4	0, 1, 2, 4, 6, 10, 14, 18, 22, 26
BMI	S; 0, 1, 2, 3, 4	0, 6, 26
Hormones (T4, TSH, prolactin)	S; 0, 4	0, 6, 26
ECG	S; 0, 1, 2, 3, 4	0, 1, 2 4, 6, 14, 22, 26
Pregnancy test	S; 0, 1, 2, 3, 4	0, 1, 2, 4, 6, 10, 14, 18, 22, 26
Urine drug screen	S; 0, 4	0, 6, 26
Fasting glucose, lipid profile, insulin, HbA1c	S; 0, 4	0, 6, 26
CDRS-R	S; 0,1,2,3,3,4	0, 1, 2, 4, 6, 10, 14, 18, 22, 26
C-SSRS	S; 0,1,2,3,3,4	0, 1, 2, 4, 6, 10, 14, 18, 22, 26
Movement disorder scales: SARS, BARS, AIMS	0,1,2,3,3,4	0, 1, 2, 4, 6, 10, 14, 18, 22, 26

Source: Protocols for Studies A1281198 and A1281201
Abbreviations: AIMS = Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; BMI, body mass index; CDRS-R, Children Depression Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; S, screening; T4, Thyroxin 4; TSH, thyroid-stimulating hormone; HbA1c, glycosylated hemoglobin; SARS, Simpson-Angus Rating Scale

8.2.4. Safety Results

Deaths

No patients died in Studies A1281198 and A1281201.

Serious Adverse Events

SAEs occurred in three patients in the ziprasidone group for Study A1281198 and one patient in Study A1281201. There were no reports of serious adverse events in the placebo group for Study A1281198. Below are case summaries of the SAEs in the safety database.

Study A1281198

Suicidal Ideation and Behavior

Patients # (b) (6) (15-year-old female) and # (b) (6) (16-year-old male) both had screening C-SSRS scores and interviews revealing suicidal thoughts; both patients received approval for study participation after a screening risk assessment by a child psychiatrist. Neither patient expressed suicidal thoughts or behaviors during the study with ziprasidone treatment. However, 2 days after study completion, Patient # (b) (6) took an overdose of quetiapine (400 mg x 17 pills). Patient # (b) (6) had suicidal thoughts, complaints of fatigue, and decreased appetite necessitating psychiatric hospitalization on the last day of the study, when his ziprasidone dose was halved, The Applicant concluded that both of these events were not related to the study drug. The Applicant believes that, based on the pharmacokinetic properties of ziprasidone, there are no withdrawal effects with short-term use of ziprasidone.

Reviewer's comment: These two case histories suggest that ziprasidone may have effectively treated symptoms of BD in these patients, and the exacerbation of symptoms could have been a combination of insufficient medication treatment of their illness and withdrawal effects. It is possible that withdrawal symptoms can occur when an antipsychotic is discontinued as a

function of neuroadaptation within the receptor system, which does not rely on pharmacokinetics (Cerovecki et al. 2013; Chouinard et al. 2017).

Anxiety, Chest Pain, Sunburn; Applicant Did Not List: Possible Pulmonary Embolism

Patient # (b) (6) was a 16-year-old female with a diagnosis of BD randomized to ziprasidone treatment with titration up to 120 mg daily by Day 11, and then lowered to 100 mg daily on Day 15. Concomitant medications included an oral contraceptive. On Day 21, the case report states that the patient was hospitalized for symptoms of chest pain, anxiety, sunburn, and exhaustion. Her work-up for a possible blood clot revealed a mild elevation in D-dimer test (a nonspecific test assessing levels of fibrin), an elevated coagulation fibrinogen, and a CT angiography scan and chest x-ray showing a possible blood clot in the left lung. Despite an unremarkable echocardiogram, electrocardiogram, and ultrasound Doppler, the patient was hospitalized and received empiric treatment for a possible pulmonary embolism (i.e., morphine, hydrocodone, paracetamol, enoxaparin, and warfarin). The Applicant did not attribute these adverse events to the study drug; the case report states that the chest pain was due to anxiety or sunburn.

Reviewer's comment: This case report was coded as serious adverse events of chest pain, anxiety, and sunburn; suspected pulmonary embolism was not listed as an SAE despite the work-up and treatment for a possible pulmonary embolism. The radiologic and laboratory evaluations were inconclusive, but the clinical symptoms appeared to resolve after empiric treatment for a pulmonary embolism. In addition to having other risk factors for the development of an embolism (i.e., oral contraception), the patient presented with symptoms that were suspicious of a pulmonary embolism while taking ziprasidone. Because the ziprasidone label lists pulmonary embolism as a rare event, it cannot be ruled out that ziprasidone contributed to the occurrence of this possible pulmonary embolism.

Study A1281201

Suicidal Ideation

Patient (b) (6) was a 15-year-old female with a diagnosis of BD who enrolled in Study A1281201 after being in the placebo group during Study A1281198. The patient's ziprasidone dose was titrated up to 160 mg by Day 158 and recorded to have a product dispensing error, receiving 200 mg ziprasidone for one day on Day 158. The patient was hospitalized for aggression and suicidal thoughts on Days 173 to 177 and again on Day 205, 28 days after study completion. Treatment during both hospitalizations included continuation of ziprasidone augmented with lamotrigine. The Investigator and the Applicant attributed this event to the underlying illness of bipolar disorder.

Reviewer's comment: This patient was exposed to an excessive dose on one study day (Day 158) because of a drug dispensing error, but it is not clear whether this contributed to this serious adverse event. Subsequently the patient was hospitalized twice for suicidal ideation and aggression, both symptoms known to occur in the context of BD. Therefore, the patient's symptoms could have been the result of her underlying disorder, but an association with

ziprasidone use cannot be ruled out. Given that the patient tolerated the medication for an extended period of time, a medication effect seems less likely.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study A1281198, a total of 14 (16.2%) patients in the ziprasidone group and four (4.7%) patients in the placebo group discontinued the study because of one or more AE. As shown in Table 22, sedation/somnolence and akathisia were the most prevalent AEs resulting in withdrawal from the ziprasidone group. In Study A12811201, four patients (17.4%) discontinued due to one or more AE; fatigue and sedation/somnolence were the most frequent AEs leading to early withdrawal (see Table 23).

Temporary discontinuations or dose reduction occurred in 18 patients in the ziprasidone group and 3 patients in the placebo group in Study A1281198 (see Table 24). In Study A1281201, 10 patients (43.5%) had a temporary discontinuation or dose reduction due to an AE (See Table 25). Sedation, somnolence, drowsiness, and fatigue were the adverse event most likely to result in temporary withdrawal or dose reduction in both studies.

Table 22. Dropouts or Discontinuations Due to Adverse Events in Study A1281198

Adverse Event	Ziprasidone (N=86) n (%)	Placebo (N=85) n (%)
Somnolence/sedation	6 (7.0)	1 (1.2)
Akathisia	2 (2.3)	0
Dysphasia	1 (1.2)	0
Oral hypo-anesthesia (numb tongue)	1 (1.2)	1 (1.2)
Nausea	1 (1.2)	0
Suspected pulmonary embolism*	1 (1.2)	0
Fatigue	1 (1.2)	0
Depressed mood	1 (1.2)	0
Trismus	1 (1.2)	0
Muscle spasms	0	1 (1.2)
Thrombocytopenia	0	1 (1.2)
Wolff-Parkinson-White syndrome	0	1 (1.2)

Source: A1281198 Study Report, Table 19, p. 67
*SAEs of chest pain, sunburn, and anxiety were reported for Patient #11281001. The Applicant's coding of terms did not reflect that the patient was hospitalized for a suspected pulmonary embolism. See discussion of SAE narratives above.

Table 23. Dropouts or Discontinuations Due to Adverse Events in Study A1281201

Adverse Event	Ziprasidone (N=23) n (%)
Fatigue	4 (17.3)
Sedation/somnolence	2 (8.6)
Memory impairment	1 (4.3)

Source: A1281201 Study Report, Table 14, p.49

Table 24. Adverse Events Leading to Temporary Withdrawal or Dose Reduction in Study A128198

Adverse Event	Ziprasidone (N=86) n (%)	Placebo (N=85) n (%)
Sedation, somnolence, drowsiness	12 (14.0)	3 (3.5)
Vomiting	3 (3.5)	0
Fatigue	2 (2.3)	0
Akathisia, jitteriness	2 (2.3)	0
Myalgia, stiff neck	2 (2.3)	0
Nausea	1 (1.1)	0
Dizziness	1 (1.1)	0
Insomnia	1 (1.1)	0

Source: A1281198 Study Report, Appendix Table 16.2.7.2, pp. 170 to 190

Table 25. Adverse Events Leading to Temporary Withdrawal or Dose Reduction in Study A1281201

Adverse Event	Ziprasidone (N=23) n (%)
Fatigue	6 (26.0)
Sedation, somnolence, drowsiness	4 (17.3)
Dizziness	2 (9.0)
Akathisia	1 (4.3)
Dystonia	1 (4.3)
Nausea	1 (4.3)
Decreased appetite	1 (4.3)
Aggressive behavior	1 (4.3)
Suicidal thoughts	1 (4.3)

Source: A1281201 Study Report Appendix Table 16.2.7.2, pp. 36 to 47

Significant Adverse Events

In the study reports for A1281198 and A1281201, the Applicant identifies the following events of special interest: extrapyramidal disorders, QT prolongation (see QT Effects, below), suicidal ideation or behavior (incidents discussed in Serious Adverse Events, above), and hyperprolactinemia (see Laboratory Findings, below). Akathisia and extrapyramidal symptoms (EPS) were the most prevalent significant adverse events observed but were not associated with dropout in this pediatric database (see Table 26 and Table 27, below).

Table 26. Significant Adverse Events Not Resulting in Dropout in Study A1281198

Adverse Event	Ziprasidone (N=86) n (%)	Placebo (N=85) n (%)
Akathisia	7 (8.1)	1 (1.2)
EPS-like symptoms[a]	6 (7.0)	2 (2.4)
Tremor	2 (2.3)	0

Source: A1281198 Study Report, Appendix Table 14.3.1.4.1, p. 207
[a] Musculoskeletal stiffness, trismus, muscle rigidity, tongue dystonia, muscle twitching, involuntary muscle contraction
Abbreviations: EPS, extrapyramidal symptoms

Table 27. Significant Adverse Events Not Resulting in Dropout in Study A1281201

Adverse Event	Ziprasidone (N=23) n (%)
Akathisia	1 (4.3)
EPS-like symptoms[a]	2 (8.7)

Source: A1281201 Study Report, Appendix Table 14.3.3.2 p. 213
[a] Dystonia, skeletal muscle stiffness
Abbreviations: EPS, extrapyramidal symptoms

Treatment-Emergent Adverse Events and Adverse Reactions

As Table 28 details, adverse events occurring in at least 5% of the ziprasidone group and at twice the frequency in the placebo group included the following: somnolence, fatigue, nausea, decreased appetite, vomiting, musculoskeletal and connective tissue disorders (e.g., joint stiffness, muscle rigidity, myalgia), sedation, dizziness, and akathisia. There was no significant difference in reported common adverse events within the two age groups of ≤13 years and >13 years. However, the incidence of somnolence was higher in the ≤13 years age group, and the incidence of fatigue was higher in patients aged >13 years (see Table 29). Both somnolence and fatigue were the most frequently reported adverse events, occuring in 7 of 23 patients (or 30%) in the open-label Study A1281201.

Table 28. Adverse Events Occurring in At Least 5% of Ziprasidone Group and Greater Than Twice the Incidence of Placebo in Study A1281198[a]

Adverse Event	Ziprasidone (N=86) n (%)	Placebo (N=85) n(%)
Somnolence	27 (31)	7 (8)
Fatigue	19 (22.1)	2 (2)
Nausea	12 (14)	5 (6)
Decreased appetite	10 (12)	0
Vomiting	9 (11)	3 (4)
Musculoskeletal and connective tissue disorders[b]	9 (11)	0
Sedation	8 (9)	3 (4)
Dizziness	6 (7)	2 (2)
Akathisia	5 (6)	0

Source: Summary of Clinical Safety: Table 8, p. 26
[a] Patients are only counted once per treatment event
[b] Joint stiffness, muscle rigidity, myalgia

Table 29. Adverse Events by Age Group in Study A1281198[a]

	Ziprasidone		Placebo	
Adverse Event	**≤13 years (N=46) n (%)**	**>13 years (N=40) n (%)**	**≤13 years (N=46) n (%)**	**>13 years (N=41) n (%)**
Somnolence	15 (37)	12 (30)	4 (9)	3 (7)
Fatigue	4 (8.7)	11 (28)	1 (2)	1 (2)
Nausea	7 (15)	4 (10)	1 (2)	3 (7)
Decreased appetite	3 (7)	5 (13)	0	0
Headache	2 (4)	3 (8)	1 (2)	0
Vomiting	4 (9)	4 (10)	1 (2)	1 (2)
Musculoskeletal and connective tissue disorders	4 (9)	3 (8)	0	1 (2)
Sedation	5 (11)	3 (8)	1 (2.3)	2 (5)
Dizziness	3 (7)	1 (3)	1 (2.3)	1 (2)
Akathisia	2 (4)	3 (8)	0	0

Source: Summary of Clinical Safety: Tables 9 (p. 27) 14.3.1.3.5a (p. 202-204), 14.3.1.3.5b (p. 205-209)
[a] If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted. Subjects are counted only once per treatment per event.
[b] Joint stiffness, muscle rigidity, myalgia

Reviewer's comment: The most commonly reported adverse events were consistent with the safety information described in current labeling of ziprasidone for the adult indications of schizophrenia and bipolar I disorder.

Laboratory Findings

Clinical laboratory tests for Study A1281198 occurred at Screening, Baseline, Week 1, and Week 4. For Study A1281201, assessments occurred at Baseline, Week 6, and Week 26. Screening laboratory tests included CBC, serum chemistry tests, liver function tests, hepatitis serology, urinalysis, urine drug screen, free T4, TSH, prolactin, fasting glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), insulin, HbA1c, urine pregnancy tests, and urine drug tests. Assessments during the study included these same laboratory tests except a urine drug screen.

Based on review of the descriptive statistics in the Applicant's Summary of Clinical Safety (located in the A1281201 CSR Appendix, Table 14.3.4.1.4) and the submitted datasets, there were no clinically meaningful differences in the mean changes from baseline for any laboratory assessments except for prolactin in the ziprasidone group. The mean change from baseline for prolactin was 3.9 ng/mL (±10.5) compared to a mean of change of -1.3 ng/mL (±7.6) in the placebo group. A total of 17.4% (15 of 86) patients in the ziprasidone group had a greater than 1.1 times the upper limit of normal for prolactin compared to 3.5% (3 of 85) in the placebo group demonstrating a clear difference between drug and placebo. Elevated prolactin was also observed in 67% (8 of 12) female patients and 38% of all patients (8 of 23) in Study A1281201. No patient had an elevated prolactin >1.5 times normal, and no patients reported galactorrhea. The Applicant's literature references included a single case report of a 15-year-old female treated with ziprasidone 80 mg daily for an unknown dosing period who developed galactorrhea (Saldana and Delgado 2007).

Reviewer's comment: The increase in the prolactin levels in the short-term study may appear relatively small, but the study was only 4 weeks. There is not enough information from A1281201 to comment on the magnitude of any prolactin elevations with long-term exposure to ziprasidone. Elevated prolactin is consistent with the current label of ziprasidone for indications of adult schizophrenia and BD. There was no indication of elevations in lipid profiles or glucose levels in the short-term study. However, there are insufficient long-term data to make any conclusions regarding dyslipidemia, hyperglycemia, and diabetes mellitus occurring with ziprasidone use in the pediatric population.

Vital Signs

Each visit included monitoring of predose sitting and standing blood pressure and pulse reading for both Studies A128198 and A128201. As seen in Table 30 and Table 31, changes in blood pressure were unremarkable for both studies.

Recording of weight, height, and waist circumference occurred at Baseline and Week 4 for Study A128198 and at Baseline, Week 6, and Week 27 for Study A1281201. BMI z-scores were also recorded during both studies. The BMI z-score represents the number of standard deviations from the population mean for a specific patient's BMI given their age and gender using CDC growth charts to determine whether the patients are growing along their predicted growth curve (i.e., decreases in mean z-score would indicate that subjects are lagging behind in growth).

As expected, for the short-term study, Study A128198, changes BMI z-scores were unremarkable (see Table 32). The limited data based on 10 patients completing Study A1281201 revealed six patients with a z-score in the range of 0.5 to <1 and one patient with a z-score of ≥1 (suggesting the possibility of greater than expected weight gain).

Reviewer's comment: It is difficult to make any conclusions regarding ziprasidone's effect on BMI based on these data because the long-term study sample size was too small, the data were uncontrolled, and changes in growth parameters during adolescence are nonlinear.

Table 30. Baseline and Mean Change in Vital Signs From Baseline to Week 4 in Study A1281198

		Ziprasidone			Placebo		
Parameter	Criteria	N	Mean	SD	N	Mean	SD
	Change from Baseline at Week 4	63	0.08	0.795	75	0.15	0.924
Sitting Diastolic Blood Pressure (mmHg)	Baseline	86	68.85	7.989	85	70.29	7.941
	Change from Baseline at Week 4	63	1.08	8.178	75	-0.56	10.217
Standing Diastolic Blood Pressure (mmHg)	Baseline	86	70.35	6.975	85	72.33	7.908
	Change from Baseline at Week 4	63	1.00	7.761	75	-0.48	9.830
Height (cm)	Baseline	86	157.88	10.627	85	159.69	11.410
	Change from Baseline at Week 4	63	0.38	0.599	75	0.68	1.767
Sitting Pulse Rate (beats/min)	Baseline	86	79.06	12.582	85	75.82	9.796
	Change from Baseline at Week 4	63	-2.27	11.489	75	-0.23	10.302
Standing Pulse Rate (beats/min)	Baseline	86	84.64	12.231	85	83.31	10.951
	Change from Baseline at Week 4	63	-0.65	11.768	75	-0.59	12.831
Sitting Systolic Blood Pressure (mmHg)	Baseline	86	110.45	9.841	85	110.86	11.447
	Change from Baseline at Week 4	63	-0.71	10.603	75	-2.21	10.391
Standing Systolic Blood Pressure (mmHg)	Baseline	86	110.74	9.527	85	112.02	10.159
	Change from Baseline at Week 4	63	-0.79	9.501	75	-2.51	10.772
Weight (kg)	Baseline	86	57.54	14.518	85	58.01	14.541
	Change from Baseline at Week 4	63	0.30	1.969	75	0.77	2.039

Source: Study Report A1281198 Table 22, p. 74
Abbreviations: SD, standard deviation

Table 31. Mean Change in Blood Pressure From Baseline to Week 26 in Study A1281201

Blood Pressure Measurement	Ziprasidone (N)
Sitting systolic blood pressure (mmHg)	-4.6±13.6, (N=13)
Standing systolic blood pressure (mmHg)	-7.8±11.5, (N=11)
Sitting diastolic blood pressure (mmHg)	-3.2±11.4, (N=11)
Standing diastolic blood pressure (mmHg)	-4.8±8.9, (N=11)

Source: Submission of 9/30/2021: Response to Information Request, Table 14.3.6.1.2a

Table 32. Absolute Change in BMI Z-Score in Study A1281198

		Ziprasidone (N= 86)		Placebo (N= 85)	
Visit	Absolute change in BMI z-score	n	%	n	%
Week 4	< 0.5	62	72.1	69	81.2
	0.5 to <1	1	1.2	6	7.1
	>= 1	0		0	
ET	< 0.5	19	22.1	5	5.9
	0.5 to <1	0		0	
	>= 1	0		0	
Week 4/ET	< 0.5	81	94.2	74	87.1
	0.5 to <1	1	1.2	6	7.1
	>= 1	0		0	

Source: Study A1281198 Final Study Report: Table 14.3.4.2.4.1, p. 272
Abbreviations: BMI, body mass index; ET, end of treatment

Electrocardiograms

For Study A1281198, every visit included ECG collections; for Study A1281201, ECG collection was at Baseline and Weeks 1, 2, 4, 6, 14, 22, 26. As can be seen from Table 33 and Table 34, there were no clinically meaningful ECG changes observed in either study.

Table 33. ECG Parameter Mean Change From Baseline to Day 28 in Study A1281198RR Interval Not Otherwise Specified (msec)

Summary Statistics	Ziprasidone (N= 85)	Placebo (N= 83)
n	63	75
Mean	19.33	22.69
Std. Dev.	103.332	97.317
Median	40.00	17.00
Min	-248.0	-184.0
Max	287.0	283.0
PR interval not otherwise specified (msec)		
n	63	75
Mean	-0.38	1.07
Std. Dev.	12.715	7.005
Median	0.00	1.00
Min	-84.0	-19.0
Max	19.0	18.0
QRS interval not otherwise specified (msec)		
n	63	75
Mean	1.19	0.20
Std. Dev.	4.500	4.436
Median	1.00	0.00
Min	-10.0	-9.0
Max	10.0	16.0
QT interval not otherwise specified (msec)		
n	63	75
Mean	8.25	3.67
Std. Dev.	21.044	18.243
Median	8.00	3.00
Min	-49.0	-31.0
Max	68.0	51.0

Source: Submission of 9/30/2021, Response to Information Request, Table 14.3.6.1.2b
Abbreviations: ECG, electrocardiogram

Table 34. ECG Parameter Mean Change From Baseline* to Week 26 in Study A1281201

ECG Parameter	Ziprasidone Mean N=12 (SD)	Ziprasidone Range N=12
PR interval (msec)	0.7 (10.8)	-12 to 24
RR interval (msec)	8.6 (113.1)	-221 to 175
QRS interval (msec)	4.3 (4.72)	-1 to 14.0
QT interval (msec)	12.2 (21.4)	-21 to 49

Source: Submission of 9/30/2021, Response to Information Request, Table 14.3.6.1.2a
*Baseline visit is the Baseline from Study A1281198
Abbreviations: ECG, electrocardiogram; SD, standard deviation

QT Effects

Ziprasidone's current label includes a warning for QT interval prolongation based on an observed 10 msec QTc interval prolongation at the dose of ziprasidone 160 mg daily in placebo-controlled studies in adults. The DP consulted the Interdisciplinary Review Team (IRT) for Cardiac Safety Studies to evaluate the collected pediatric data in Studies A1281198 and A1281201.

The protocols for both studies excluded patients with a history of cardiac arrhythmias, conduction abnormalities or known personal history of QT prolongation (including congenital long QT syndrome), known genetic risk for prolonged QT syndrome, a clinically significant ECG abnormality at screening or baseline, a QTcF >450 msec at screening or baseline, or a need for treatment with QT prolonging drugs.

In Study A1281198, 12-lead ECG was performed at Screening, Baseline (Day 1, triplicate), Day 8, 15, 22, 29 (triplicate, predose), and at Follow-Up, before or at least 3 hours after food intake and before blood draw. The IRT consult found that the mean QTcF intervals in the ziprasidone group were prolonged (from 3.63 msec to 6.58 msec) relative to the placebo group at all evaluation intervals from Week 1 through the end of treatment. No participants had QTcF intervals ≥480 msec or a change from Baseline of ≥60 msec during the study, and there were no observations of meaningful gender differences.

For Study A1281201, a 12-lead ECG was performed at Weeks 1, 2, 4, 6, 14, 22, and 26; ECGs were repeated at the follow-up visit if there were observed abnormalities at the Week 26 (or Early Termination) visit. The IRT consult concluded that no cardiac AEs or AEs related to ECGs were reported, and no participants had QTcF intervals ≥460 msec or a change from baseline of ≥60 msec during the study. Mean QTcF change from Baseline, defined as the value from the Baseline visit in the double-blind Study A1281198, to the end of treatment (Week 26) was 6.7 msec (range -14.0 to 49.0).

The IRT consult concluded that there were no new QT-related safety concerns in the data in this pediatric submission. See the QT-IRT consultative review for full details of the analysis of the QTc interval data (DARRTS: Zheng, 7/27/2021).

Reviewer's comment: Although the mean QT changes in this pediatric bipolar program were smaller than the mean changes observed in adult clinical trials, there is not enough exposure data to conclude that there is less risk of QT prolongation in pediatric patients than in adults with ziprasidone use, especially considering this limited long-term pediatric safety database. The Applicant's literature submission included three articles that identified and discussed the presence of QTc prolongation with ziprasidone use in pediatric patients (Blair et al. 2005; Correll et al. 2011; Jensen et al. 2015)(see Section 8.2.9).

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Metabolic Changes

The prescribing information for ziprasidone describes the risk of metabolic changes such as hyperglycemia, dyslipidemia, and weight gain (which may increase cardiovascular or cerebrovascular risk) in adults with schizophrenia and BD. No clinically meaningful differences between the ziprasidone and placebo groups in laboratory parameters or weight were noted in study A1281198. However, the long-term safety database in pediatric patients with BD is limited to a small number of patients who had exposure for no more than 6 months. Therefore, it is not possible to assess the long-term metabolic effects of ziprasidone in pediatric patients with BD from this current database.

Suicidal Ideation and Behavior

Three treatment-emergent AEs related to suicidal ideation and behavior were reported in Study A1281198. As described in Section 8.2.4 (Serious Adverse Events), one patient in the ziprasidone group reported a suicide attempt and one patient each in the ziprasidone and placebo groups reported suicidal ideation. Reports of suicidal ideation or behavior on the C-SSRS in Study A1281198 were uncommon and comparable in the ziprasidone and placebo groups. One patient who received ziprasidone in Study A1281201 reported suicidal ideation. The effects of long-term ziprasidone use on suicidal ideation and behavior could not be assessed with the limited data in this application.

Extrapyramidal Symptoms

EPS were reported more commonly in patients receiving ziprasidone in Study A1281198 than in the placebo group. In the ziprasidone group, akathisia was reported in five patients (5.8%), tremor was reported in two patients (2.3%), and oromandibular dystonia was reported in one patient (1.2%); no patients in the placebo group reported these symptoms. In addition, four patients (4.7%) exposed to ziprasidone reported muscle stiffness or unusual movements (including preferred terms of muscle contractions involuntary, muscle rigidity, muscle spasms, muscle twitching, and musculoskeletal stiffness) compared to two patients (2.4%) in the placebo group. No meaningful differences between the ziprasidone and placebo groups were noted on structured safety assessments intended to monitor for EPS (BARS, AIMS, SARS). In Study A128201, one patient reported dystonia and one patient reported musculoskeletal stiffness. Mean changes on the BARS, AIMS, SARS were small and not clinically meaningful. However, as noted for other safety assessments, the small number of patients completing the open-label extension limits conclusions about safety signals with chronic use in the pediatric population.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Of the 117 patients in Study A1281198 who reported an AE, 65% were white, 27% were Black, 1.7% were Asian, and 6% did not report a racial identification; 58% of patients reporting an AE were female. Among patients in the ziprasidone group who reported an AE, 66% were white, 28% were Black, and 1.5% were Asian. 4.5% did not report a racial identification. 55% of patients in the ziprasidone group who reported an AE were female. The proportion of patients in each demographic subgroup who experienced adverse events appeared generally consistent with the demographic makeup of the study population. However, this study was not powered to detect differences in the safety profile between subgroups and no definitive conclusions can be drawn from these exploratory subgroup analyses.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

The Applicant submitted 71 published articles to support the safety profile of ziprasidone's use in the pediatric population. These articles were reviewed in depth; however, none of these articles provided sufficient data about ziprasidone use in pediatric patients that could be used to support safety information in labeling for BD in the pediatric population. The majority of articles described the general use of antipsychotics in the pediatric population. When an article did mention ziprasidone use, the ziprasidone cohort was small or the data contained insufficient information to make any conclusions (i.e., missing information about dose, demographics, length of treatment, adverse events, diagnoses, or concomitant medication). For a full listing of the submitted literature articles, please refer to the submission of December 28, 2021 (Summary of Clinical Safety: sections 2.7.4 or 5.4).

As noted above, QT prolongation is listed as a warning in approved labeling for ziprasidone. The following list includes a summary of the articles on QTc prolongation with ziprasidone use that the Applicant submitted.

- Three articles discussed findings of QTc prolongation in children and adolescents treated with ziprasidone:
  - One article described an association of ziprasidone and a dose- and level-independent, significant, QTc prolongation in seven of the 29 patients in a prospective, observational, mixed inpatient and outpatient cohort study of treatment-naïve patients ages 4 to 9 years (Correll et al. 2011).

Reviewer's comment: The patients in this study were treated with ziprasidone for off-label indications (e.g., disruptive behavior disorders, attention-deficit/hyperactivity disorder, psychosis not otherwise specified). No information about concomitant medications was provided. No standard times for ECG collection (relative to medication administration) were noted. Given these limitations, this article was considered not informative for the purposes of labeling.

- One article described an open-label study in 20 patients with a mean age of 13 years treated with low dose ziprasidone (average 30 mg daily) for approximately 5 months with preliminary findings of a statistically significant mean increase in QT interval of 28±16 milliseconds; there were no identified diagnoses in the article (Blair et al. 2005).

Reviewer's comment: If confirmed in larger and well-controlled studies, the mean changes in QTc described in this article would be clinically meaningful and appear to be consistent with the safety profile observed in adults. However, the study was uncontrolled, the sample size was small, and the study population was not well defined (for example, there was no information about diagnosis). Therefore, this article was not informative for the purposes of labeling. In addition, given the study design limitations, it is difficult to compare the magnitude of the QTc changes observed in this study with those seen in the adult development programs.

- One article described a meta-analysis of 55 articles assessing QTc prolongation in nine antipsychotics; 10 of the articles included a total of 523 pediatric patients taking ziprasidone. The meta-analysis revealed that ziprasidone was the only antipsychotic with a statistically significant increase in QT interval compared to placebo. The authors did not specify the diagnoses, dose, or length of treatment. They also reported their concern that there was significant reporting bias (Jensen et al. 2015).

Reviewer's comment: This article was missing crucial information regarding dose, dose effects, concomitant medications, diagnoses, length of treatment, and demographics. Because of this missing data, this article does not offer useful information that can be described in labeling for the use of ziprasidone in patients with bipolar disorder.

Other articles submitted by the Applicant are summarized below.

- One article described a case report of a 15-year-old female with galactorrhea and elevated prolactin taking 80 mg daily of ziprasidone without mentioning the length of treatment (Saldana and Delgado 2007).
- 15 articles discussed general topics such as assessment scales, puberty, antipsychotics in children (not specific to ziprasidone).
- 17 articles described pediatric ziprasidone data from the Applicant's submission to FDA in 2008. These data were determined to be unreliable because of unresolved compliance issues (as discussed in the FDA CR letters of October 30, 2009 and April 21, 2011).
- 34 articles discussed comparisons of several antipsychotics in pediatric patients from various databases (e.g., Medicaid, poison control centers, etc.) with insufficient data on dose, diagnoses, demographics, adverse events, concomitant medications, and contained a small sample of ziprasidone patients in the cohort, study, or meta-analysis.
- One article submitted by the Applicant was written in Chinese with no English translation.

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

Because of the paucity of long-term data in this submission, it is not possible to make any conclusions regarding ziprasidone's effect on pediatric growth. For details, see Section 8.2.4 (Safety Results).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The major safety concerns associated with the chronic use of ziprasidone in the adult population are QTc interval prolongation, dyslipidemia, diabetes, and obesity (resulting from elevated levels of insulin and glucose with associated cardiovascular risks).

Expectations on Safety in the Postmarket Setting

There continues to be a need to assess the long-term safety effects of ziprasidone use in for the pediatric population.

8.2.11. Integrated Assessment of Safety

In the 4-week efficacy and safety study, notable findings included higher mean prolactin levels and greater mean QTcF interval changes in the ziprasidone treatment group compared to the placebo group. Possible pulmonary embolism was observed in one female patient taking ziprasidone with concomitant oral contraception. Otherwise, there were no remarkable safety findings in this submission. However, too few patients had sufficient chronic exposure to make any conclusions regarding the long-term safety of ziprasidone use in the pediatric population.

8.3. Conclusions and Recommendations

The efficacy results are based on improvement of the primary endpoint, the YMRS. Reduction in the YMRS total score is evidence of improvement in BD symptoms (b) (4)

(b) (4)

There are several antipsychotics that received approval for the treatment of BD in the pediatric population during the years 2007 and 2009 based on safety and efficacy data from a single shot-term study. Since then, the Agency has recognized the importance of understanding the long term effects of antipsychotic treatment in pediatric patients, because these drugs are treating chronic diseases requiring chronic drug use. Therefore, long-term clinical studies with sufficient exposure are considered crucial to demonstrate safe chronic use and to support labeling for the pediatric population. There are insufficient safety data in this database to support labeling ziprasidone for the treatment of BD in the pediatric population.

In addition to proposing labeling in this submission, the Applicant intended this submission to fulfill their PREA deferred postmarket requirement (PMR 682-1) issued upon the approval of ziprasidone use in adults for the treatment of BD in August 2004. At the time that PMR 682-1 was issued, the Agency did not have the requirements for long-term safety data to support labeling for use in the pediatric population.

In considering whether the data from the short-term study A1281198 were adequate to fulfill PREA, the Division considered the impact of the quality and integrity issues raised in this review. The clinical reviewer noted that there was confusion concerning the quantity and seriousness of protocol violations and deviations. However, sensitivity analyses conducted by the biometrics review team did not suggest that protocol violations impacted the efficacy result. OSI concluded after conducting clinical site inspections that the data generated from the sites appeared to be acceptable and that the study appeared to have been conducted adequately. Therefore, the Division concluded that Study A1281198 meets the terms under PREA that were specified in PMR 682-1 at the time it was issued and that the postmarketing requirement has been fulfilled. Section 8 of labeling (Pediatric Use) will be updated to reflect that Study A1281198 was conducted but will indicate that safety and effectiveness in pediatric patients have not been established.

9. Advisory Committee Meeting and Other External Consultations

There was no Advisory Committee convened for this submission.

APPEARS THIS WAY ON ORIGINAL

10. Pediatrics

The Division of Pediatrics and Maternal Health (DPMH) provided consultative review of the Applicant's proposed labeling and of the appropriateness of the submitted study to fulfill the outstanding PREA PMR. The review team concluded that Study A128198 fulfills the PMR. As noted in the DPMH consultative review (filed in DARRTS on December 17, 2021):

> *PREA mandates that studies conducted in response to PREA requirements be included in labeling regardless of whether the study was positive, negative, or inconclusive. For studies not resulting in pediatric approval of the indication, this information should be placed only in the Pediatric Use subsection following an appropriate pediatric use statement, clarifying that safety and effectiveness in pediatric patients have not been established. Studies should be briefly summarized in labeling to avoid the implication that the drug is safe and effective in pediatric patients.*

The review team considered how much information to include in the Pediatric Use subsection of labeling given that presenting a full description of results from Study A128198 despite the lack of sufficient long-term safety data to support pediatric use might promote off-label use in the pediatric population. As also noted in the consultative review:

(b) (4)

Study A128198 will therefore be briefly described in section 8.4 without references to dose, effect size, frequency of adverse reactions, or other specifics of the study findings. The prescribing information will indicate that safety and effectiveness in pediatric patients have not been established. Please see Section 11 for the full text of the proposed language

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant proposed addition of pediatric information to the following sections of the Prescribing Information: (b) (4) section 8.4 (Pediatric Use) (b) (4)

As described above, the data submitted with the application were insufficient to support an indication for treatment of pediatric bipolar disorder. The safety profile with short-term use was similar to the safety profile in adults. Study A1281198, which fulfills the outstanding PREA PMR, will be described section 8.4 (Pediatric Use) of the Prescribing Information with the following language:

- The safety and effectiveness of Geodon have not been established in pediatric patients.
- Geodon was studied in one 4-week, placebo-controlled trial in patients 10 to 17 years of age with bipolar I disorder. However, the data were insufficient to fully assess the safety of Geodon in pediatric patients and therefore a safe and effective dose for use could not be established.

12. Risk Evaluation and Mitigation Strategies (REMS)

There is currently no REMS for ziprasidone. No new safety issues necessitating a REMS were identified in this submission.

APPEARS THIS WAY ON ORIGINAL

13. Postmarketing Requirements and Commitment

This current submission addresses an outstanding post market requirement to fulfill PREA requirements. The Division determined that Study A1281198 submitted with this application fulfilled the outstanding PREA PMR.

APPEARS THIS WAY ON ORIGINAL

14. Division Director (Clinical) Comments

The above Unireview reflects my input and edits. I agree with the findings of the primary review teams.

APPEARS THIS WAY ON ORIGINAL

15. Appendices

15.1. References

Blair, J, L Scahill, M State, and A Martin, 2005, Electrocardiographic changes in children and adolescents treated with ziprasidone: a prospective study, J Am Acad Child Adolesc Psychiatry, 44(1):73-79.

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Rowland, TA and S Marwaha, 2018, Epidemiology and risk factors for bipolar disorder, Ther Adv Psychopharmacol, 8(9):251-269.

Saldana, SN and SV Delgado, 2007, Ziprasidone-associated galactorrhea in an adolescent female, J Child Adolesc Psychopharmacol, 17(2):259-260.

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15.2. Financial Disclosure

The Applicant reported that there were no financial interests or arrangements for any investigator participating in the studies in this submission.

APPEARS THIS WAY ON ORIGINAL

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Pharmacometric Review

Summary of Findings

The Applicant submitted an efficacy supplement for the use of ziprasidone in the treatment of bipolar disorder in pediatric patients ages 10 to17 years. This submission is intended to fulfill PREA PMR-682-1, which was issued during the approval in 2004 of ziprasidone for the treatment of bipolar disorder in adults. (b) (4)

This document is a review of the applicant's popPK analysis (b) (4)

Based on the pooled retrospective popPK analysis, the pharmacokinetics of ziprasidone from 479 patients (458 adults and 21 pediatric patients) were described by a 1-compartment model with body weight identified as the only significant covariate affecting clearance and volume of distribution. The results of this popPK analysis support the conclusion that the pharmacokinetics of ziprasidone in pediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Question Based Review

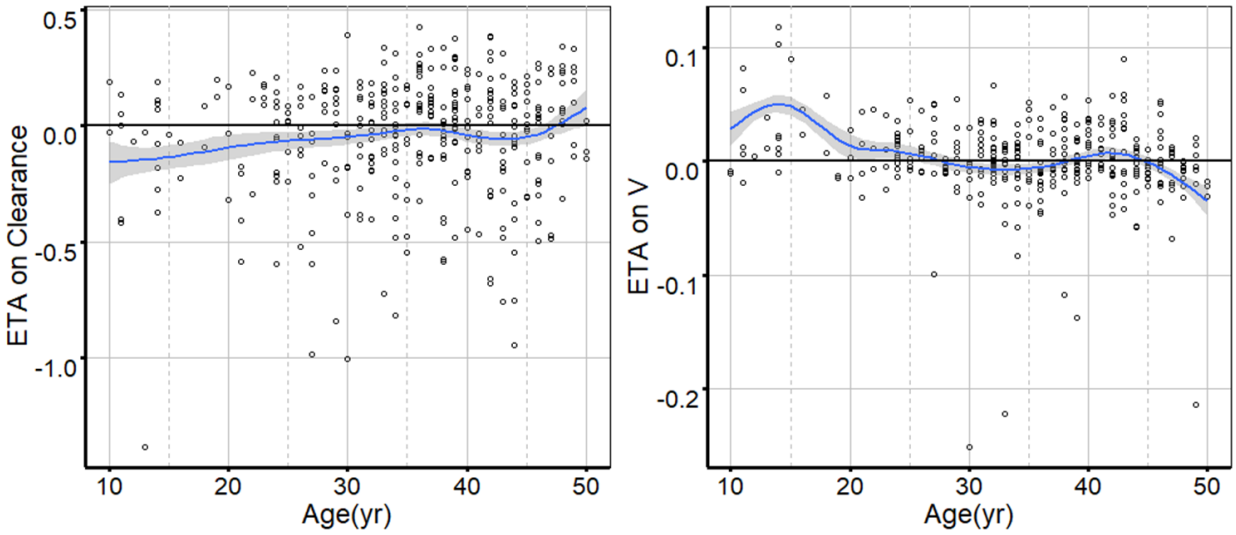
(b) (4)

(b) (4)

Overall, the concentration time in the pediatric data from Study A1281198 (only one trough concentration was assessed per patient) appears to be in the same range as adults (Refer to section 1.5.2 Clinical Pharmacology Question 1 for more detail).

Population PK analysis showed no trend in between-subject variability (ETA) for clearance with age (Figure 8). (b) (4)

Figure 8. Random Effects on Clearance and Volume of Distribution vs. Age for PopPK Model With Only Weight Allometric Scaling



Source: Clinical Pharmacology Reviewer's Analysis
Abbreviations: popPK, population pharmacokinetic; V, volume

Applicant's Analysis

Objectives

- To characterize the popPK of ziprasidone in schizophrenic patients.
- To identify any population characteristics, that may influence the pharmacokinetic behavior of ziprasidone, e.g., patient age or weight.

Method

The popPK data of ziprasidone was modeled using NONMEM (Version 6.1) using nonlinear modeling. The structural popPK model developed by the applicant consisted of a one-compartment model with first order absorption and linear clearance. Interindividual variability (IIV) was identified for clearance and the volume of the peripheral compartments (V2). Lastly, a combined constant coefficient of variation and additive model was used to characterize the residual variability. In addition, allometric scaling was used to describe the covariate model.

Covariate identification was conducted by graphic assessment followed by generalized additive modeling approach. Subsequently, a forward addition method was conducted, and statistical significance of covariate-parameter relationship was evaluated based on likelihood ratio test. The applicant noted that these covariates were selected based on clinical or physiological relevance.

Data

The pharmacokinetic data used in the popPK represent ziprasidone concentration data collected in several Pfizer Phase 1, 2, and 3 studies. A summary of these studies is shown in Table 35.

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Table 35. Overview of Clinical Studies Contributing to Ziprasidone PopPK Analysis

Protocol	Design	Duration	Subject Criteria	PK Sampling	Planned Treatments
128-109	A double-blind, randomized, fixed- dose, parallel group study comparing two ziprasidone treatment regimens: 20 mg four times a day (QID) or 80 mg twice a day (BID).	42 days	Subjects (males and females; 18-65 years old) with recent exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder	Blood samples were to be collected prior to the administration of the morning dose of study drug on days 7, 14, 21, 28, 35, and 42. In addition, samples were to be obtained four hours following the morning dose on days 7 and 14.	Group 1: 20 mg QID (20 mg capsule) Group 2: 80 mg BID (20 mg capsule)
128-114	A double-blind, placebo-controlled, parallel group, fixed-dose study comparing 40 or 80 mg BID ziprasidone to placebo.	42 days	Subjects (males and females; >18 years old) with recent exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder	Blood samples were to be collected at baseline and prior to the administration of the morning dose of study drug on days 7, 14, and 42 or at the time of early discontinuation; analyses at 21 day were included for some subjects	40 mg BID ziprasidone (40 mg capsule) 80 mg BID ziprasidone (40 mg capsule) Placebo BID
128-115	A double-blind, placebo-controlled, parallel group, fixed-dose study comparing 20, 60, or 100 mg ziprasidone BID, Haloperidol or placebo BID.	42 days	Subjects (males or females, >18 years old) with a recent exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder	Blood samples were to be collected at baseline and prior to the administration of the morning dose of study drug on days 7, 14, and 42 or at the time of early discontinuation. In addition, samples were to be collected at predefined sampling windows (1-4 hours, 4-7 hours, or 7-10 hours) after dosing on days 14 and 21	20, 60, 100 mg BID ziprasidone (20 mg capsule) 15 mg daily Haloperidone (5 mg AM, 10 mg PM) Placebo BID
128-303	A randomized, double-blind study, placebo-controlled, parallel group study comparing fixed doses of 20, 40, or 80 mg ziprasidone BID vs. placebo.	52 weeks	Subjects (males or females, >18 years old;) with a DSM-III-R diagnosis of chronic or subchronic schizophrenia	Blood samples were to be collected from each subject at screening and during the visits at Week 4 (1-3 hours postdose), Week 12 (3-6 hours postdose), Week 28 (6-9 hours postdose) and 52 (9-12 hours postdose).	20, 40, 80 mg ziprasidone BID (20 or 40 mg capsules) Placebo BID

Protocol	Design	Duration	Subject Criteria	PK Sampling	Planned Treatments
A1281037	Phase I Open, Randomized, 4- Period, 2-Treatment, Multiple-Dose Study to Compare the Pharmacokinetics of 20 mg ziprasidone Administered as a Suspension and as a Capsule in the Fed State to Healthy Subjects	12 days	16 healthy male and female subjects from 18-45 years inclusive	On last day of each treatment period, (Days 3, 6, 9, and 12), blood collection was be done at 0 (just prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 11.5 hours after morning administration. In addition, a sample was to be collected just prior to morning dosing on Day 1.	20 mg BID oral suspension (10 mg/mL) 20 mg BID research capsules
128-044	Phase I open, three group, parallel study to evaluate the single dose oral pharmacokinetics and safety of ziprasidone hydrochloride in children and adolescents with Tourette's syndrome (TS) or chronic motor or vocal tic disorder (CTD).	1 day	Males and females ranging in age from 7-16 years and meeting DSM-IV criteria for TS or CTD were enrolled	Blood samples were to be collected immediately prior to (time zero), and 1, 2, 4, 6, 8, 12, 16, 24, and 32 hours following study drug administration.	Group 1 (>60 kg): 20 mg oral suspension (40 mg/mL), single dose Group 2 (31-60 kg): 10 mg oral suspension (40 mg/mL), single dose Group 3 (16-30 kg): 5 mg oral suspension (40 mg/mL), single dose
128-122	Phase II DB, PC, randomized, flexible dose-escalating, parallel study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ziprasidone in children and adolescents with TS or CTD and to establish the tolerated dose range of ziprasidone in these subjects	56 days	Male and female subjects, 7-16 years old, diagnosed with moderate to severe TS or CTD.	Blood samples were to be collected from each subject at screening (day -5 to -7), prior to the administration of the morning dose on days 8 and 57, and at a randomly selected sampling interval (i.e., 2-4 hours, 4-6 hours, or 6-8 hours postdose) following the administration of the morning dose on days 29 and 57.	5 mg/day increased to a maximum of 40 mg/day (20 mg BID; 5, 10, 20 mg capsules) as tolerated and clinically indicated Placebo

Source: Applicant's study-retrospective-popPK report, Table 1 on page 14-15
Abbreviations: DB, double-blind; DSM, Diagnostic and Statistical Manual of Mental Disorders; PC, placebo-controlled; popPK, population pharmacokinetic

The final dataset for the popPK analysis consisted of a total of 1557 ziprasidone plasma concentrations (73% of original observations) from 479 patients (99.8% of the original subjects). A listing of the baseline demographics for these subjects is given in Table 36.

Table 36. Summary of Baseline Demographics for the Pharmacokinetic Model Building Database (n=479)

Baseline Characteristic	Mean (SD)	Median	Range
Age (y)	40.6 (14.3)	39.0	7 - 82
Height (cm)	171 (11.5)	173	127 - 198
Weight (kg)	74.6 (17.0)	72.1	26.8 - 155
Sex	Males = 336; Females = 143		

Source: Applicant's study-retrospective-popPK report, Table 4 on page 14-15
Abbreviations: SD, standard deviation

2.4 Results

The final parameter estimates of the final popPK model along with the precision are shown in Table 37. The validation of the final popPK model was conducted using bootstrap analyses, goodness of fit diagnostics and limited predictive check.

Table 37. Parameter Estimates and Associated Standard Errors for Final Pharmacokinetic Model

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h)	θ_1	49.3 (2.70)	33.7 (13.4)
Effect of WT	θ_4	0.460 (21.0)	
Effect of AGE	θ_5	0.0747 (72.7)	
V/F (L)	θ_2	68.1 (12.6)	34.9 (165)
KA (h-1)	θ_3	0.0638 (11.4)	52.6 (19.2)
Effect of AGE	θ_6	-0.253 (87.4)	
CCV Residual Error (as %CV)		49.5 (10.3)	
Additive Residual Error (ug/L)		7.65 (81.0)	

* - SE given as %CV

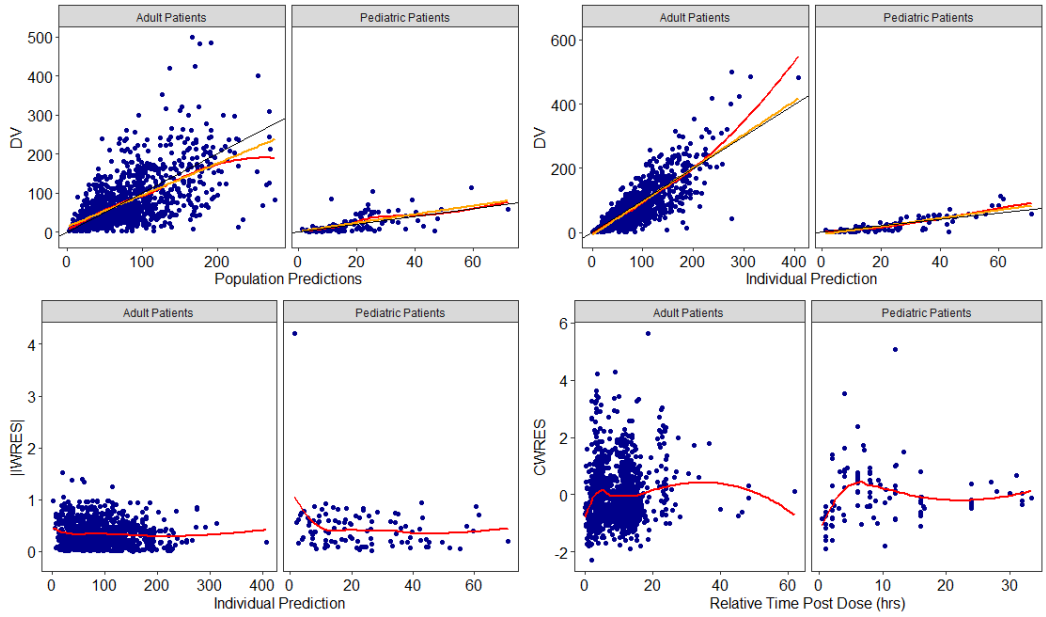
Source: Applicant's study-retrospective-popPK report, Table 14 on page 149
Abbreviations: CCV, constant coefficient of variation; CL/F, apparent clearance; KA, absorption rate constant; SE, standard error; V/F, volume of distribution; WT, weight

Reviewer's Analysis

The reviewer was able to reproduce the applicant's popPK results with NONMEM (version:7.4.3). No additional modeling analysis was conducted.

Reviewer's comments: (b) (4)

Figure 9. Goodness-of-Fit Plots for Final PopPK Model of Ziprasidone in Adult and Pediatric Patients



Source: Reviewer's Analysis
Abbreviations: popPK, population pharmacokinetic

(b) (4)

Table 39. Listing of Analysis Codes and Output Files

File Name	Description	Location
PopPK.R	Exploratory PK and pop PK analysis	M:\\Review\\NDA_020825S-63_Ziprasidone\\PPK\\198

15.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/s/

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