CLINICAL REVIEW

Application Type	NDA
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Submission Code	SE5
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Reviewer Name	Mark Ritter, MD, RPh.
Review Completion Date	April 24, 2009
Established Name	GEODON®
(Proposed) Trade Name	Ziprasidone HCl
Therapeutic Class	Antipsychotic
Applicant	Pfizer, inc.
Priority Designation	P
Formulation	Capsule
Dosing Regimen	Daily
Indication	Treatment of acute mania
Intended Population	Adolescents aged 10-17 years old.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Regulatory action will be taken on this submission after recommendations from a scheduled June 2009 advisory committee have been received and analyzed.

1.2 Recommendation on Post marketing Actions

1.2.1 Risk Management Activity

Post marketing regulatory actions will be considered for this submission after recommendations have been received and analyzed from a scheduled June 2009 advisory committee.

1.2.2 Required Phase 4 Commitments

Any Phase 4 commitments will be considered for this submission after recommendations have been received and analyzed from a scheduled June 2009 advisory committee.

1.2.3 Other Phase 4 Requests

Additional phase 4 study requests will be considered for this submission after recommendations have been received and analyzed from a scheduled June 2009 advisory committee.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Pursuant to the Written Request, the sponsor conducted a single 4-week, outpatient, randomized (2:1 ziprasidone to placebo), double-blind, parallel-group, placebo controlled study of 238 pediatric patients aged 10-17 years of age with a diagnosis of bipolar I disorder, manic or mixed, as determined by a child psychiatrist using DSM-IV criteria via use of the K-SADS interview with symptoms for at least 7 days prior to screening. All patients were titrated off their current medication regimen during a 1 to 10 day screening/washout period. Flexible dosing was employed up to the first two weeks of the double-blind period with two *a priori* defined target dose ranges based on the patients weight at time of entry into study (patients weighing <45kg target dose 60-80mg/day; patients weighing ≥45kg, target dose 120-160mg/day).

The sponsor also conducted two (2) 6-month open-label studies to obtain additional data on the tolerability and safety of ziprasidone for use in pediatric bipolar disorder. A total of 201 bipolar

patients were enrolled in either the long term extension study to the double blind efficacy trial (N=162) or a dose titration study with a 6 month extension trial (N=39). The latter study also enrolled 17 pediatric patients with schizophrenia or schizoaffective disorder; however the primary focus of this review involved the review of the efficacy and safety data obtained from the 201 bipolar patients. Safety results from two double-blind studies of ziprasidone use in pediatric patients with Tourette's disorder were also reviewed. Pertinent safety data that has been submitted as part of this NDA for pediatric patients enrolled in schizophrenia trials were also reviewed and discussed within this review.

1.3.2 Efficacy

The sponsor conducted one 4-week outpatient, flexible dose, double blind, randomized (2:1 drug: placebo) study to demonstrate efficacy for the treatment of pediatric bipolar disorder. Patients were diagnosed by a child psychiatrist with pediatric bipolar disorder using the K-SADS interview and personal evaluation by study psychiatrists. All patients were aged 10-17 years of age. The primary efficacy endpoint was the mean change from baseline in the Young Mania Rating Scale (YMRS) at week 4 with a mixed model of repeated measures (MMRM) analysis employed for hypothesis testing.

The results clearly showed a statistically significant mean change decrease from baseline in the YMRS score at week 4 in ziprasidone treated subjects as compared to placebo.

Table 1: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from placebo (SE)	-5.22 (1.48)	
95% Confidence interval for difference from placebo	(-8.12, -2.31)	
P-value	0.0005	

*modified Intent to treat (i.e. those patients with at least one post-dose efficacy measurement)

Even with the exclusion of all subject efficacy data obtained from two sites that were identified by the Division of Scientific Investigations (DSI) as having invalid data (sites 1013 and 1087) in addition to a sponsor-excluded site (site 1089), efficacy was still clearly demonstrated.

Table 1a: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population: Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=118	PLACEBO N=76
Least squares mean (SE)	-14.08 (0.99)	-8.74 (1.19)
Difference from placebo (SE)	-5.34 (1.56)	
95% Confidence interval for difference from placebo	(-8.40, -2.27)	
P-value	0.0007	

Also, a statistically significant decrease in the key secondary endpoint, CGI-S score, was also seen at week 4, even after excluding all subjects from the three sites mentioned above in the key secondary efficacy analysis.

The employment of a flexible-dose study design for the double blind, placebo controlled study precluded the assessment of a dose-response relationship. In addition, the pediatric bipolar studies imposed maximum dose limits and titration schedules according to patient weight, where patients <45kg could receive a maximum dose of 80mg/day and all others potentially receiving a maximum dose of 160mg/day. These limits were identified as part of a dose titration phase in a previous study and were used to limit overall exposure of ziprasidone to smaller pediatric patients.

Overall this reviewer finds that the efficacy results demonstrate that ziprasidone is effective for the treatment of pediatric bipolar disorder.

1.3.3 Safety

Generally the adverse event profile for treatment of pediatric bipolar disorder was similar to the current labeling of the adult treatment of bipolar disorder. Sedation, dystonia and extrapyramidal symptoms appear to be frequently noted in the pediatric studies. A closer analysis of the adverse events by patient weight revealed that patients who weighed less than 45kg were most likely to report EPS, tremor and abdominal pain adverse events in the double-blind trials.

The sponsor also conducted a concentration-QTcF analysis from concentration-QTcF data points obtained from 4 pediatric trials and from 21 adult trials. The result showed a linear concentration-dependent increase in QTcF prolongation in the pediatric population. Of particular note is the pediatric population overall had a 58% increase in concentration dependant QTcF prolongation rates at any given concentration when compared to the adult population. This suggests that the pediatric population is at least as sensitive to the QT prolongation effects associated with ziprasidone use as adults and may potentially be at greater risk for developing torsades de pointes and other serious cardiac arrhythmias when administered ziprasidone when compared to the adult population.

A review of the post-marketing reports revealed eight (8) pediatric deaths from the sponsor's database, including one case of cardiac failure after receiving 160mg/day of ziprasidone for over 1 year. An Agency review of the FDA post-marketing database concluded that the safety profile of ziprasidone in the pediatric population is similar to the adult population, including QTc-related events. As a result of the FDA internal database review conducted by the Office of Surveillance and Epidemiology (OSE), the Office recommends enhancing the Warnings section of the current ziprasidone label to include the risk of QT prolongation for both adult and pediatric patients.

Although post marketing data is subject to many limitations from which to draw firm regulatory conclusions, reports of cardiovascular deaths in patients who received ziprasidone is of concern to this reviewer in light of the more prominent concentration dependant QTcF prolongation seen in pediatric patients as compared to the adult population. This reviewer therefore recommends that there is sufficient evidence to warrant a change in the current Warnings section of the QT prolongation to include children as being at risk for QT prolongation-related adverse events with ziprasidone use.

1.3.4 Dosing Regimen and Administration

Pediatric bipolar dosing recommendations for ziprasidone labeling were proposed by the sponsor to set maximum daily dosing limits based on a patients' weight as pharmacokinetic studies submitted within this submission. These proposed dosing recommendations are to limit maximum doses for patients who weigh less than 45kg are recommended to a maximum daily dose of 80mg/day, whereas patients who weigh 45kg or greater are recommended to receive up to the daily maximum dose of 160mg/day as currently labeled.

1.3.5 Drug-Drug Interactions

Drug interaction studies were not required under the Written Request. Please refer to the current product labeling and previous Agency reviews for details regarding drug-drug interactions. Include

1.3.6 Special Populations

The sponsor did not conduct any pharmacokinetic studies in patients with cardiovascular, hepatic or renal diseases.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ziprasidone hydrochloride, marketed under the brand name GEODON®, is pharmacologically classified as an antipsychotic medication. Although the *in vivo* mechanism of action is not well-

delineated, *in vitro* binding studies demonstrated that ziprasidone functioned as an antagonist at the dopamine 2 (D2), serotonin 2A ($5HT_{2A}$) and serotonin 1D ($5HT_{1D}$) receptors , and an agonist at the serotonin 1A ($5HT_{1A}$) receptor. ziprasidone is also noted for alpha-1 receptor and histamine-1 receptor antagonist properties as well, leading to potential side effects of orthostatic hypotension and sedation respectively.

2.2 Currently Available Treatment for Indications

Ziprasidone oral capsules are currently FDA approved for the treatment of adult schizophrenia and for the acute treatment of adult manic or mixed episodes associated with bipolar disorder. An intramuscular form (IM) of ziprasidone is available and approved for the treatment of acute agitation in schizophrenic patients for rapid control of agitation.

2.3 Availability of Proposed Active Ingredient in the United States

Ziprasidone HCl is available as a capsule in 20, 40, 60 and 80mg strengths, and as an IM formulation (with directions for reconstitution before use) with two strengths: 10mg and 20mg.

2.4 Important Issues with Pharmacologically Related Products

The Agency has recently mandated class labeling boxed warnings for all antipsychotic medications for an association of antipsychotic use and increased mortality in elderly patients with dementia-related psychosis. Agency action was taken after a review of placebo-controlled studies revealed a 1.6 to 1.7 times increased risk of death in elderly patients with dementia related psychosis who took antipsychotic medications compared to those who took placebo.

2.5 Presubmission Regulatory Activity

Ziprasidone hydrochloride capsules received initial Agency approval on February 5, 2001 for the treatment of adult schizophrenia. ziprasidone then received approval for the acute treatment of acute mania in adults on August 19, 2004. An oral suspension formulation of ziprasidone received Agency approval on March 29, 2006 for both indications.

Previous to the approval for the adult acute mania indication in August 2004, the Agency had issued a Written Request letter on February 11, 2003 to submit information from trials in pediatric patients with 1.) schizophrenia and 2.) acute mania as part of bipolar I disorder. At the request of the sponsor, the Written Request letter timeframe was amended on November 7, 2007 to extend the deadline for reporting data from the pediatric schizophrenia and bipolar studies to September 30, 2011. This was granted after review of recruitment data submitted by the sponsor in 2007 for the pediatric schizophrenia program demonstrated severe difficulties in recruitment and an inability to meet the original WR deadline for submission of reports. At the time of the extension, the sponsor clearly noted that studies for pediatric bipolar disorder were completed within the timeframe of the original WR and would be submitted in 2008.

On April 18, 2008, the sponsor and division met via teleconference as part of a pre-NDA meeting for submission of pediatric bipolar studies that were completed as part of the WR letter. It was re-iterated at the time of the pre-NDA meeting that the pediatric schizophrenia studies would still be conducted and that a Prior Approval Efficacy Supplement would be submitted to the Agency once the pediatric schizophrenia studies were completed.

On October 21, 2008, the sponsor submitted NDA supplement (#32) for the treatment of pediatric bipolar disorder. This document summarizes the review of this NDA application.

Post- Submission Regulatory Activity

Regarding the most recent status of the pediatric schizophrenia study, the Agency was informed on March 30, 2009 by the sponsor that "…based on the results of the interim analysis of the placebo-controlled pediatric schizophrenia efficacy study A1281134, Pfizer Inc has decided to stop the A1281134 and A1281135 (open-label extension) protocols." The sponsor stated that results of the interim analysis performed on March 23, 2009 was reviewed by the DSMB and recommended that "…the study be stopped per meeting the pre-defined stopping criteria for futility (lack of efficacy)."

2.6 Other Relevant Background Information

No other relevant pediatric background information is available for ziprasidone as this formulation has not received a pediatric mania indication in any other country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

At the time of this review there do not appear to be any major CMC issues pending. Please see the formal CMC review for further details and analysis.

3.2 Animal Pharmacology/Toxicology

Although the formal pharmacology/toxicology review is not available, no issues have been raised to this reviewer with regards to the approvability of ziprasidone from a pharmacology/toxicology perspective.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Pursuant to the Agency's Written Request, the efficacy of Geodon® for the treatment of mania in the child and adolescent population was determined after completion and analysis of a single phase 3 study (A1281132, a randomized double blind, placebo controlled flexible dose study).

The safety of Geodon® in adolescent mania was assessed from safety data submitted from study A1281132 with longer term safety data derived from a six-month open label extension study (A1281133) and an additional six month open label study (A1281123) whose initial objective was to determine the safety and tolerability of dosing regimens for use in both double-blind efficacy studies and 6-month safety studies. The safety data from studies A1281123 and A1281133 was summarized in an Integrated Safety Summary (ISS)

For completeness, additional safety data was submitted with this NDA supplement from several open-label Phase IIR studies including two studies of Geodon® use in patients with Tourette's (128-044 and 128-122) and bipolar disorder (20020501-8 weeks and 20030094); in patients with Autism (20010457- 6 weeks duration) and schizophrenia-spectrum disorders (20020012-one year study). Only pertinent positive or negative safety findings will be reviewed from each of these studies as part of the safety review.

4.2 Tables of Clinical Studies

Table 2: Geodon® Pediatric Bipolar Table of Studies

Phase 3 Studies	
A1281132 Flexible Dose	A four–week, outpatient, multicentered, double-blind, parallel-group, placebo controlled, randomized (2:1 drug: placebo), flexible dose study of 238 adolescent patients (ages 10-17 years of age) with a current clinical diagnosis of bipolar I disorder, manic or mixed (according to DSM-IV criteria using the K-SADS instrument) titrated with Geodon® according to weight to a target dose of 60-80mg/day (<45kg) or 120-160mg/day (≥45kg) for the first two weeks with stable dosing at weeks 3 and 4.
A1281133 Open label Safety	Six month multicentered, open label extension safety study of study A1281132 in 162 enrolled adolescent patients with mania.
A1281123 Open label Safety	24 week multicentered, two-period, open label safety study with an initial three week fixed-dose titration period followed with flexible dosing in period two for 56 treated adolescent patients with either mania (N=39) or schizophrenia/schizoaffective disorder (N=17).

4.3 Review Strategy

Table 3 below provides a listing of documents that were reviewed during the NDA review process.

Table 3: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
October 21, 2008	• Study reports: A1281132, A1281133 and A1281133 • Integrated Safety Summary • Review of pertinent SAEs and safety data from Tourette Syndrome and submitted phase IIR studies • Proposed labeling • Written Request • Financial Disclosure Certification • Application Summary • Case Report Tabulations (.xpt files) • Case Report Forms
February 17, 2009	• Response from sponsor with regards to additional analyses of the data requested by this reviewer
April 23, 2008	• Response from sponsor regarding re-analyses of primary and key secondary endpoint excluding all data from sites 1013, 1087 and 1089

4.4 Data Quality and Integrity

Routine NDA site investigations were performed by the Division of Scientific Investigations (DSI) at the following sites: Site 1040 (Dr Delbello), Site 1013 (Dr Punjwani) and Site 1087 (Dr Gazda). The sites were selected based on number of patients enrolled, as well as those sites with numerous protocol violations and dosing errors noted during the trial.

The inspection of these sites resulted in a recommendation of "No Action Indicated" for site 1040. However the review of sites 1013 and 1087 resulted in a FDA Form 483 being issued and an initial recommendation of official action indicated (OAI) for site 1013 and verbal action indicated (VAI) for site 1087. After further discussions within DSI, site 1013 (Dr Punjwani) was downgraded to verbal action indication as the site provided detailed corrective plan to the FDA Form 483.

After further consideration of the evidence from site 1087, DSI has concurred to upgrade the recommendation from a VAI to an OAI. In addition, a for-cause inspection was conducted for site 1089 (Dr. Summers) due to questions regarding inadequate sponsor monitoring and contract

research organization (CRO) monitoring. Additional audits of the sponsor and the CRO are being conducted at this time.

It is the recommendation of DSI that data from sites 1087 and 1013 are not considered valid to support this NDA. Consequently this reviewer requested that the sponsor re-analyze the primary efficacy and key secondary efficacy data excluding all data obtained from sites 1013, 1087 and additionally for site 1089 (Dr Tim Summers)-whose data was excluded by the sponsor from the per protocol analysis due to widespread good clinical practice violations. The results of the reanalyses are discussed in section 6.

4.5 Compliance with Good Clinical Practices

Studies A1281132, A1281123 and A1281133 were conducted in compliance with the ethical standards according to the Declaration of Helsinki and the International Conference on Harmonization guidelines of Good Clinical Practice. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997. The reader is directed to review the DSI inspection report for a full analysis of GCP variances and violations that occurred during the routine NDA DSI inspection process.

4.6 Financial Disclosures

There were eleven (11) financial disclosures filed from eight (8) investigators from five studies (A1281132, 1123, 1133, 128-044 and 128-122). These investigators indicated that they had significant payments from the sponsor requiring submission of FDA form 3454. Three investigators filed two disclosure forms as a result of participating in studies A1281132 and A1281133.

For the pivotal trial A1281132, approximately 18% (42/238) of the total patient population were randomized by the listed investigators below. Approximately 70% of these 42 patients (nearly 12% of the total study population 29/238) were randomized by Dr Delbello. Based upon results obtained from the DSI inspection for Dr Delbello, it is unlikely that financial payments were a significant bias in the efficacy results obtained from this site.

Table 4: Investigators with financial disclosure

NAME	SITE	AMOUNT (USD)
Study 1281123		
Jeffrey Lee Blumer	1004	*(b) (6)*
Melissa DelBello	1002	
Robert Findling	1004	
Jean Frazier	1003	
Floyd Randy Sallee	1002	
Study 1281132 and 1281133		

Haisam Al-Khouri	1031		(b) (6)	
Melissa DelBello	1040		(b) (6)	
Arnold Mech	1132		(b) (6)	

5 CLINICAL PHARMACOLOGY

Note: Please see the biopharmacology/clinical pharmacology review for a more detailed pharmacokinetic review. This review is based upon information contained in the submitted Summary of Clinical Pharmacology Studies.

Pursuant to the Written Request, the sponsor obtained ziprasidone pediatric pharmacokinetic (PK) data from four (4) completed studies: A1281132, A1281123, 128-044 and 128-122 (the latter two were studies done in patients with Tourette's disorder). In addition to standard analyses of pharmacokinetic parameters, the sponsor evaluated the relationship of pediatric plasma drug levels to changes in QT intervals using statistical modeling for studies A1281123 and A11281132.

Of note, the sponsor also conducted a multistudy pooled analysis of population pharmacokinetic data to compare the ziprasidone concentration change in QTcF from data obtained from the two pediatric Tourette studies above plus the three submitted pediatric studies (N=180), as well as data obtained from 31 adult studies (N=1383). The purpose of this comparison was to conduct an analysis to characterize the relationship between ziprasidone concentration (and its' metabolites M9 and M10) to changes in QT/QTc intervals in children and adults. QTcF/concentration data primarily from study A1281132 was used for the majority of the pediatric analyses, though a pooled analysis of all pediatric and adult data was performed. The descriptive results showed a similar distribution pattern of data points between the two populations. At the request of this review, a linear regression analysis was performed to objectively compare the slopes of the linear regression lines obtained from the pediatric data vs. the adult data. The results showed that the pediatric dataset exhibited a steeper slope to the regression line as compared to the adult dataset, suggesting that the pediatric population is at least as sensitive to the concentration-dependant QTcF prolongation effects of ziprasidone administration as compared to adults or potentially may be at more at risk for QTc related cardiac arrhythmias. Despite the absence of reports or adverse events of torsades de pointes seen in the pediatric clinical trials and post-marketing reports thus far, this reviewer recommends that the QTc warning language be re-worded to include adults and children.

5.1 Pharmacokinetics

In general, ziprasidone appears to adhere to first-order, one compartmental model kinetics in both the adult and pediatric population. Clearance tended to be higher in adults (41-72L/hr vs. 27-75L/hr children) with body weight having the most influence over clearance (age had a small effect). Once body weight was corrected for in the analyses, pharmacokinetic exposure appeared to be similar between adults and children. Absorption tended to be higher in children as well.

Overall, the clearance of ziprasidone increases as body weight increases. Therefore a direct relationship exists between ziprasidone clearance and body weight.

Pharmacokinetic results from study A1281132 and 1281123

The QTcF/concentration effect will be discussed in greater detail in section 7.1.9.4.1. However ziprasidone was associated with a concentration dependant increase in QTcF in study A1281132. The rate of change increase to concentration for study A1281132 was estimated to be 0.0852 msec per ng/ml concentration of ziprasidone. For study A1281123, the rate of change increase in QTcF to concentration was 0.139 msec per ng/ml. A similar concentration dependant increase in QTcF was also observed with the M9 and M10 metabolite concentrations in children.

5.2 Pharmacodynamics

There is not expected to be a difference in the pharmacodynamic properties of ziprasidone in adults and children.

5.3 Exposure-Response Relationships

An analysis of ziprasidone exposure to changes in QT/QTcF intervals was performed and will be reviewed in depth in section 7.1.9.4 of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The submitted pediatric efficacy study (A1281132) was performed pursuant to the Written Request, for the treatment of mania or mixed episodes in children and adolescents aged 10-17 years old with a current bipolar I disorder diagnosis according to DSM-IV criteria.

6.1.1 Methods

Pursuant to the Written Request, a single randomized, double-blind, placebo controlled trial was performed to evaluate the efficacy of ziprasidone in the treatment of adolescent mania.

Study A1281132
This multicentered U.S. study was conducted at 36 sites from January 13, 2006 to July 26, 2007 with Paul Wang, MD as the coordinating investigator.

Protocol Amendments
There was one (1) Protocol amendment to this study on December 6, 2007 with numerous changes made to the protocol. Although a review of the pertinent changes are described below,

the changes do not appear to substantially alter the study design or objectives of the study and thus unlikely to have introduced bias into the study results.

- Change in the procedures for primary and secondary analyses of the ITT and PP populations
- Clarification of statistical methods to be used for analysis of the raw CGI-I score
- Reiterated that maximum dose for subjects weighing <45kg was 80mg/day
- Added the requirement to have a child psychiatrist determine diagnostic eligibility with K-SADS administration provided by qualified and experienced rater.
- Increased safety monitoring/DQ criteria for patients with clinically significant ECG abnormalities

6.1.2 General Discussion of Endpoints

The primary objective of this study was to establish the efficacy of oral ziprasidone compared with placebo in the treatment of children and adolescents with Bipolar I disorder (manic or mixed).

Primary efficacy was assessed by the change from baseline to week 4 on the YMRS total score between the ziprasidone treated groups compared to placebo for the intent to treat population (ITT). The YMRS has reported validity and reliability and has been previously accepted by the Agency as a standard measure for measuring mania symptom response in clinical trials. This measure also has wide acceptance and use within the pediatric population.

Although no key secondary efficacy variables were specified *a priori* in the protocol, the sponsor pre-specified that the change from baseline in the Clinical Global Impression of Severity scores (CGI-S) and the Clinical Global Impression of Improvement (CGI-I) scores between the ziprasidone group and placebo treatment as additional secondary efficacy endpoints in this study. It was noted by this reviewer that upon review of this application, the sponsor referred to the change from baseline in CGI-S score as a "Key" secondary endpoint in the statistical analysis plan. Therefore for purposes of this review, the CGI-S is noted throughout this review as a key secondary endpoint despite the lack of an *a priori* agreement between the sponsor and the Agency specifying a key secondary endpoint.

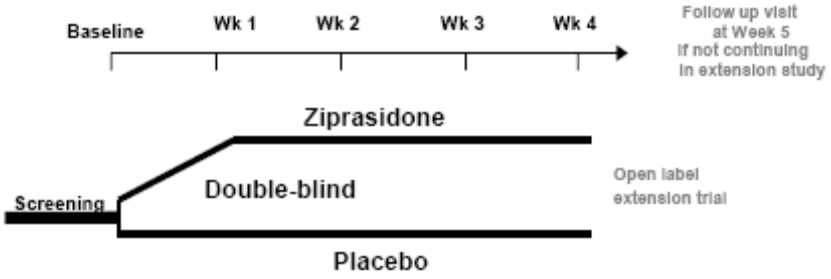
6.1.3 Study Design

Placebo Controlled Study (using ziprasidone Oral Capsules)

Study A1281132 was a 4-week outpatient, randomized (2:1 drug to placebo), double-blind, placebo-controlled, parallel group, flexible dose trial. Patients who met inclusion criteria at the end of a preceding one to ten (10) day wash-out period were then randomized at baseline to receive ziprasidone or placebo in a 2:1 ratio.

Over an initial two-week titration period, two (2) dosing arms for ziprasidone were pre-specified based upon the weight of the patient. Patients who weighed ≥ 45kg and tolerated 120mg/day were allowed to continue titration up to a target range of 120-160mg/day by the end of week two. Patients who weighed <45kg we allowed to achieve a maximum dose of 80mg/day by the end of week two.

In patients who did not require a rapid onset of action, treatment began with 20mg/day with dose increases of 20mg/day every second day. For those patients whose clinical symptoms required a more rapid titration schedule, the dose of ziprasidone could be increased 20mg daily in order to achieve the target dose as soon as possible. However a target dose of 160mg/day was not to be attained by day 8 for those patients who required a fast titration. Those patients who had an insufficient response to treatment one week after completing their titration and maximum tolerated dose were recommended to discontinue the study and consider enrolling in the open-label extension study A1281133, provided no safety concerns were seen.



During the first two weeks of the titration, the investigator or his/her staff would have daily contact (phone or in person) to ensure proper administration was obtained. Once the target dose was achieved, the dose of the medication could be reduced for concerns over tolerability or safety. Patients in the 160mg/day dosing group who could not tolerate 80mg/day (or those patients in the 80mg/day group not tolerating 40mg/day) were discontinued from the study. There were six (6) pre-specified in person weekly visits for all subjects in the study (baseline, Week 1-Week 4, 1 week post study Follow-up).

Open label Safety Studies

Study A1281123 (ziprasidone Oral suspension and capsules both administered)

Study A1281123 was organized into two (2) distinct dosing periods: A 3-week short-term, open label, fixed dose titration period (period 1) followed by a 27-week long term flexible dose period (Period 2) in patients aged 10-17 with bipolar I, schizophrenia and schizoaffective disorder. Adolescent patients with schizophrenia/schizoaffective disorder were included into this study to support the future NDA submission for adolescent schizophrenia as per the original Written Request. Since the sponsor has not completed studies for the schizophrenia indication under the Written Request at this time, this review will focus on the safety results obtained from only those patients in study A1281123 with a bipolar I diagnosis. However, serious and pertinent safety

findings obtained from patients with a diagnosis of schizophrenia and/or schizoaffective disorder were reviewed by this reviewer.

For period 1, 46 subjects with bipolar I disorder (17 subjects with schizophrenia/schizoaffective disorder) were screened with bipolar subjects scoring at least 17 or higher on the YMRS score being eligible for enrollment. Eligible subjects who continued to meet inclusion criteria were then randomized to one of two 10-day fixed titration dosing groups:

- Low dose group-patients began treatment at 10mg bid with sequential dose titration of 10mg bid increments to final dose of 40mg bid by day 10.
- High dose group- patients began treatment at 20mg bid with sequential dose titration of 20mg bid increments to final dose of 80 mg bid by day 10.

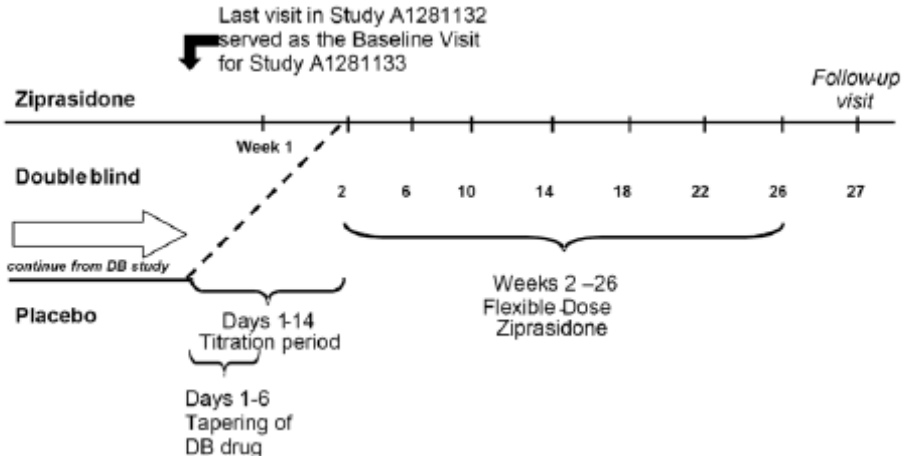
Patients who weighed <45 kg in body weight were to receive 50% of the stated mg strength associated with their respective Study Group Assignment for period 1. The rationale for administering 50% less medication to patients <45kg was to compensate for a possible increase in systemic exposure of ziprasidone in lower body weight subjects. All patients were prescribed ziprasidone oral suspension for period 1.

On August 4, 2004, the sponsor discontinued randomization into the low dose group in order to correct for low recruitment and poor completion rates for the high dose group. Sufficient data was obtained from the low dose group prior to discontinuation. Interim analyses showed that the low dose group showed better toleration as opposed to the high dose group over the initial 10 day dosing titration, but many low dosed patients needed additional medication in order to control symptoms. The results of these interim analyses were presented to the Agency on November 8, 2004 during a teleconference. It was agreed during the teleconference that the study results identified an allowable maximum tolerated dosing range and titration schedule to permit phase III studies.

For period 2 of the study, patients were allowed to take open label ziprasidone with concomitant medications (if required) for an additional 24 weeks after the completion of period 1 or early termination from period 1. In contrast to period 1 however, patients who weighed <45kg may receive doses up to 80mg BID, based upon symptomatology. The sponsor was to be notified for any patients <45kg who was titrated to doses above 40mg BID/day. Follow-up outpatient assessments were collected at weeks 4 (1 week after completion/ET from period 1), week 8, and weeks 12, 18 and 27. Patients were administered ziprasidone as either an oral capsule or oral suspension for period 2.

Study A1281133 (ziprasidone capsules)

This study was the open-label extension study to the placebo controlled study A1281132. Patients who completed at least three weeks of double-blind treatment under study A1281132 were eligible to enter this 26-week open label study. Patients were first tapered off their double blind medication for the first five days of the study and then re-titrated with active open label ziprasidone with flexible dosing to maintain optimal efficacy and tolerability. Patients who weighed less than 45kg were permitted to be titrated to a maximum dose of 80mg/day. The schematic below delineates the study design for study A1281133:



6.1.3.1 Patient Samples

Important inclusion criteria were:

- Patients aged 10-17 at time of study entry
- Had a primary diagnosis of bipolar I disorder, manic or mixed, as defined by DSM-IV through a K-SADS interview with symptoms for at least 7 days prior to screening.
    - "…as determined by a board-certified or board eligible child psychiatrist" was added as of the December 6, 2006 protocol amendment; original protocol issued September 22, 2005.
- Had both a screening and baseline YMRS score $\geq$17
- Patients were willing to discontinue all prohibited medications within 4.5 half lives or 10 days (whichever is less) prior to randomization.
- Female patients of childbearing potential are using appropriate birth control procedures.

Patients were excluded from participating for the following reasons:

Psychiatric Exclusions

- Patients who are stable on current regimen or have a substance abuse disorder
- Patients with rating of seven (7) on the single item suicidal ideation item #13 of the CDRS-R or thought to be at imminent risk of suicide or homicide.
- Patients with IQ <70 or with autism/PDD

Medical Exclusions

- Patients with any unstable serious medical condition
- Patients with a history of non-vasovagal syncope
- Abnormal liver function tests at screening (twice the upper limit of normal (ULN) or 1.5 X ULN for bilirubin), significant liver disease

- Clinically significant hypokalemia/hypomagnesaemia either not corrected or needing daily supplementation
- History of AIDS

Cardiovascular Exclusions

- History of significant cardiovascular disease requiring treatment and/or evaluation.
- History of cardiac arrhythmias, conduction abnormalities, QT prolongation or genetic risk for long QT prolongation
- Patients with clinically significant ECG abnormalities at baseline and screening, including a QTcF $\geq$460msec.

Medication Exclusions

- Patients who have taken Clozaril within 12 weeks of randomization or a depot antipsychotic within four weeks or an MAOI two weeks before baseline.
- Patients taking a concomitant medication known to prolong the QTc interval
- Patients who were non-responsive to a previously adequate trial of ziprasidone.

6.1.3.2 Concomitant medications

Patients were allowed to take the following medications during the study.

- Lorazepam for agitation and for insomnia
- Benadryl or Ambien for insomnia
- Anticholinerigcs or propranolol for EPS
- Non-sedating antihistamines, Tylenol, aspirin, pseudoephedrine
- Laxatives

6.1.3.3 Schedule of Assessments

The following table delineates the scheduled assessments that were performed for all subjects under study A1281132.

	Screening	Baseline	Treatment			EOT	FU[a]
Study Day	**-10 to –1**	**0**	**7**	**14**	**21**	**28**	**35**
Informed consent, assent	X						
Medical, psychiatric, family, suicidality history	X						
K-SADS	X						
Physical exam including body temperature	X					X	
Height/weight/BMI/waist circumference	X					X	
Electrocardiogram[b]	X	X[c]	X	X	X	X[d]	X[e]
Pharmacokinetic sample		X[f]				X[d]	
Blood pressure/pulse rate	X	X	X	X	X	X[d]	X[e]
Safety laboratory tests	X	X[e]		X		X	X[e]
Hormone assessment[g]	X	X[e]				X	X[e]
Fasting glucose, lipids, insulin, $HbA1_c$	X	X[e]				X	X[e]
Hepatitis serology	X						
Urine drug screen	X	X		X		X	
Serum pregnancy test	X	X		X		X	
Anonymized pharmacogenomics[h]		X					
Randomization		X					
Study drug dispensed		X	X	X	X		
Drug accountability			X	X	X	X	
YMRS	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	
CGI-I			X	X	X	X	
CGAS	X	X		X		X	
CHQ		X				X	
School placement		X		X		X	
CPBAQ	X	X	X	X	X	X	
CDRS-R	X	X	X	X	X	X	
CNS Vital Signs, including sedation item	X	X				X	
SARS, BAS, AIMS		X	X	X	X	X	X[e]
Tanner staging		X					
Adverse event assessments		X	X	X	X	X	X
Prior medications	X						
Concomitant medication		X	X	X	X	X	X

Source: Protocol (Appendix A1)
AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Rating Scale, BMI = body mass index, CDRS-R = Child Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity, CHQ = Child Health Questionnaire, CPBAQ = Children's Problem Behavior and Aggression Questionnaire, ECG = electrocardiogram, EOT = end-of-treatment, FU = follow up, $HbA1_c$ = glycosylated hemoglobin, IRB = institutional review board, K-SADS = Schedule for Affective Disorders and Schizophrenia for School Age Children, PK = pharmacokinetic, SARS = Simpson Angus Rating Scale, T4 = free thyroxine, TSH = thyroid-stimulating hormone, YMRS = Young Mania Rating Scale
[a]Subjects who did not enter the open extension returned for a post-treatment follow-up visit at Week 5.
[b]ECGs administered at least 3 hours after food intake.
[c]Triplicate ECGs after all assessments (except PK and before dosing).
[d]Obtained before and after dosing.
[e]Only if abnormalities present at the previous visit.
[f]Sample obtained twice after first dose of study medication.
[g]Free T_4 and TSH, prolactin, testosterone, IGF-1, IGFBP-3.
[h]Optional and subject to IRB approval

6.1.4 Efficacy Findings

Subject Disposition
Out of a total of 327 subjects screened, 238 were randomized to treatment, with 237 taking at least one dose of study medication (modified ITT population).

As seen below, the completion rates were 65% for ziprasidone vs. 58% for placebo.

TABLE 5: Study A1281132 Completion rates

	PLACEBO	**ZIPRASIDONE**
No. treated	88	149
Total No. of early discontinuations	37 (42%)	52 (35%)
Reason for Discontinuation		
Adverse event	13 (15%)	18 (12%)
Withdrew Consent	2 (2%)	9 (6%)
Lost to Follow up	1 (1%)	8 (5%)
Lab Abnormality	0	1 (1%)
Other*	21 (24%)	16 (11%)
Total	**37**	**52**

*Primarily included lack of efficacy or therapeutic response and insufficient response

In addition, the sponsor also characterized the discontinuation rates related to the fast (i.e. daily titration) vs. slow (every 2nd day) titration schedule. The results are seen below and indicate that slow titration was associated with more discontinuations due to adverse events compared to fast titration for both groups of patients and more overall discontinuations in the ziprasidone group when compared to fast titration:

TABLE 6: Patient Discontinuation by titration speed

	PLACEBO N=88		**ZIPRASIDONE N=149**	
	Fast (n=37)	**Slow (n=51)**	**Fast (n=56)**	**Slow (n=93)**
Adverse Event	2 (5%)	11 (22%)	3 (5%)	15 (16%)
Withdrew Consent		2 (4%)		9 (10%)
Lost to F/U		1 (1%)	2 (4%)	6 (6%)
Lab Abnl.			1 (2%)	
Other	15 (41%)	6 (12%)	6 (12%)	10 (11%)
Total	**17 (46%)**	**20 (39%)**	**12 (21%)**	**40 (43%)**

Protocol Deviations

There were a total of 113 protocol violations from 83 patients (ziprasidone 53; Placebo 25; not received any treatment 5). A listing of the top 6 protocol violations are seen below. The largest

number of protocol violations (40) occurred as a result of dosing/medication errors with study medication.

TABLE 7: Listing of Top 6 Protocol Deviations

PROTOCOL DEVIATION	NUMBER OF SUBJECTS
Dosing/medication errors*	40
Two or more positive UDS at any two visits	13
Subject not contacted daily during titration period	11
Week 4 visit more than 3 days outside of window	10
Informed Consent obtained by study coordinator	7
KID-SCID administered rather than K-SADS	5

*Defined as dosing errors from: 1) sites Punjwani, Lopez, Thebaud; 2) all subjects from site 1089 (Tim Summers MD) due to widespread protocol and GCP violations; 3) Exceeded maximum allowed dose for 6 or more doses (10 patients); 4) failure to reach target dose by day 14; 5) missed 20% of dose between first and last dose; 6) dosed below minimum allowed dose for 3 or more doses after reaching max dose.

At the request of this reviewer on January 30, 2009, the sponsor delineated the 40 dosing/medication errors, which included seven (7) patients who exceeded the maximum dose for greater than 6 doses and three (3) patients who misunderstood the dosing instructions. A further analysis performed by the sponsor to identify all patients who took at total daily dose of drug the exceeded the maximum dose on any occasion delineated a total of 26 patients (14 ziprasidone, 12 placebo) which includes nine (9) subjects from the previously described 10 patients. These additional 17 patients were not considered to be a protocol deviation as the number of overdoses was less than 6. Of the additional nine ziprasidone patients identified, five (5) subjects had adverse events during the period of overmedication. However there were no serious adverse events (SAEs) or patient's discontinuations noted for these additional patients. Adverse events for these patients included sedation, headache, somnolence, nausea, and vomiting.

Baseline Demographics

As seen in the table below, the majority of patients in this study were white adolescent males aged 13.6-13.7 years old.

Table 8: Demographic Characteristics of Study A1281132

DEMOGRAPHIC VARIABLE	PLACEBO N= 88	ZIPRASIDONE N= 149
Male (%)	47	84
White (%)	72 (82%)	121 (81%)
Black (%)	14 (16%)	21 (14%)
Mean Age (years)	13.7 $\pm$ 2.0	13.6 $\pm$ 2.2
Mean Weight (kg)	60.0 $\pm$ 16	57.2 $\pm$ 14.4

Baseline Psychiatric History

There appeared to be little difference in the duration length from initial diagnosis of bipolar disorder prior to screening between the ziprasidone and placebo treated subjects. The mean duration of illness ranged from 9.1 months (range 0-103.1 months) in the placebo group to 11.6 months (range 0-111.9 months) in the ziprasidone group. The majority of the patients had a primary diagnosis of bipolar I disorder, most recent episode mixed. Although the number of psychiatric hospitalizations (an indicator of severity of disease) was not reported in the study report, there were a greater proportion of patients with bipolar illness with psychotic features in the placebo group compared to ziprasidone (18% vs. 9% respectively).

Table 8a: Characteristics of the Presenting DSM-IV Bipolar Diagnosis

DSM-IV BIPOLAR I DISORDER DIAGNOSIS	PLACEBO N=88	ZIPRASIDONE N=149
Manic Episode	23 (26%)	45 (30%)
Mixed Episode	57 (60%)	90 (65%)
Single Manic Episode	8 (9%)	14 (9%)
Psychotic Features (all categories)	16 (18%)	13 (9%)

Concomitant medication use

Lorazepam use was permitted on an as needed basis during the double-blind treatment period up to maximum of 2mg/day, except within 6 hours prior to any assessments. In addition, 68% (101/149) of ziprasidone treated subjects received a concomitant medication during the study compared to 59% (52/88) of placebo treated subjects. The study allowed for lorazepam, diphenhydramine or zolpidem for treatment of insomnia. The top 6 concomitant medications used in ziprasidone treated patients are presented below:

TABLE 9: Concomitant Medication use In Study A1281132

CONCOMITANT MEDICATION	ZIPRASIDONE N=149	PLACEBO N=88
Benztropine Mesylate	26 (17%)	5 (6%)
Lorazepam	24 (16%)	15 (17%)
Paracetamol	19 (13%)	15 (17%)
Ibuprofen	16 (11%)	8 (9%)
Diphenhydramine	20 (13%)	12 (14%)
Zolpidem	10 (7%)	5 (6%)

Review of the database also showed that one patient each in the ziprasidone treatment groups received haloperidol and olanzapine vs. none in the placebo group. In addition three (3) ziprasidone treated patients vs. 0 placebo patients received quetiapine. For placebo treated subjects, two (2) patients were reported as taking ziprasidone.

The sponsor did not provide any data regarding the duration of concomitant medication use during the study. However since the percentage of concomitant medication use was generally similar between treatment groups, it is unlikely that concomitant medication significantly biased the efficacy results.

The nearly 3:1 increase in use of benztropine mesylate in the ziprasidone treatment group suggests that a significant proportion of patients taking ziprasidone likely experienced extrapyramidal symptoms with ziprasidone use. Extrapyramidal use is associated with atypical antipsychotic use. However the proportion of pediatric patients with likely EPS symptoms based on benztropine use (17%) is greater than the percentage of adult bipolar patients who reported EPS during clinical trials as per current approved labeling [11% (31/279) vs. 9% (12/136) ziprasidone to placebo].

Exposure Data

The mean duration of exposure for study A1281132 in the ziprasidone group was 22.0 days vs. 23.7 days in the placebo controlled group. The mean daily dose during weeks 3, 4 and early termination in patients ≥ 45kg was 118.8 mg, with a mean modal dose of 69.23 for patients <45kg.

Efficacy Results

Despite a moderate placebo effect on YMRS scores, the results from the primary statistical analysis demonstrated a statistically significant mean change decrease in YMRS scores from baseline at week 4 for the ziprasidone treated group as compared to placebo treated patients. The primary statistical model pre-specified the use of a mixed model of repeated measures analysis.

Table 10: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from placebo (SE)	-5.22 (1.48)	
95% Confidence interval for difference from placebo	(-8.12, -2.31)	
P-value	0.0005	

*modified Intent to treat (i.e. those patients with at least on post-dose efficacy measurement)

Even after excluding subjects from sites 1013, 1087 and 1089 as a result of widespread GCP violations identified by the FDA DI and the sponsor, efficacy was still maintained.

Table 10a: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population: Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=118	PLACEBO N=76
Least squares mean (SE)	-14.08 (0.99)	-8.74 (1.19)
Difference from placebo (SE)	-5.34 (1.56)	
95% Confidence interval for difference from placebo	(-8.40, -2.27)	
P-value	0.0007	

Efficacy was still seen for the primary efficacy endpoint in the per-protocol analysis even after sites 1013, 1087 and 1089 were excluded from the per-protocol analysis. The per-protocol analysis excluded ITT subjects from the analysis that did not violate any major inclusion/exclusion criteria or have major protocol violations and completed at least 1 week of study treatment post medication titration.

Table 10c: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the Per Protocol Population: Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=90	PLACEBO N=62
Least squares mean (SE)	-14.47 (1.06)	-8.35 (1.36)
Difference from placebo (SE)	-6.13 (1.81)	
95% Confidence interval for difference from placebo	(-9.68, -2.58)	
P-value	0.0008	

Using the standard Last-Observation Carried Forward (LOCF) analysis of the primary endpoint, a similar statistically significant mean change reduction in the week 4 YRMS scores was also seen between the ziprasidone group as compared to placebo.

Table 11: Mean change from baseline analysis at week 4 in YMRS scores in the modified Intent to Treat population- LOCF Analysis

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-13.23 (0.79)	-7-.14 (0.93)
Difference from placebo (SE)	-6.09 (1.08)	
95% Confidence interval for difference from placebo	(-8.23, -3.96)	
P-value	<0.0001	

*modified Intent to treat (i.e. those patients with at least one post-dose efficacy measurement)

Although formal statistical testing was not pre-specified for efficacy between the fast and slow titration sub-groups, a review of their respective week 4 mean change from baseline scores reveals overlapping 95% confidence intervals for the fast titration group as compared to placebo whereas patients with a slower titration schedule did not have overlapping confidence intervals as compared to placebo. This suggests that a slower speed of titration in adolescent patients may be associated with improved efficacy over a faster titration schedule.

Table 12: Descriptive Statistics for YMRS total score at baseline and change from baseline at week 4 by slow and fast titration sub-group-Modified ITT population

GROUP	$N_{BASELINE}$	MEAN BASELINE SCORE (SD)	$N_{WEEK\ 4}$	MEAN CHANGE WEEK 4 SCORE (SD)*	95% CI
Fast Titration					
ziprasidone	56	27.1 (7.2)	42	-11.7 (9.3)	(-14.25,-9.20)
Placebo	37	27.9 (6.6)	37	-7.0 (8.2)	(-9.76,-4.30)
Slow Titration					
ziprasidone	87	25.5 (6.2)	79	-13.6 (7.8)	(-15.32,-11.82)
Placebo	49	26.3 (6.6)	48	-7.1 (7.5)	(-9.28,-4.93)

*Last Observation Carried Forward (LOCF)

Key Secondary Endpoint

For the key secondary endpoint-change from baseline in the CGI-S score at week 4, patients in the ziprasidone group had a statistically significant reduction in severity scores as compared to placebo treated subjects at week 4. This additional analysis further supports the clinical efficacy of ziprasidone in the treatment of childhood and adolescent bipolar disorder.

Table 13: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in CGI-S scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-1.43 (0.13)	-0.74 (0.13)
Difference from placebo (SE)	-0.69 (0.18)	
95% Confidence interval for difference from placebo	(-1.03, -0.34)	
P-value	0.0001	

*modified Intent to treat (i.e. those patients with at least on post-dose efficacy measurement)

As with the results from the primary efficacy reanalyses excluding subjects from three sites listed, ziprasidone patients continued to demonstrate less severe symptoms when compared to placebo subjects.

Table 13a: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in CGI-S scores in the modified Intent to Treat population Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=118	PLACEBO N=76
Least squares mean (SE)	-1.44 (0.15)	-0.75 (0.14)
Difference from placebo (SE)	-0.69 (0.19)	
95% Confidence interval for difference from placebo	(-1.05, -0.33)	
P-value	0.0002	

Additional Secondary Endpoints
In addition, scores on the CGI-I instrument also indicates that patients taking ziprasidone had improvement in their clinical functioning from baseline to week 4 when compared to patients taking placebo.

Table 14: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in CGI-I scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=132*	PLACEBO N=85*
Least squares mean (SE)	2.30 (0.13)	3.06 (0.16)
Difference from placebo (SE)	-0.76 (0.21)	
95% Confidence interval for difference from placebo	(-1.18, -0.34)	
P-value	0.0004	

*modified Intent to treat (i.e. those patients with at least on post-dose efficacy measurement)

Patients who were taking ziprasidone also had improved scores at week 4 on the Childhood-Global assessment of functioning [58.2 $\pm$ 12.4 vs. 51.5 $\pm$ 15.2 ziprasidone to placebo respectively). The proportion of patients whose CGAS scores indicated a return to normal functions (i.e. score $\geq$ 70) was higher in the ziprasidone group [21.6% (27/125)] as compared to placebo patients [12% (10/83)] by week 4 using an LOCF approach. The proportions of normal functioning subject reported to be in school were even higher fro ziprasidone treated patients [27% (14/52)] vs. placebo [3% (1/36)] at week 4.

Also mean change from baseline scores at week 4 between ziprasidone and placebo treated subjects on the Child Health Questionnaire form appeared to be similar across the different domains and subscales, though no formal statistical testing was performed.

6.1.4.1 Subgroup Efficacy Analysis of Primary Endpoint

At the request of this reviewer in January 2009, the sponsor conducted additional efficacy analyses for patients gender, race, age and weight for the primary endpoint YMRS. It should be

noted that the sponsor did not power the study to demonstrate statistical significant for subgroup efficacy analyses.

By Weight

The sponsor conducted a primary statistical analysis of the primary and secondary endpoints by subject weight. Using the ITT population, a treatment effect was demonstrated for patients weighing ≥45kg in ziprasidone treated subjects when compared to placebo. Although a trend towards improvement on the YMRS scores was noted for ziprasidone treated subjects vs. placebo who weighed less than 45kg, statistical significance was not achieved in this very small subgroup analysis.

TABLE 15: Change from baseline in YMRS at Week 4 repeated measures by weight

METRIC	**≥45KG**		**<45KG**	
	ziprasidone N=102	**Placebo N=71**	**ziprasidone N=31**	**Placebo N=14**
Least Squares Mean (SE)	-14.15 (0.90)	-8.21 (1.11)	-12.83 (1.86)	-10.97 (2.92)
Difference from placebo	-5.93		-1.86	
p-value	<0.0001		0.5643	

By Gender

Using a repeated measures ANCOVA analysis, both male and female patients demonstrated efficacy on the primary endpoint at week 4, though the treatment effect was greater for males than for females.

TABLE 16: Change from baseline in YMRS at Week 4 repeated measures by gender

METRIC	**MALE**		**FEMALE**	
	ziprasidone N=74	**Placebo N=44**	**ziprasidone N=59**	**Placebo N=41**
Least Squares Mean (SE)	-13.41 (1.12)	-6.50	-14.44 (1.15)	-10.70 (1.45)
Difference from placebo	-6.91		-3.74	
p-value	<0.0001		0.0445	

Age Group

Patients 14 years of age and older demonstrated efficacy with ziprasidone for bipolar symptoms whereas patients who were younger failed to demonstrate efficacy despite numerical

improvement in symptoms. Although both age groups receiving placebo achieved nearly identical response rates, a smaller treatment effect was seen.

TABLE 17: Change from baseline in YMRS at Week 4 repeated measures by age group

METRIC	AGE 10 TO <14 YEARS		AGE 14 YEAR TO <=18 YEARS	
	ziprasidone N=66	Placebo N=35	ziprasidone N=67	Placebo N=50
Least Squares Mean (SE)	-12.44 (1.12)	-8.57 (1.71)	-15.36 (1.15)	-8.33 (1.31)
Difference from placebo	-3.88		-7.03	
p-value	0.0510		<0.0001	

Race

White patients demonstrated efficacy as compared to other races. However generalization of this finding is not possible from this study as there were too few black and "other" races leading to a lack of statistical power to detect any treatment effects based on race alone.

TABLE 18: Change from baseline in YMRS at Week 4 repeated measures by Race

METRIC	WHITE		BLACK		OTHER	
	ziprasidone N=112	Placebo N=69	ziprasidone N=15	Placebo N=14	ziprasidone N=5	Placebo N=2
Least Squares Mean (SE)	-13.98 (0.95)	-7.68 (1.21)	-12.44 (2.30)	-11.38 (2.51)	-11.96 (2.62)	-17.54 (4.01)
Difference from placebo	-6.29 (1.37)		-1.06 (3.26)		5.59 (4.80)	
p-value	<0.0001		0.7461		0.2640	

6.1.4.2 Subgroup Efficacy Analysis of Secondary Endpoint

At the request of this reviewer in January 2009, the sponsor conducted additional efficacy analyses for patient's weight for the key secondary endpoint CGI-S. As with the primary efficacy subgroup analysis, only patients who weighed ≥45kg demonstrated efficacy on the key secondary endpoint.

Table 19: Mean change from baseline in CGI-S scores by subject weight

METRIC	≥45KG		<45KG	
	ziprasidone N=102	**Placebo N=71**	**ziprasidone N=31**	**Placebo N=14**
Least Squares Mean (SE)	-1.48 (0.12)	-0.70 (0.15)	-1.32 (0.20)	-1.03 (0.32)
Difference from placebo	-0.78		-0.28	
p-value	<0.0001		0.4122	

6.1.4.3 Per Protocol Analysis

A separate per-protocol analysis was performed by the sponsor that excluded the following subject data for the analysis:

1. Subjects affected by dosing errors
2. All subjects at site 1089 (Tim Summers) due to widespread protocol and GCP violations
3. Patients taking prohibited concomitant medications
4. Patients with a week 4 visit more than 5 days out-of-window
5. Patients that failed to reach target dose (based on weight) by day 14
6. Patients that missed more than 20% of doses
7. Patient dosed below the minimum for 3 or more days after reaching target dose
8. Patients with two or more positive drug screens

The results from this analysis again demonstrated that patients randomized to ziprasidone were statistically more likely to have improved YMRS scores as compared to placebo patients.

Table 20: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the per-protocol population

STATISTIC	ZIPRASIDONE N=95	PLACEBO N=65
Least squares mean (SE)	-14.46 (1.01)	-8.16 (1.35)
Difference from placebo (SE)	-6.30 (1.70)	
95% Confidence interval for difference from placebo	(-9.77, -2.82)	
P-value	0.0004	

6.1.5 Clinical Microbiology

Clinical microbiology data is not applicable to this clinical study.

6.1.6 Efficacy Conclusions

The results from study A1281132 clearly demonstrates that patients with ziprasidone had significant improvements in acute bipolar symptoms and acute symptom severity when compared to placebo treated subjects. Taken together with the results from the adult bipolar trials, ziprasidone is effective for the acute treatment of pediatric bipolar symptoms.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This review is primarily focused on the safety data and analysis that took place during the pediatric bipolar studies. For purposes of analysis, two separate reviews will be performed on the safety data: one from the double-blind study and the other focused on the combined safety data from the two open-label studies. Pertinent safety data that has been submitted as part of this NDA for pediatric patients enrolled in schizophrenia trials were also reviewed and discussed within this review.

7.1.1 Deaths

No deaths occurred during any of the pediatric bipolar trials. However one reported death (completed suicide) did occur in a patient with schizophrenia enrolled in the long-term extension part of the pediatric schizophrenia double-blind, flexible dose study AS1281134 at the time of her death.

Subject 2007000210-a 17 year old female in Singapore with an approximate 2-year history of disorganized type schizophrenia (paranoid delusions, auditory hallucinations, psychosis with depressive symptoms), biochemical hyperthyroidism (not clinically significant by endocrinologist) and a past history of thyrotoxicosis 2 years prior, was enrolled into the flexible dose study A1281134 for schizophrenia. She then entered into the extension study A1281135 after reaching the maximum dose ziprasidone in study A1281134 (160mg).

The patient continued to have psychotic symptomatology during her inpatient stay, however the patient was granted home leave with her mother by the inpatient clinicians as the patient did not verbalize any suicidal ideations or display self-harm behavior to hospital staff. Her mother was planning to return her daughter to the hospital two days earlier due to worsening psychotic symptomatology with agitation but decided to let the patient rest at home after a successful visit to her grandmother's house. Upon arriving at home, the patient was left at home alone by the mother to rest as the mother determined that her son (the patient's brother) should see a doctor for abdominal pain. After the mother and brother completed the doctor's visit and returned home, both the mother and brother failed to locate the patient until the brother discovered that the patient had jumped out a window in the apartment to her death. No suicide note was written.

Based on the information presented in this case study, it is unlikely that ziprasidone use was causally related to the suicide of this patient, though the possibility of such an association (though remote) is still present. Suicidal behavior and completed suicides has been consistently associated with psychotic illnesses, particularly in an agitated psychotic state. The case report suggests that this patient continued to suffer from psychotic processes with increasing agitation while on home leave and fell to her death while home alone. It is this reviewer's opinion that the worsened psychotic state of this patient is more likely causal to this patient's death than is the use of ziprasidone.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were defined by the sponsor as those events that led to:

- Death
- were life threatening (immediate risk of death)
- led to a congenital anomaly/birth defect
- prolonged a pre-existing hospital stay
- led to a persistent or significant disability

Double-Blind Study A1281132

There were a total of 13 reported SAEs- six (6) in the ziprasidone group; seven (7) in the placebo group, that occurred during study A1281132 as listed below.

TABLE 21: Listing of Serious Adverse Events for study A1281132

SUBJECT NUMBER	WEIGHT GROUP	MEDDRA PREFERRED TERM	TOTAL DAILY DOSE	ACTION TAKEN	OUTCOME
ziprasidone N=6					
10261001	<45kg	Overdose Dystonia	100mg 100mg	Discontinued	Recovered
10281002	≥45kg	Viral Infection	20mg	Discontinued	Unknown
10401008	≥45kg	Suicidal Ideation	100mg	None	Recovered
10401022	≥45kg	LFTs abnormal	40mg	Discontinued	Recovered
10831001	≥45kg	Mania	80mg	Discontinued	Recovered
11241003	≥45kg	Aggression, physical aggression, verbal hyper sexuality	160mg	None	recovered
Placebo N=7					
10211004	<45kg	Bipolar I	0	None	Recovered
10331005	<45kg	Bipolar	-	Discontinued	Unknown

		Disorder			
10401015	≥45kg	Suicidal ideation	0	Discontinued	Recovered
10401023	<45kg	Suicidal ideation	0	Discontinued	Recovered
10891009	≥45kg	Suicidal ideation	0	Discontinued	Recovered
11241002	≥45kg	Aggression, hallucination, paranoia	0	Discontinued	Recovered
11241004	≥45kg	Aggression, verbal aggression, violence	0	None	recovered

Subject 10261001 was an 11 year old patient who incorrectly took her medication on the drug dispensing card. Instead of taking 20mg twice daily for the first two days of the trial, the subject took 80mg in the first evening, followed by 20mg in the morning and 80mg the second evening. The subjects went to the emergency room with an acute dystonic reaction, treated with anticholinergic medication and recovered without clinical sequealae.

Subject 10401022 was a 17 year old female who complained of abdominal and back pain 6 days after initiation of ziprasidone. Four days later laboratory tests indicated elevated liver enzymes. The investigator attributed the increase to mononucleosis. This patient was consequently discontinued from the study and recovered without sequelae.

Subject 10401008 was a 15 year old male who was reported to have had an altercation with his family 7 days after randomization. After the patient threatened to hurt himself and his stepfather once police were called, the subject was taken to the hospital, subsequently admitted and discharged one week later without clinical squealae.

Open Label Studies

From a total population of 201 patients, 35 patients reported 45 serious adverse events as delineated below. The vast majority of the SAEs that occurred in the open label trials were psychiatric SAEs, with bipolar disorder and suicidal ideation being the main two psychiatric SAEs of note. One additional SAE of "suicidal ideation" was reported in a patient with schizophrenia or schizoaffective disorder.

TABLE 22: SAEs from the Combined open-label studies

PREFFERED TERM	NUMBER OF EVENTS BIPOLAR PATIENTS ONLY N=201	NUMBER OF EVENTS BIPOLAR, SCHIZPHRENIA AND SCHIZOAFFECTIVE PATIENTS N=218
GI Disorders		
Constipation	1	1
General Disorders		
Drug Ineffective	2	2
Injury, Poisoning and procedural complications		
Overdose	1	1
Investigations		
ECG QT Prolonged	1	1
Nervous System Disorders		
Sedation	1	1
Psychiatric Disorders		
Aggression	3	3
Agitation	1	1
Bipolar/Bipolar I Disorder	13	13
Conversion Disorder	1	1
Delusion	1	1
Depressive Symptom	1	1
Hallucinations (auditory, visual, mixed)	3	3
Homicidal Ideation	2	2
Intentional Self injury-self injurious behavior	2	2
Mania	1	1
Negative Thoughts	1	1
Oppositional defiant disorder	2	2
Suicidal Ideation	8	9

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Placebo Controlled Trial

Please see table 5 in Section 6.1.4

Open Label Trials

Out of the 201 bipolar patients enrolled into the open label safety study, 188 received ziprasidone =<160mg/day. The remaining 13 patients received doses of ziprasidone above the maximum daily dose of 160mg/day. A total of 107 bipolar patients (57%) out of 188 discontinued from the trial early as seen below. Adverse events (24%) and subjects no longer willing to participate (18%) accounted for the majority of the reasons for subject discontinuation.

TABLE 23: Reason for Discontinuation by dose, combined open label studies

	≤40MG N=18	**<40 TO ≤80MG N=54**	**>80 TO ≤120MG N=29**	**>120 TO ≤160MG N=87**	**>160MG N=13**	**ALL SUBJECTS ≤160MG N=188**
Adverse Event	6 (33%)	15 (28%)	4 (14%)	20 (23%)	3 (23%)	45 (24%)
Insuff. Response	1 (6%)	3 (6%)	0	0	0	4 (2%)
Protocol Violations	1 (6%)	0	0	1 (1%)	0	2 (1%)
Subject no longer willing to participate	0	8 (15%)	9 (31%)	17 (20%)	1 (8%)	34 (18%)
Other*	1 (6%)	1 (2%)	3 (10%)	5 (6%)	1 (8%)	10 (5%)
Total Discontinued	**12 (67%)**	**30 (56%)**	**18 (62%)**	**47 (54%)**	**5 (38%)**	**107 (57%)**

*Includes long term care, investigator request, site closure, psychotherapy, scheduling conflicts, lack of efficacy (2) and withdrew consent (1).

7.1.3.2 Adverse events associated with dropouts

Placebo-Controlled study
Sedation, bipolar disorder/mania, dystonia and abnormal LFTs accounted for majority of the adverse event causes for patient dropouts assigned to ziprasidone in this study. Bipolar disorder/mania and suicidal ideation were associated with the majority of patient dropouts in the placebo group. Overall 13% (19/149) of ziprasidone patients compared to 15% (13/88) of placebo patients prematurely discontinued the study due to adverse events as seen below in table 24. Also the sponsor reported that the percentage of patients who discontinued due to an adverse event during fast vs. slow titration was 7.1% vs. 15.1% in the ziprasidone group and 5.4% vs. 17.6% in the placebo group.

Discontinuations due to adverse events were grouped by patient weight at the request of this reviewer in January 2009. The result of the subgroup analysis revealed a similar proportion of

patients stopping treatment in that 9% of patients weighing <45kg discontinued the study due to an all cause adverse event compared to 13% of patients weighing ≥45kg.

TABLE 24: Adverse Event DISCONTINUATION RATES FROM PLACEBO CONTROLLED TRIAL-Preferred Term

REASON FOR DISCONTINUATION	PLACEBO N=88	ZIPRASIDONE N=149
Sedation	---	4
Bipolar disorder/mania	5	2
Suicidal Ideation	4	---
Dystonia	1	2
QT Prolongation	---	1
LFT's increased/abnormal	---	2
Pregnancy	---	1
Extrapyramidal symptoms	---	1
Restlessness	---	1
Viral Infection	---	1
Syncope	---	1
Dysphagia	---	1
Nausea/Vomiting	---	1
Muscle Spasm	---	1
Self-Injurious behavior	1	---
Loss of Consciousness	1	---
Aggression	1	---
Total	**13**	**19**

Patient 11031004-a 15 year old female with a history of ADHD and allergic rhinitis assigned to placebo, experienced a loss of consciousness for 15 minutes with symptom resolution on the same day (day 7 of treatment with placebo). The causality or etiology of the event was not documented for this particular patient. No additional information regarding the event was provided within the submission. As a result of the event, the patient was discharged from the study.

Patient 10161008-a 13 year old male with history of asthma, excessive sweating, joint pain, seasonal rhinitis and frequent cough, was discontinued from the study on day 16 after experiencing an episode of moderate syncope. He was receiving 40mg/day of ziprasidone at the time of the syncopal event. It was noted that from day 3 to day 9, the patient exhibited tremor, sedation and poor balance leading to a temporary reduction in his dose. A review of his ECG reports indicate that the last ECG recording revealed a mean QTcF of 399 msec compared to his baseline mean QTcF value of 370msec (a 29 msec increase in QTcF over his baseline value). His mean baseline heart rate was 52bpm with a final mean heart rate of 61 bpm.

Open Label Studies

There were a total of 45 adverse events that led to subject discontinuation in the open label studies. However only 41 TEAEs led to discontinuation in patients given ziprasidone ≤ 160mg/day as described below. The four (4) TEAEs that led to discontinuation in those patients given doses above 160mg were reported as 'Overdose" and "Bipolar disorder" with two reports each respectively.

TABLE 25: Adverse Events associated with Dropouts, Studies A1281123 and 1133

MEDDRA TERM	N
Sedation	7
Bipolar I/Bipolar I disorder	5
Somnolence	4
Suicidal ideation	3
Fatigue, aggression, depression, mania	2 each
Chest pain, disease progression, AST increased, QT prolonged, Akatheisa, bradykinesia, headache, agitation, conversion disorder, delusion, hallucinations (mixed), homicidal ideation, negative thoughts, Oppositional defiant disorder, self injurious behavior, rash	1 each

7.1.3.3 Other significant adverse events

One patient-patient 10801001, who was randomized to ziprasidone and received a single dose of 20mg of ziprasidone became pregnant with subsequent study discontinuation. As of time of this submission, the patient has remained pregnant with no additional information noted at this time.

Open Label Studies

A review of the adverse events from the open label studies did not reveal any other significant adverse events.

7.1.4 Other Search Strategies

The sponsor assessed the suicidality risk during the double-blind, placebo controlled trial using the Columbia Classification system. All possible suicide-related adverse events (PSRAEs) were reviewed and categorized by a panel of experts, led by Dr Kelly Posner of Columbia University. In brief, the Columbia Classification system assigns a numerical value (1 through 8) to each PSRAE after review of the narrative for each PSRAE performed by the panel of experts. Though all possible suicide-related cases are classified using this scale, the Agency has previously focused suicidality analyses on cases classified 1 through 4 of the Columbia classification system, corresponding to the following definitions:

Table 26: Columbia Classification system definitions

COLUMBIA CLASSIFACTION	DEFINITION
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation

The results of PSRAEs analyses performed on the double-blind, placebo controlled trial data are listed below. There were no completed suicides in the trial, with two adjudicated suicide attempts (one each ziprasidone and placebo) that occurred in the trial. There were no cases of preparatory acts noted, however there were four (4) cases of suicidal ideation in the ziprasidone group and three (3) in the placebo group. In this reviewer's opinion, there was not an increased risk of suicidality observed in the placebo controlled trial between patients who took ziprasidone compared to placebo. However the small sample size of this trial limits the generalizability of this finding to the pediatric bipolar population. Thus more large scale double-blind, placebo controlled studies of ziprasidone in pediatric bipolar patients is required in order to appropriately examine the risk of suicidality with ziprasidone use in this population.

Subject Number	MedDRA Preferred Term	Total Daily Dose at Onset	Start Day/ Stop Day	Severity	Outcome	Columbia Classification
Ziprasidone						
10131007	Skin laceration	20 mg	1/11	Mild	Resolved	8
10171013	Accident	60 mg	11/17	Mild	Still present	8
	Joint sprain	60 mg	11/17	Mild	Still present	8
10401008	Self-injurious ideation[a]	100 mg	8/17	Severe	Resolved	4
	Suicidal ideation[a]	100 mg	8/17	Severe	Resolved	4
10401017	Skin laceration	60 mg	29/29	Mild	Resolved	2
11141004	Self mutilation	160 mg	21/21	Moderate	Resolved	7
	Self mutilation	80 mg	28/28	Moderate	Resolved	7
11141005	Suicidal ideation	40 mg	22/30	Mild	Resolved	4
11141008	Self-injurious ideation	160 mg	17/28	Mild	Resolved	4
11171006	Muscle strain	120 mg	16/[>29]	Moderate	Still present	8
Placebo						
10161013	Excoriation	0 mg	3/11	Moderate	Resolved	8
10401015	Suicidal ideation[a]	0 mg	8/13	Severe	Resolved	4
10401023	Suicidal ideation[a]	0 mg	14/[>14]	Severe	Still present	4
10861004	Self-injurious behavior	0 mg	13/[>15]	Mild	Still present	2
10891009	Suicidal ideation[a]	0 mg	15/[>16]	Severe	Unknown	4

MedDRA = Medical Dictionary for Regulatory Activities (Version 10.1)
[ ] imputed values from incomplete dates and times.
[a]SAE

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events are any untoward medical occurrences (or signs and/or symptoms of such) in subjects administered a pharmaceutical product with or without a causal relationship to the treatment as determined by the investigators through a review of clinical and laboratory assessments. Symptoms were collected during on-site visits and telephone contacts from both spontaneous patient reports and responses to queries. Direct observations of patients during on-site visits by site personnel were also used to collect adverse events.

Serious adverse events were collected from the time the subject signed the assent form until 28 days following discontinuation of the study drug administration had elapsed. For all other adverse events, adverse event reporting began at the time of study drug administration until 28 days following discontinuation of the study drug.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Standard adverse event dictionaries were used to categorize both documented and verbatim reports of all adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. The investigators' terminology (i.e. the 'verbatim' report) was preserved and made available.

A review of the coding audit conducted revealed no discrepancies in categorization between database and adverse event reports.

7.1.5.3 Incidence of common adverse events

Table 27 in section 7.1.5.4 below enumerates the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with ziprasidone in the placebo controlled study. Upon visual inspection of the data, a greater proportion of ziprasidone patients tended to complain of more gastrointestinal symptoms, blurry vision, sedation/somnolence and extrapyramidal symptoms, insomnia, restlessness, musculoskeletal stiffness and hot flushes than those patients randomized to placebo.

7.1.5.4 Common adverse event tables

Table 27: Adverse events occurring in 2% or more in ziprasidone patients

SYSTEM ORGAN CLASS/PREFERRED TERM	PLACEBO N=88	ZIPRASIDONE N=149
Gastrointestinal disorders		
Abdominal Pain	4 (5%)	14 (9%)
Dysphagia	0	3 (2%)
Salivary Hypersecretion	0	3 (2%)
Nausea	6 (7%)	20 (13%)
Stomach Discomfort	2 (2%)	6 (4%)
Vomiting	1 (1%)	11 (7%)
Infections		
Upper Respiratory Infection	0	7 (5%)
Influenza	1 (1%)	3 (2%)
Sinusitis	0	4 (3%)
Eye Disorders		
Vision Blurred	1 (1%)	9 (6%)
Metabolism		
Decreased Appetite	2 (2%)	6 (4%)
Increased Appetite	3 (3%)	3 (2%)
Nervous System Disorders		
Akathesia	1 (1%)	7 (5%)
Dizziness	2 (2%)	16 (11%)
Drooling	0	4 (3%)
Dyskinesia	1 (1%)	3 (2%)
Dystonia	1 (1%)	6 (4%)
Extrapyramidal Disorder	1 (1%)	7 (5%)
Abnormal Glabellar Reflex	0	3 (2%)
Headache	19 (22%)	31 (21%)
Hypersomnia	0	3 (2%)
Sedation	4 (5%)	49 (33%)
Somnolence	7 (8%)	37 (25%)
Tremor	0	8 (5%)
Psychiatric Disorders		
Depression	0	3 (2%)
Insomnia	3 (3%)	13 (9%)
Restlessness	1 (1%)	8 (5%)
Reproductive System		
Dysmenorrhea	1 (1%)	3 (2%)
General Disorders		
Fatigue	6 (7%)	20 (13%)
Pain	0	3(2%)

Injury		
Medication/Drug Dispensing Error	1 (1%)	4 (3%)
Overdose	5 (6%)	7 (5%)
Musculoskeletal		
Joint Stiffness	1 (1%)	3 (2%)
Musculoskeletal stiffness	0	8 (5%)
Myalgia	4 (5%)	3 (2%)
Respiratory System		
Nasal Congestion/discomfort	1 (1)	3 (2%)
Pharyngolaryngeal pain	4 (5%)	5 (3%)
Vascular		
Hot Flush	0	4 (3%)

Open label Safety Studies
The following table represents those adverse events that occurred in at least 2% of patients during the 6 month open label safety trial.

Table 28: Adverse events occurring in 2% or more in Open Label Patients taking ziprasidone ≤160mg/day

SYSTEM ORGAN CLASS/PREFERRED TERM	BIPOLAR PATIENTS ≤160MG/DAY N=188	BIPOLAR, SCHIZOPHRENIA AND SCHIZOAFFECTIVE PATIENTS N=205
Gastrointestinal disorders		
Abdominal Pain	14 (7%)	15 (7%)
Toothache	6 (3%)	7 (3%)
Constipation	6 (3%)	6 (3%)
Nausea	17 (9%)	17 (9%)
Stomach Discomfort	10 (5%)	10 (5%)
Vomiting	12 (6%)	12 (6%)
Infections		
Upper Respiratory Infection	8 (4%)	9 (4%)
Streptococcal Pharyngitis	5 (3%)	5 (3%)
Nasopharyngitis	4 (2%)	4 (2%)
Viral Gastroenteritis	4 (2%)	4 (2%)
Eye Disorders		
Vision Blurred	7 (4%)	8 (4%)
Metabolism		
Decreased Appetite	5 (3%)	5 (2%)
Increased Appetite	5 (3%)	5 (2%)

Nervous System Disorders		
Akathesia	5 (3%)	6 (3%)
Dizziness	14 (7%)	15 (7%)
Drooling	4 (2%)	4 (2%)
Extrapyramidal Disorder	8 (4%)	8 (4%)
Headache	34 (18%)	34 (17%)
Sedation	54 (29%)	56 (27%)
Somnolence	40 (21%)	46 (22%)
Tremor	8 (4%)	8 (4%)
Dystonia	2 (1%)	5 (2%)
Psychiatric Disorders		
Depression	7 (4%)	8 (4%)
Anxiety	6 (3%)	6 (3%)
Bipolar/Bipolar I	9 (5%)	9 (5%)
Insomnia	22 (12%)	24 (12%)
Aggression	4 (2%)	4 (2%)
Suicidal Ideation	6 (3%)	8 (4%)
General Disorders		
Fatigue	16 (9%)	18 (9%)
Chest Pain	6 (3%)	7 (4%)
Irritability	7 (4%)	7 (3%)
Musculoskeletal		
Arthralgia	5 (3%)	5 (2%)
Muscle spasms	4 (2%)	4 (2%)
Pain in Extremity	4 (2%)	5 (2%)
Urinary System		
Enuresis	4 (2%)	4 (2%)
Respiratory Disorder		
Pharyngolaryngeal pain	7 (4%)	7 (4%)
Nasal Congestion	12 (6%)	12 (6%)
Skin and Subcutaneous Disorder		
Contact Dermatitis	4 (2%)	4 (2%)
Rash	7 (4%)	7 (4%)
Investigations		
Weight Increase	10 (5%)	11 (5%)

7.1.5.5 Identifying common and drug-related adverse events

Those events that were common (≥5% frequency) and drug related (frequency rate at least twice the rate of placebo) are summarized below in Table 29.

Table 29: Common, Drug-Related Adverse Experiences

ADVERSE EVENT-PREFERRED TERM	PLACEBO (N=88)	ZIPRASIDONE (N=149)
Sedation	4 (5%)	49 (33%)
Somnolence	7 (8%)	37 (25%)
Dizziness	2 (2%)	16 (11%)
Insomnia	3 (3%)	13 (9%)
Vomiting	1 (1%)	11 (7%)
Vision Blurred	1 (1%)	9 (6%)
Musculoskeletal stiffness	0	8 (5%)
Tremor	0	8 (5%)
Restlessness	1 (1%)	8 (5%)
Akathesia	1 (1%)	7 (5%)
Extrapyramidal Disorder	1 (1%)	7 (5%)
Upper Respiratory Infection	0	7 (5%)

This reviewer had also requested an analysis of treatment emergent adverse events categorized by weight. A review of those adverse events that are common and drug related are presented below:

Table 30: Treatment Adverse Events by Weight-placebo controlled study

ADVERSE EVENT-PREFERRED TERM	<45KG		≥45KG	
	Placebo N=15	ziprasidone N=34	Placebo N=73	ziprasidone N=115
Sedation	0	30%	6%	34%
Somnolence	0	21%	10%	26%
Dizziness	0	18%	3%	9%
Insomnia	0	12%	4%	8%
Vomiting	0	12%	1%	6%
Vision Blurred			1%	7%
Dystonia	0	12%		
Musculoskeletal Stiffness			0	6%
Tremor	0	12%		
Restlessness			1%	7%
Akathesia			1%	6%

Extrapyramidal Disorder	0	9%		
Upper Respiratory Infection	0	6%		
Abdominal Pain/stomach Discomfort	7%	21%		
Nausea	0	15%		
Fatigue	0	9%	8%	15%
Headache	7%	27%		

Reviewers Assessment of Common, Drug Related Adverse Events
Sedation, tremor, akathesia, and extrapyramidal symptoms were more common in ziprasidone treated patients. In particular, patients who weighed less than 45 kg were much more likely to report tremor, dystonia and extrapyramidal symptoms than heavier patients. However when compared to the common, treatment emergent adverse events seen in the adult bipolar trials, the side effect profile is similar (see table 29a below).

It is the opinion of this reviewer that the common, drug related adverse events table 29 be included into ziprasidone labeling. No additional labeling recommendations regarding adverse event warnings or precautions are indicated at this time based on this reviewers' analysis of the placebo controlled safety data contained in this NDA.

Table 29a: Common, Drug-Related Adverse Experiences between

Pediatric and Adult 3 week Bipolar Studies

	PEDIATRIC		**ADULT**	
Adverse event-preferred term	**Placebo (N=88)**	**ziprasidone (N=149)**	**Placebo (N=136)**	**ziprasidone (N=279)**
Sedation	5%	33%		
Somnolence	8%	25%	12%	31%
Dizziness	2%	11%	7%	16%
Insomnia	3%	9%		
Vomiting	1%	7%	2%	5%
Vision Blurred	1%	6%	3%	6%
Musculoskeletal stiffness	0	5%		
Tremor	0	5%		
Restlessness	1%	5%		
Akathesia	1%	5%	5%	10%
Extrapyramidal Disorder	1%	5%	12%	31%*

Upper Respiratory Infection	0	5%	3%	8%
Asthenia			2%	6%

* includes the preferred terms EPS, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching.

7.1.5.6 Additional analyses and explorations

The sponsor also explored the relationship of adverse events between fast and slow titrations in the placebo controlled trials. In general, placebo-corrected patients who were titrated fast reported more abdominal pain, nausea, vomiting, dizziness, dystonia, extrapyramidal symptoms, tremor and insomnia than slowly-titrated patients. Conversely, placebo corrected slow titrated patients exhibited more symptoms of blurry vision, appetite changes, restlessness and fatigue than patients titrated quickly in the placebo controlled study.

Table 31: Adverse events occurring in 2% or more in ziprasidone patients

SYSTEM ORGAN CLASS/PREFERRED TERM	**FAST**		**SLOW**	
	ziprasidone N=56	**Placebo N=37**	**ziprasidone N=93**	**Placebo N=51**
Gastrointestinal disorders				
Abdominal Pain	8 (14%)	1 (3%)	6 (6%)	2 (4%)
Dysphagia			2 (2%)	0
Salivary Hypersecretion			2(2%)	0
Nausea	7 (13%)	0	13 (14%)	6 (12%)
Stomach Discomfort	2 (4%)	1 (3%)	4 (4%)	1 (2%)
Vomiting	5 (9%)	0	6 (7%)	1 (2%)
Constipation			2 (2%)	0
Cardiac				
Tachycardia	2 (4%)	0		
Respiratory				
Epistaxis	2 (4%)	1 (3%)		
Pharyngolaryngeal pain	2 (4%)	1 (3%)	3 (3%)	3 (6%)
Infections				
Upper Respiratory Infection	3 (5%)	0	4 (4%)	0
Influenza	2 (4%)	0		
Sinusitis			3 (3%)	0
Gastroenteritis-viral			2 (2%)	1 (2%)
Eye Disorders				
Vision Blurred	2 (4%)	1 (3%)	7 (8%)	0
Digestive				
Decreased Appetite			5 (5%)	1 (2%)
Increased Appetite			2 (2%)	2 (4%)

Nervous System				
Akathesia			7 (8%)	0
Dizziness	7 (13%)	0	9 (10%)	2 (4%)
Drooling	2 (4%)	0	2 (2%)	0
Dyskinesia			2 (2%)	1 (2%)
Dystonia	4 (7%)	1 (3%)	2 (2%)	0
Extrapyramidal Disorder	5 (9%)	0	2 (2%)	1 (2%)
Abnormal Glabellar Reflex			2 (2%)	0
Headache	18 (32%)	5 (13%)	13 (14%)	14 (28%)
Hypersomnia			2 (2%)	0
Sedation	18 (32%)	0	31 (33%)	4 (8%)
Somnolence	12 (21%)	3 (8%)	25 (27%)	4 (8%)
Tremor	5 (9%)	0	3 (3%)	0
Musculoskeletal				
Musculoskeletal Stiffness	3 (5%)	0	5 (5%)	0
Jaw Pain	2 (4%)	0		
Myalgia			2 (2%)	4 (8%)
Psychiatric				
Depression			2 (2%)	0
Anxiety	2 (4%)	1 (3%)		
Insomnia	6 (11%)	0	7 (8%)	3 (6%)
Restlessness			8 (9%)	1 (2%)
Reproductive				
Dysmenorrhea			3 (3%)	0
Skin				
Hyperhidrosis	2 (4%)	0		
General Disorders				
Fatigue	5 (9%)	3 (8%)	15 (16%)	3 (6%)
Pain			2 (2%)	0
Irritability			2 (2%)	0
Injury				
Medication/Drug Dispensing Error	3 (5%)	1 (3%)		
Overdose	7 (13%)	5 (14%)		
Vascular				
Hot Flush	2 (4%)	0	2 (2%)	0

At the request of this reviewer, the sponsor performed a sub-group analysis of extrapyramidal adverse events based on weight. The results demonstrate that EPS symptoms are more prevalent in smaller children than in heavier children, suggesting more sensitivity to the adverse pharmacological properties of ziprasidone in smaller children.

TABLE 32: Adverse events associated with Extrapyramidal syndrome by body weight

ADVERSE EVENT (PREFERRED TERM)	<45KG		≥45KG	
	ziprasidone N=34	Placebo N=15	ziprasidone N=115	Placebo N=73
Gait Disturbance	0	0	1%	0
Muscle Spasms	3%	0	0	4%
Muscle Twitching	3%	0	1%	0
Musculoskeletal stiffness	3%	0	6%	0
Cogwheel Rigidity	0	0	1%	0
Drooling	0	0	4%	0
Dyskinesia	3%	0	2%	1%
Dystonia	12%	0	2%	1%
Extrapyramidal disorder	9%	0	4%	1%
Tremor	12%	0	4%	0
Tic	3%	0	0	0
TOTAL	**41%**	**0**	**19%**	**10%**

7.1.6 Less Common Adverse Events

A review of all of the adverse events from the open label data revealed one report each of syncope and vasovagal syncope. There were two (2) reports of tachycardia and one case of atrial fibrillation during the open label trials, however no reports of tachyarrhythmia's or other cardiovascular arrhythmia of clinical concern noted.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory assessments of all patients occurred at screening, baseline, day 14 of treatment, at day 28 (end of treatment) or day 35 for those patients who did not enter the open label extension study. Included in the laboratory assessments were the following tests: CBC with diff and platelet count; blood chemistry-including AST, ALT, LDH, total bilirubin, albumin and total protein; urinalysis; urine drug screen.

Also the sponsor collected fasting glucose, lipids, insulin, free T4 and TSH, prolactin, testosterone, IGF-1, IGFBP-3 and HbGA1c in all patients at screening, baseline, and at end of treatment day 28 (or day 35 follow-up for patients not entering into the open-label safety study). Urine drug screens and serum pregnancy tests on female patients were also performed at screening, baseline, day 14 and day 28-end of treatment.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The focus of this analysis is the single double-blind, placebo controlled study.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The mean change from baseline analysis is provided below. Overall there were minor mean changes from baseline differences noted between the two treatment groups. Of note, lower mean change from baseline serum testosterone levels were noted in ziprasidone treated subjects. This is most likely related to the increased mean change from baseline serum prolactin levels induced from ziprasidone administration and inhibitory changes in the hypothalamic-pituitary axis.

A mean change for baseline decrease in insulin-like growth factor 1 (IGF1) was more pronounced in ziprasidone treated patients compared to placebo patients. IGF1 is a polypeptide primarily secreted by the liver that acts to stimulate growth and development of various tissues via interactions with a receptor and tyrosine kinase in vivo.[1] Although it is premature to link the use of ziprasidone to a decrease in IGF-1 serum levels, the clinical significance of a decrease in IGF1-1 is not clearly delineated. Further studies are needed to determine if ziprasidone use is associated with a consistent decrease in IGF-1 and what, if any, long term effects may result from such an association.

Table 33: Mean Change from Baseline to Week 4/Early Termination in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	ziprasidone			Placebo		
	N	Baseline	Mean Change	N	Baseline	Mean Change
HEMATOLOGY						
RBC Count ($x10^6$/mm3)	114	4.8	-0.1	74	4.9	-0.1
Hemoglobin (G/L)	114	14.2	-0.2	75	14.3	-0.2
Hematocrit (%)	114	42.2	-0.7	74	43.2	-1.0
WBC Count ($x10^3$/mm3)	114	6.8	-0.3	74	6.8	-0.4
Neutrophils (%)	114	55.2	1.1	74	55.4	0.7

1 Laron Z " Insulin-like Growth factor 1: a growth hormone" *Molecular Pathology* 2001:54:311-316

Table 33: Mean Change from Baseline to Week 4/Early Termination in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	ziprasidone			Placebo		
	N	Baseline	Mean Change	N	Baseline	Mean Change
Lymphocytes (%)	114	35.7	-0.8	74	35.1	-1.5
Monocytes (%)	114	5.8	0.1	74	5.7	0.8
Eosinophils (%)	74	2.7	-0.5	53	3.0	0.2
Basophils (%)	114	1.0	0	74	1.0	0
Platelet Count ($x10^3$/mm3)	114	295.9	-4.7	74	302.6	-16.0
CLINICAL CHEMISTRY						
Potassium (MEq/L)	121	4.2	0	75	4.3	0
Sodium (MEQ/L)	119	141.2	-0.6	76	141.0	-0.4
Chloride (mEq/l)	121	103.3	-0.2	76	102.9	0.4
Bicarbonate (mEq/l)	121	22.4	-0.1	77	22.3	0.1
BUN (mg/dL)	122	12.2	-0.1	77	11.8	0.5
Creatinine (mg/dL)	80	0.7	0	54	0.7	0
Glucose-fasting(mg/dL)	99	87.2	-1.5	67	87.1	-0.2
Calcium (mg/dl)	122	9.9	0	76	9.9	-0.1
Phosphate (mg/dl)	80	4.6	-0.1	54	4.6	-0.1
Magnesium (mg/dl)	122	2.1	0	75	2.1	0
ALT (IU/L)	122	18.7	1.1	77	19	-0.7
AST (IU/L)	122	23.9	-0.5	77	22.6	-0.6
LDH (IU/L)	80	173.1	0.8	54	174.7	-1.8
Total Bilirubin (mg/dL)	122	0.4	0	77	0.4	0
Total Protein (g/L)	122	7.5	0	77	7.6	-0.1
Albumin (g/L)	122	4.7	0	77	4.7	-0.1
HORMONES						
Insulin (uu/dl)	79	11.5	1.4	49	13.2	
Free T4 (ng/dl)	123	1.1	0.0	78	1.1	0
Testosterone (ng/dl)	90	185.4	-5.2	59	192.3	16.1
Prolactin (ng/dl)	118	8.9	3.1	75	8.0	-0.2
TSH (UIU/ml)	123	2.0	-0.2	77	2.0	-0.2
Insulin-like growth factor-1 (ng/ml)	94	248.7	-6.7	61	261.6	1.4
Insulin-like growth factor binding protein 3 (mcg/ml)	94	5.4	-0.2	61	5.4	-0.1
LIPIDS						
LDL cholesterol (mg/dl)	122	87	-2.5	77	91.1	-1.4
HDL cholesterol (mg/dl)	122	52.4	0.3	77	53.2	-1.5
Cholesterol-fasting	122	158.6	-3.6	76	164.3	-4.3

Table 33: Mean Change from Baseline to Week 4/Early Termination in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	ziprasidone			Placebo		
	N	Baseline	Mean Change	N	Baseline	Mean Change
Triglycerides-fasting	122	96.8	-8.1	77	100.6	-7.8

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Placebo Controlled Study
The following table delineates ziprasidone patients who had at least one post-treatment abnormal laboratory value despite having a normal baseline status. In general patients who received ziprasidone had elevated prolactin levels (11% vs. 1%) and insulin levels (6% vs. 0) above threshold criteria compared to placebo patients respectively.

Table 34: Incidence of abnormal post dose laboratory parameter in ziprasidone patients who had normal baseline parameters.

PARAMETER (UNITS)	CRITERIA FOR ABNL	ZIPRASIDONE % (N/TOTAL)	Placebo % (n/total)
White Count (10*3/mm3)	>17.5	1% (1/118)	0
Lymphocyte (%)	<0.8 X LLN	2% (2/123)	1% (1/76)
Total Neutrophils (1000/mm3)	<0.8 X LLN	4 % (4/107)	4 % (3/74)
	>1,2 X ULN	4 % (4/107)	0
Neutrophils (%)	<0.8 X LLN	1% (1/117)	0
Basophils (5)	>1.2 X ULN	2 % (2/127)	5% (4/81)
Eosinophils (%)	>1.2 X ULN	1 % (1/79)	9 % (5/55)
Monocytes (5)	>1.2 X ULN	3% (4/124)	10 % (8/79)
AST (IU/L)	>3.0 X ULN	1% (1/127)	0
ALT (IU?L)	>3.0 X ULN	1 % (1/115)	0
HDL	<0.8 X LLN	1 %	1 %

Cholesterol (mg/dl)		(1/111)	(1/73)
Triglycerides (mg/dl)	>1.3 X ULN	3 % (3/110)	3 % (2/63)
Sodium (mEq/l)	>1.05 X ULN	1% (1/125)	0
Potassium (mEq/l)	>1.1 X ULN	1 % (1/131)	0
Magnesium (mg/l)	> 1.1 X ULN	2% (2/122)	0
Phosphate (mg/dl)	> 1.2 X ULN	4 % (2/55)	2 % (1/41)
Bicarbonate (mEq/l)	<0.9 X LLN	13% (12/90)	15% (8/53)
TSH (UIU/ml)	<0.8 X LLN	1% (1/122)	1% (1/77)
Prolactin (ng/ml)	>1.1 X ULN	11% (12/114)	1% (1/71)
Testosterone (ng/ml)	>1.2 X ULN	5% (4/75)	2% (1/48)
Insulin (UU/ml)	> 1.2 X ULN	6% (5/88)	0
Urine Ketones (qual)	$\geq$1	16% (21/133)	24% (20/84)
Urine Blood (qual)	>1	26% (35/133)	24% (20/84)
Urine Specific Gravity	>1.030	5% (7/133)	10% (8/84)
Urine RBC (HPF)	$\geq$6	6% (8/133)	6% (5/84)
Urine WBC (HPF)	$\geq$6	5% (7/133)	5% (4/84)

Open Label Safety Data

The following table provides the proportion of patients who shifted above the pre-specified laboratory parameters who received $\leq$160 mg/day of ziprasidone from normal baselines. When compared to results from the placebo controlled study, a greater proportion of patients had exceeded threshold criteria for low bicarbonate levels (25% vs. 13%) and high testosterone levels (13% vs. 5%) respectively during the 6 months of open label treatment.

TABLE 35: Incidence of abnormal post dose laboratory parameter in ziprasidone patients who had normal baseline parameters, Open label studies

PARAMETER (UNITS)	CRITERIA FOR ABNL	ZIPRASIDONE % (N/TOTAL)
Lymphocyte (%)	>1.2 X ULN	3% (5/167)
Total Neutrophils (1000/mm3)	<0.8 X LLN	2% (3/142)
	>1,2 X ULN	4% (6/142)
Eosinophils (%)	>1.2 X ULN	3% (4/150)
Monocytes (5)	>1.2 X ULN	4% (6/149)
HDL Cholesterol (mg/dl)	<0.8 X LLN	2% (3/140)
Triglycerides (mg/dl)	>1.3 X ULN	5% (7/142)
Sodium (mEq/l)	>1.05 X ULN	3% (4/154)
Phosphate (mg/dl)	> 1.2 X ULN	2% (2/128)
Bicarbonate (mEq/l)	<0.9 X LLN	25% (21/85)
TSH (UIU/ml)	<0.8 X LLN	2% (3/124)
Prolactin (ng/ml)	>1.1 X ULN	9% (14/152)
Testosterone (ng/ml)	>1.2 X ULN	13% (17/133)
Insulin (UU/ml)	> 1.2 X ULN	6% (6/100)
Urine Ketones (qual)	$\geq$1	22% (31/143)
Urine Specific Gravity	>1.030	8% (12/152)
Urine RBC (HPF)	$\geq$6	8% (12/146)
Urine WBC (HPF)	$\geq$6	6% (8/145)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The sponsor notes that there was one case of a 'moderate' increase in testosterone and one case of 'severe' LFT abnormalities.

Subject 10401022 was a 17 year old female patient who received 40mg ziprasidone during the trial. On day 10, this patient had an AST of 202 u/l and an ALT of 242 u/l on day 11. She was discontinued from the study due to the event and her liver enzymes were not resolved at the time of termination.

Although only one patient was discontinued from the study for elevated liver enzymes, three (3) additional patients were noted by the sponsor to have some elevation of liver enzymes as follows:

- Subject 10171007-15 year old female with an ALT of 31 u/l (nl 5-20) while on 160mg/day with normal ALT by day 28.
- Subject 10171005- 16 year old male on placebo with elevated ALT at screening (35 u/l) and elevated total bilirubin levels (1.4 mg/dl).
- Subject 11221002-16 year old male taking ziprasidone 100mg/day had an AST of 89 u/l (nl 0-41) on day 16 which returned to WNL by day 23. However this patient had elevated ALT levels of 50, 147 and 56 u/l on days -5, 16 and 23 respectively that did not resolve at the time of termination.

Open Label Studies

There were no patients that were discontinued from the open label studies as a result of laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

No additional laboratory analyses were conducted by the sponsor.

7.1.7.5 Special assessments

Since ziprasidone has generally not been associated with laboratory abnormalities, special assessments of particular laboratory parameters are not indicated at this time.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

For the double blind study, ambulatory blood pressure and heart rate measurements were collected at all weekly visits. Additionally patient weight was obtained at screening, randomization and study completion with a physical examination performed at screening and at

day 28. The sponsor also obtained blood pressures at 5-7 hours (~around Tmax) post dose on day 28 only.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The focus of this analysis is the single double-blind, placebo controlled study. Pertinent vital sign abnormalities from the open label studies will be reviewed as well.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Below is the mean change from baseline in the blood pressure and pulse recordings at various times post dose in patients that were both supine and standing. It appears that ziprasidone treated patients were consistently noted to have slightly elevated parameters in blood pressure and pulse parameters 5-7 hours post dose while standing when compared to placebo treated subjects. Although a similar trend was seen in supine measurements, the magnitude of increase was smaller in ziprasidone treated subjects, with a larger increase in supine pulse rates seen in placebo patients taken 5-7 hours post dose.

In this reviewer's opinion, these slight elevations are unlikely to be clinically significant acutely. Larger studies of longer duration are recommended to confirm this trend and determine if clinically significant risks are evident.

Mean Change from Baseline on Supine Blood pressure and pulse

TABLE 36: MEAN CHANGE FROM BASELINE IN SUPINE VITAL SIGN PARAMETERS

VARIABLE	N_{ZIP}	ZIPRASIDONE	N_{PBO}	PLACEBO
Supine Systolic Blood Pressure (mmHg)				
Baseline mean (SD)	148	110.0 (11.1)	87	110.1 (10.3)
Mean Change from Week 4 - predose (SD)	95	0.2 (10.7)	50	-0.4 (10.8)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	85	1.4 (9.6)	48	0.1 (12.1)
Supine Diastolic Blood Pressure (mmHg)				
Baseline mean (SD)	148	67.6 (8.5)	87	67.4 (8.3)
Mean Change	95	-0.8 (9.3)	50	-0.5 (7.0)

from Week 4 - predose (SD)				
Mean Change from Week 4-5 to 7 hrs post dose (SD)	85	1.2 (9.0)	48	0.2 (8.3)
Supine Pulse Rate (bpm)				
Baseline mean (SD)	148	74.5 (11.8)	87	73.3 (8.7)
Mean Change from Week 4 - predose (SD)	95	-2.9 (12.1)	50	-1.4 (9.0)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	85	2.5 (12.6)	48	3.1 (10.6)

Mean Change from Baseline on Standing Blood pressure and pulse

TABLE 37: MEAN CHANGE FROM BASELINE IN STANDING VITAL SIGN PARAMETERS

VARIABLE	N_{ZIP}	ZIPRASIDONE	N_{PBO}	PLACEBO
Standing Systolic Blood Pressure (mmHg)				
Baseline mean (SD)	147	109.7 (10.8)	87	111.2 (110.8)
Mean Change from Week 4 - predose (SD)	94	0.6 (10.8)	50	-0.5 (10.5)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	84	2.4 (10.8)	48	-0.2 (11.3)
Standing Diastolic Blood Pressure (mmHg)				
Baseline mean (SD)	147	70.2 (8.8)	87	69-08 (7.7)
Mean Change from Week 4 - predose (SD)	94	1.6 (9.6)	50	0.9 (7.4)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	84	2.3 (9.9)	48	0.9 (8.1)
Standing Pulse Rate (bpm)				

Baseline mean (SD)	147	80.7 (12.1)	87	80.4 (11.8)
Mean Change from Week 4 - predose (SD)	94	-0.5 (12.5)	50	-3.1 (12.6)
Mean Change from Week 4- 5 to 7 hrs post dose (SD)	84	5.5 (15.6)	48	0.2 (12.3)

The sponsor did not examine the relationship between dosing group and vital sign changes

Mean Change from Baseline on Weight and BMI

The mean change from baseline at week 4 or early termination for weight and BMI were virtually identical regardless of the treatment a patient was randomized to.

TABLE 38: MEAN CHANGE FROM BASELINE IN Weight and BMI Z- Score PARAMETERS

VARIABLE	N_{ZIP}	ZIPRASIDONE	N_{PBO}	PLACEBO
Weight (Kg)				
Baseline mean (SD)	149	57.2 (14.4)	88	60.0 (16.0)
Mean Change from Week 4/ET (SD)	131	0.5 (2.2)	81	0.6 (2.3)
BMI Z-Scores				
Baseline mean (SD)	149	0.7 (0.9)	88	0.8 (0.9)
Mean Change from Week 4/ET (SD)	131	0	81	0

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following table delineates the proportion of patients who developed at least one post – randomization blood pressure or pulse recording that met or exceeded criteria thresholds for abnormal. Patients taking ziprasidone were more likely to experience clinically significant decreases of supine blood pressure parameters that met or exceeded threshold limits when compared to placebo treated subjects. This is likely as a result of the pharmacological alpha-1 antagonistic properties noted with ziprasidone and addressed in current approved labeling.

TABLE 39: Post-Baseline Vital sign outlier data

CRITERIA	ZIPRASIDONE N=144*	PLACEBO N=86
Standing Systolic BP		
<90 mmHg	2%	4%
≥30mmHg decrease	<1%	1%
≥30mmHg increase	3%	0
Standing Diastolic BP		
<50 mmHg	<1%	4%
≥20mmHg decrease	4%	6%
≥20mmHg increase	8%	11%
Supine Systolic BP		
<90 mmHg	6%	2%
≥30mmHg increase	3%	2%
Supine Diastolic BP		
<50 mmHg	3%	2%
≥20mmHg decrease	5%	2%
≥20mmHg increase	7%	6%
Supine Pulse Rate		
>120 bpm	<1%	0

* n=143 for Standing systolic and Standing diastolic measurements

Open Label Studies

The sponsor provided the mean change from baseline data for patients participating in the open label trial. Results from the open label studies revealed a dose-related increase in diastolic blood pressures in patients who took ziprasidone over a 26 week time period.

Table 40: Mean change from baseline parameters by dose in Open label Safety studies in patients with bipolar, schizophrenia and schizoaffective disorder

PARAMTER	≤ 40MG N=21	>40- ≤80MG N=68	>80- ≤120MG N=29	120- ≤160MG N=87	ALL SUBJECTS ≤160MG N=205
Mean Change Systolic BP (mmHg)	-6.4	0.5	-1.0	1.5	0
Mean Change Diastolic BP (mmHg)	-1.2	-0.3	0.8	1.6	0.6
Mean Change Heart Rate (BPM)	-1.5	0.6	1.7	0.2	0.4

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no reported marked outliers or dropouts as a result of vital sign abnormalities in the placebo controlled trial.

One subject, 11241005- a 10 year old male, who received ziprasidone 40mg had a week 4 weight gain of 4.99 kg compared to baseline weight which did not lead to study termination. In addition, subject 11001002 was an 11 year old male who received placebo during the study who had a weight gain of 9.8 kg from screening on day 29 of the study.

Subject 10311003 was a 14 year old male patient in the placebo group who had a 9.23 kg decrease in weight by day 29 of the study.

Open Label Studies

During the open label trials there were no patients who had a clinically significant increase or decrease in mean change from baseline systolic or diastolic blood pressure, or heart rate. In addition, there were no patients who were discontinued from the studies due to vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed by the sponsor with regards to vital sign abnormalities.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were performed in the placebo controlled study at baseline (performed in triplicate), every onsite visit and an ECG performed at the time to Tmax (5-7 hrs post dose) time point to analyze the effect of maximum ziprasidone concentrations on ECG parameters.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The placebo controlled study data results were used as the basis for the electrocardiogram analysis. Pertinent ECG abnormalities from the open label studies will be reviewed as well.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Due to the known QTc prolongation associated with ziprasidone, this review will primarily focus on the mean change from baseline on the QTcF parameters.

The table below delineates the QTc effect of ziprasidone at various time points throughout the study as compared to placebo treated subjects. Consistent with the adult data, ziprasidone is associated with a maximum, non-corrected 8-10msec increase in QTcF in pediatric subjects.

Table 41: Mean baseline and baseline change from baseline in QTcF at various time points

TIME	N_{ZIPR}	MEAN (SD)	N_{PBO}	MEAN (SD)
Mean baseline	147	396.1 (18.6)	87	399.6 (12.6)
Change from Baseline				
Week 1	131	7.1 (15.3)	83	-2.9 (14.0)
Week 2	112	10.1 (17)	69	-4.3 (16.2)
Week 3	99	6.7 (15.6)	54	-5.4 (15.8)
Week 4 predose	93	5.9 (16.9)	50	-0.9 (18)
Week 4/0.75 to 3 hrs post dose	90	5.1 (17.3)	50	-3.0 (16.8)
Week 4/5 to 7 hrs post dose	84	8.3 (15.0)	48	-2.9 (16.1)
End of Treatment/predose	27	4.7 (19.2)	4	-3.4 (16.9)
End of treatment/0.75 to 3 hrs post dose	16	10.3 (17.9)	19	-2.3 (12.2)
End of treatment/5 to 7 hrs post dose	17	10.8 (16.4)	21	-5.5 (12.5)
Combined week 4/ET pre-dose	120	5.6 (17.4)	77	-1.8 (17.6)
Combined week 4/ET/0.75 to 3 hrs post dose	106	5.9 (17.4)	69	-2.8 (15.6)
Combined week 4/ET/5 to 7 hrs post dose	101	8.7 (15.2)	69	-3.7 (15.1)

Open Label Studies

With the exception of the 120-160mg dosing group, there was a dose-dependant increase in the QTcF that was observed in the open label safety studies.

TABLE 42: Mean change from baseline ECG parameters by dose in Open label Safety studies in patients with bipolar, schizophrenia and schizoaffective disorder

PARAMTER	≤ 40MG N=21	>40- ≤80MG N=68	>80- ≤120MG N=29	120- ≤160MG N=87	ALL SUBJECTS ≤160MG N=205
Mean Baseline QTcF (msec)	391.5	394.4	401.1	396.1	395.8
Mean Change from Baseline in QTcF (msec)	0.3	4.4	6.9	3.5	3.9

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

A review of data from outliers demonstrates that treatment with ziprasidone is associated with a two-fold increase at least a 30 msec increase of QTcF over baseline as compared to placebo treated patients. Nearly 11 out of 50 patients treated with ziprasidone will experience at least s 30 msec increase in QTcF from baseline as compared to 11 out of 100 treated with placebo.

Table 43: Proportion of patients meeting QTcF outlier criteria in study A1281132

QTCF OUTLIER CRITERIA	ZIPRASIODNE N=140	PLACEBO N=85
≥ 450 msec	4%	1%
≥ 460 msec	1%	0
≥ 480 msec	0	0
≥ 500 msec	0	0
≥ 30 msec increase over baseline	22%	11%
≥ 60 msec over baseline	<1%	0

Open Label Study

No patients during the open label study had a recorded QTcF reading ≥450 msec. However 21% of bipolar-only patients who received ziprasidone ≤160mg had an increase of QTcF ≥30msec as compared to the recording from the pre-study drug ECG. Two (2) patients had a recorded increase of at least 60 msec in their QTcF. These cases will be described in section 7.1.1.3.3 below.

Table 44: QTcF outliers by dose: Open label studies

INCREASE FROM PRE-STUDY DRUG	≤ 40MG N=18	>40- ≤80MG N=54	>80- ≤120MG N=29	120- ≤160MG N=87	ALL SUBJECTS ≤160MG N=188
≥30 msec	1 (7%)	12 (22%)	4 (14%)	23 (26%)	40 (20%)
≥60 msec	0	0	1 (3%)	1 (1%)	2 (1%)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Patient 10401007, a 16 year old female who received ziprasidone 60mg/day, was discontinued from the study on day 16 of the study due to an ECG finding of a QTcF greater than 460 msec before, 45 minutes after and 5 hours after dosing. Her previous ECG on day 8 showed a QTcF of 464 msec. Her follow-up ECGs on day 23 and 38 showed that here QTcF was returning to the screening measurement. Her maximum recorded QTcF was 478 msec.

An additional subject, patient 10671010, had a QTcF of 461 msec on day 29. However all other QTcF values were below 460 msec and the investigator did not consider this to be an adverse event.

Open Label Studies

Subject 11081003, a 14 year old female who participated in extension study 1281133, had a 59 msec increase in QTcF at week 10 (QTcF 438 msec) when compared to her baseline QTcF (QTcF 369 msec).Subsequent QTcF values were less than 45 msec and this subject had no associated adverse events.

Patient 10861006, a 12 year old female, had a 66 msec increase in QTcF at day 10 when compared to her baseline QTcF (baseline: 365msec; week 1: 431 msec) while receiving 80mg/day of ziprasidone. Repeated QTcF measurements over the next 55 days indicated a persistent prolonged QT interval and this subject was discontinued from the study on day 65 due to the prolonged QT interval.

One patient, patient 11081007- a 12 year old female-initially developed an increased heart rate (52 bpm to 72 bpm) on day 38 while receiving 80mg/day ziprasidone. The automated ECG interpretation stated that the patient had atrial fibrillation however central reading of the ECG was interpreted as an intermittent junctional rhythm. The patient continued in the study, with her last ECG being recorded on Week 18 (day 135).

7.1.9.4 Additional analyses and explorations

Although the proportion of female patients with ≥ 450 msec increases in QTcF from baseline was higher than for males, there appears to be no gender difference in the proportion of patients with ≥ 30msec increases from baseline ECGs on QTcF parameters:

Table 45: QTcF outliers by Gender

QTCF PARAMTER	ZIPRASIDONE	PLACEBO
Males	*N=79*	*N=44*
≥ 450 msec	1%	1%
≥ 460 msec	1%	0
≥ 30 msec increase	23%	9%
Females	*N=61*	*N=41*
≥ 450 msec	7%	0
≥ 460 msec	2%	0
≥ 30 msec increase	21%	12%
≥ 60 msec increase	<1%	0

7.1.9.4.1 Concentration Dependant QTc Effect analyses

As part of this submission, the sponsor performed two analyses within the pediatric development program to assess for a concentration/QTcF relationship with pediatric ziprasidone administration from data collected from studies A1281123 and A1281132.

Study A1281132 Concentration Dependant QTc Effect

For study A1281132, pharmacokinetic (PK) sampling was collected at baseline 0.5-1.5 hrs post dose and a 2nd PK sample 1.5-3hrs post dose. Baseline ECGs were administered in triplicate. At week 4, trough PK samples and ECG tracings were collected prior to morning dose administration, as well as a 2nd PK sample/ECG tracing 0.75-3 hrs post dose and a 3rd PK sample/ECG tracing 5-7 hrs post dose.

The concentration/QTcF (dose dependant) relationship results from the placebo controlled pediatric bipolar study A1281132 are described in the table below. Using linear regression, a positive relationship between increasing concentrations of ziprasidone and QTcF prolongation was seen. Using the population mean with a 90% confidence interval, ziprasidone administration to pediatric patients is associated with a 0.0852 msec/(ng/ml) increase in QTcF [90% CI 0.067-0.106 msec/(ng/ml)]. Using the predicted steady state Cmax data obtained from the population PK study of patients enrolled in study A1281132, patients would be predicted to have a mean 15 msec increase in QTcF at Cmax during at steady state if taking 160mg/day.

Table 33 Descriptive Statistics of the Predicted ΔQTcF (msec) Prolongation at Predicted Steady State Cmax based on Various Geodon™ Dosing Regimens

Dose	Minimum	1st.Quartile	Median	Mean	3rd.Quartile	Maximum
30 mg BID	1.497	4.112	5.205	5.794	7.086	17.59
40 mg BID	1.996	5.482	6.94	7.725	9.448	23.45
60 mg BID	2.995	8.223	10.41	11.59	14.17	35.18
80 mg BID	3.993	10.96	13.88	15.45	18.9	46.9

Study A1281123 Concentration Dependant QTc Effect

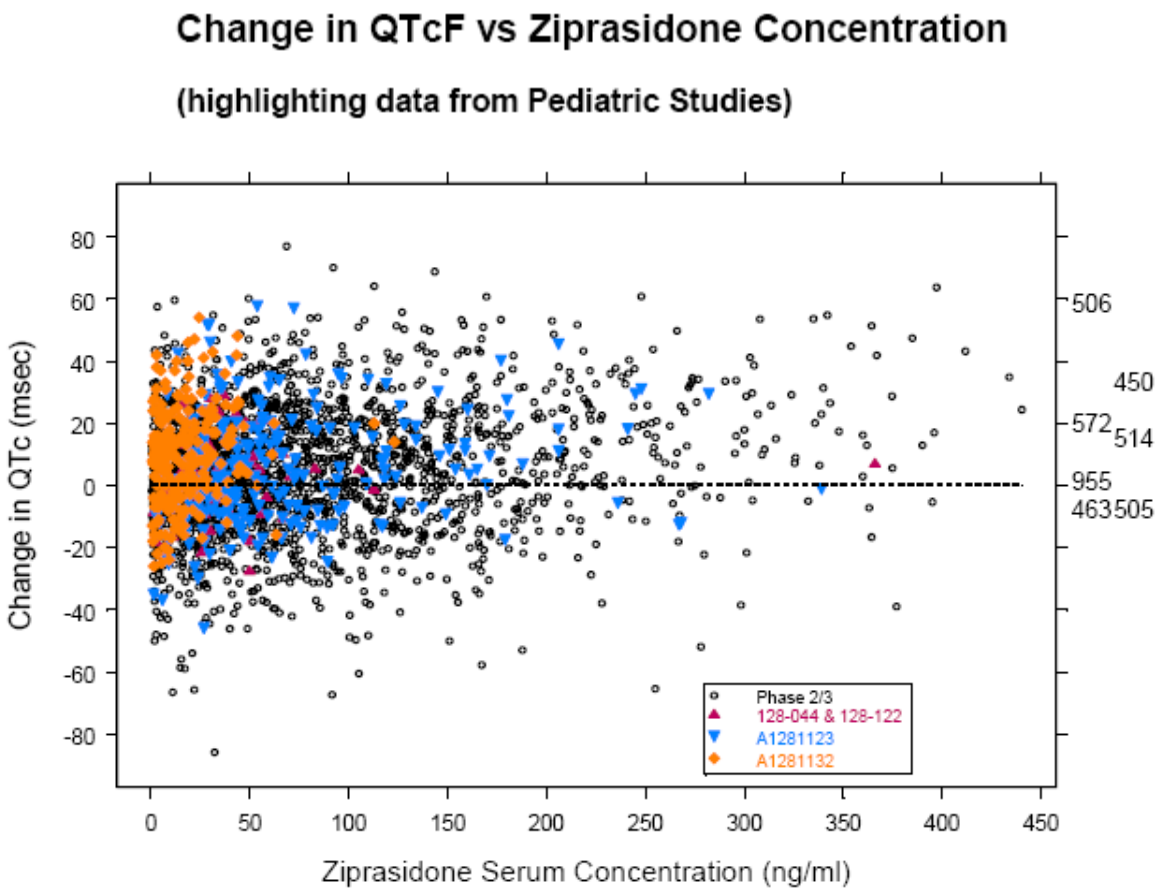
During the initial three week open label dose titration phase for this study, all patients received oral ziprasidone suspension. During the 27 week open label extension phase, patients could either take ziprasidone oral suspension or capsules. Pharmacokinetic measurements occurred at the following periods:

- Period 1 week 3-immediately prior to and 5-7 hours after the morning dose
- Period 2 week 1-random time
- Period 2 week 12- random time
- Period 2 week 27- random time

Again a positive linear relationship was seen between ziprasidone concentration and QTcF prolongation in this study. Using a 95 % confidence interval, ziprasidone administration to pediatric patients is in study A1281123 associated with a greater increase in QTcF prolongation of 0.139 msec/(ng/ml) increase in QTcF [95% CI -0.0132 to0.299 msec/(ng/ml)] as compared to the results seen in study A1281132.

Comparison of dose-dependant QTcF effects in pediatric and adult studies

The sponsor submitted a scatter plot diagram to compare ziprasidone concentration-change from baseline QTcF data pairs from QTcF/concentration data from 4 pediatric studies and 31 adult studies. The sponsor's conclusion was that "…the distribution of change from baseline QTcF values across the range of concentrations was similar between pediatric and adult subjects". The scatter plot is shown below for reference. The sponsor notes that subjects with a single change from baseline QTcF-ziprasidone concentration pair (i.e. those that did not also have a baseline QTcF/concentration data point) were included in the graph below.



At the request of this reviewer, the sponsor performed a regression analysis of the data points obtained in the pediatric studies and adult trials that were presented in the figure above. Of primary interest to this reviewer is the comparison of the slope of the regression lines between the pediatric and adult datasets as this data can be used to compare the rate of change in the QTcF- ziprasidone concentration relationship to see if differences exist between the two populations on this important variable. In the sponsor's analysis, only data from subjects with more than 1 data point were used to calculate the regression lines. In total, data (as reported by the sponsor in their correspondence to the Agency) from 21 studies (17 adult, 4 pediatric) were included in this analysis with a total of 2420 change in QTcF from baseline vs. concentration data pairs from 857 subjects (684 adult, 173 pediatric).

Of the 857 subjects, 419 (309 adult; 110 pediatric) had at least two or more concentration-QTcF data points but had no baseline concentration-QTcF data points. The remaining 438 patients did have baseline data points.

The results of the regression analysis indicate that the slope of the regression line for the pediatric dataset is 1.58 times steeper (i.e. a greater change in QTcF prolongation for a given concentration) as compared to the slope of the regression line from the adult dataset (0.0824 msec/ng/ml vs. 0.0521 msec/ng/ml). Of note, the slope of the pediatric regression line is

consistent with the data obtained from Pk-PD modeling from study A1281132 as described above.

TABLE 46: Summary of Regression of Change in QTcF vs. ziprasidone Concentration

PARAMETER (UNITS)	POPULATION MEAN (SE*)	STANDARD DEVIATION-INTER-INDIVIDUAL VARIANCE (SE*)
Intercept-Adult (msec)	0.744 (70.7)	9.04 (14.3)
Intercept-Pediatric (msec)	3.29 (28.5)	
Slope-Adult (msec/ng/ml)	**0.0521 (11.4)**	0.0601 (24.6)
Slope-Pediatric (msec/ng/ml)	**0.0824 (18.0)**	
Stand Deviation Additive Residual Error (msec)	13.0 (5.01)	

The result of the regression analysis suggests that the pediatric population is potentially more sensitive to the concentration dependant QTcF prolongation seen with ziprasidone use when compared to the adult population at any given concentration. For example, for a steady state Cmax of 150ng/ml, an adult patient could be predicted to experience an 8msec QTcF prolongation compared to baseline QTcF whereas a patient aged 0-17 years of age would experience a 12msec QTcF prolongation at the same concentration.

Although the regression analysis is limited by fewer pediatric data points and a large variance, the results of this data (given the limitations) is of particular clinical relevance since pediatric patients may be clinically exposed to higher concentrations of ziprasidone as a result of decreased clearance of ziprasidone with decreased weight. The results suggests that the pediatric population is at least as sensitive to the concentration-dependant QTcF prolongation effects of ziprasidone administration as compared to adults or potentially may be at more at risk for QTc related cardiac arrhythmias. Despite the absence of reports or adverse events of torsades de pointes seen in the pediatric clinical trials and post-marketing reports thus far, this reviewer recommends that the QTc warning language be re-worded to include children as being at risk to QTc prolongation associated with ziprasidone use.

7.1.10 Immunogenicity

Immunogenicity was not studied as part of the pediatric bipolar program.

7.1.11 Human Carcinogenicity

Although the studies performed under the pediatric bipolar development programs cannot fully address the potential carcinogenicity that may be associated with long term use, there is a low likelihood that ziprasidone use is associated with tumor growth.

Though there has been an association with some antipsychotics with D2 antagonistic properties and pituitary prolactinomas, a review of the Agency Post-marketing database using the terms

"GEODON®" and "PROLACTINOMA" revealed only one case of suspected prolactinoma suspected from only elevated prolactin levels. This patient was switched to a lower dose of ziprasidone with improvement in the prolactin levels.

7.1.12 Special Safety Studies

CNS Vital Signs test

The sponsor administered the CNS Vital Signs Computerized cognitive test battery to all patients in the double-blind placebo controlled study. The batter of tests included computerized tests to assess cognitive changes in verbal and visual memory, symbol digit coding, nonverbal reasoning, attention shifting, and reaction and recall times. There was no difference in the mean change from baseline index scores between ziprasidone and placebo treated patients (p=0.9571), however ziprasidone treated patient tended to have slower processing speeds at week 4 as compared to placebo treated patients [-3.5 (95% CI -6.01,-0.91) vs. 0.4 (95% CI -0.77,1.64)] drug to placebo respectively.

CDRS-R

Depression symptoms for both treatment groups, as measured by the CDRS-R, improved over baseline treatments, regardless of randomized treatment.

Table 47: Mean Change from baseline: CDRS-R scores, placebo controlled study

MEASURE	ZIPRASIDONE (95% CI)	PLACEBO (95% CI)
Mean Baseline	35.2 (33.45,36.86)	34.2 (31.84,36.63)
Mean Change from Baseline at Week 4	-8.0 (-10.23,-5.81)	-6.1 (-8.49,3.68)

Simpson Angus Rating Scale (SARS)
The SARS instrument is administered by clinicians to assess for Parkinsonian and extrapyramidal symptoms during the trial. Patients who were treated with ziprasidone were significantly more likely to have Parkinsonian symptoms/extrapyramidal side effects as compared to placebo controlled patients, as measured by the Simpson-Argus Rating Scale:

Table 48: Mean Change from baseline: Simpson Angus Rating Scale (SARS) scores placebo controlled study

VISIT	ZIPRASIDONE		PLACEBO		
	N	Mean Change from baseline (95% CI)	N	Mean Change from baseline (95% CI)	
Baseline	147	0.1	88	0.2	

		(0.06-0.22)		(0.08-0.33)	
Week 4-LOCF	133	0.5 (0.21-0.70)	85	-0.1 (-0.23-0.11)	

Barnes Akathesia Rating Scale (BARS)

ziprasidone treated patients were noted by clinicians to have a slight increase in Akathesia symptoms at week 1 as compared to placebo controlled patients [0.2 (95%CI 0.03,0.31) vs. -0.1 (95%CI -0.26,0.02)]. However no significant Akathesia symptoms were noted for the remaining visits in the ziprasidone treated group as compared to placebo.

Clinical Trial Suicidality Assessment

The sponsor assessed the suicidality risks associated with ziprasidone treatment through independent evaluation of cases that were identified in the double-blind placebo controlled study. Investigators, led by Dr Poser, reviewed the identified cases and classified each case according to the Columbia Classification scores. Please refer to section 7.1.4 for details.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No new information was presented as part of this submission that was relevant to the abuse potential of ziprasidone. Since ziprasidone is neither a controlled nor scheduled substance per the Drug Enforcement Agency (DEA), the abuse potential of ziprasidone is likely to be very low.

A review of the adverse events and cases does not suggest that withdrawal symptoms have been reported with the use of ziprasidone.

7.1.14 Human Reproduction and Pregnancy Data

The reader is referred to the current approved labeling and the original pharmacology/toxicology reviews completed with the original NDA submission for further details.

7.1.15 Assessment of Effect on Growth

During the placebo controlled trial, no significant differences were noted on height or weight parameters as measured by standard conventional units or through a derived z-score. A mean height increase of 0.9 cm was seen in the 6 month extension studies, in addition to a 1.4kg weight increase from baseline in all patients. The corresponding derived BMI only increased 0.3 units over the six month of observation with open label ziprasidone treatment. Increasingly

7.1.16 Overdose Experience

During the study, a total of 10 patients (6 in the ziprasidone group and 4 in the placebo group) received total daily doses of study medication that exceeded the maximum allowable dose in the protocol as a result of dosing errors. All ten of these cases occurred at three sites:

- site 1013 (Dr. Sohail S. Punjwani),
- site 1026 (Dr. Adly Thebaud) and
- site 1100 (Dr Steven Lopez)

These ten cases were identified in the study as an "overdose" adverse reaction. A table of these ten (10) cases is below.

Subject ID	Age (yrs) and Sex	Weight (kg)	Start Day/ Stop Day	Range of Overdosing (mg/day)	AE of Overdose	Other AEs	SAE	Disposition
Ziprasidone								
10131001	13 M	45.5	8/28	80-400	✓	Dizziness, headache, medication error, sedation	–	Completed
10131002	14 F	60.9	NA	80-120	–	EPS	–	Lost to follow-up
10131004	16 M	67.3	8/11	80-320	✓	Vomiting, sedation, drug dispensing error	–	DC due to AE (sedation)
10131006	13 M	35.5	9/30	80-400	✓	EPS, sedation, medication error	–	Completed
10131007	10 M	39.1	16/29	60-120	✓	Laceration, leg; medication error	–	Completed
10261001	11 F	34.1	2/2	80-100	✓	Dystonia	✓	DC due to SAEs (dystonia and overdose)
Placebo								
10131003	15 F	64.1	7/[>27]	0	✓	None	–	Completed
10131005	15 M	55.5	8/23	0	✓	Medication error	–	DC due to noncompliance
11001001	15 M	74.1	10/22	0	✓	Somnolence, fatigue, agitation	–	DC due to urine drug screen
11001002	11 M	42.0	8/29	0	✓	Weight increased	–	Completed

Source: Appendices B1.1, B2.1, B6
AE = adverse event, DC = discontinued, EPS = extrapyramidal symptoms, NA = not applicable, SAE = serious adverse event, ✓ = yes, - = no or none
Placebo subjects took 1 additional capsule.

These errors occurred as a result of incorrect understanding of the blinded study medication packaging by the personnel at the three investigative sites. Each dosing card had different columns representing 20,40, 60 and 80 mg of ziprasidone for each columns (distinguished by different sixe and color). The investigators at these sites incorrectly believed that all of the capsules were of the 20mg strength and thus instructed patients to ingest multiple capsules in order to achieve doses greater than 20mg. Once these errors were discovered, the information was immediately communicated to the DSMB, their IRBs and the patients and guardians.

The sponsor immediately suspended the three sites from additional patient enrollment. In addition, the sponsor re-trained all sites and study monitors on the use of the dosing cards, with 100% accountability requested from all sites. At the request of the DSMB, the sponsor reviewed the patient records for significant changes in QTc as delineated by the protocol. It was determined that none of the six patients who were overmedicated as a result of the dosing errors exhibited any significant QTc changes.

A sponsor review of all participating sites after the dosing errors occurred failed to detect any other instances of dosing errors or misunderstandings of dosing procedures.

7.1.17 Post marketing Experience

The sponsor provided an analysis of pediatric post-marketing use of ziprasidone for the three year time period between March 2005 to March 2008. The data based used for to collect exposure data was the IMS database which captures prescription retail data in 10 countries (Brazil, Canada, France, Germany, Italy, Japan, Mexico, Spain, UK and US). The Marketing Authorization Holder's (MAH) global safety database was used to search for pediatric adverse events associated with ziprasidone use, in addition to cases reported to health authorities and published cases in literature from 05 Feb 1998 to 30 Apr 2008.

During the three year period, there were approximately 631,000 pediatric patients (aged 0-17 years) exposed to ziprasidone. A review of the MAH database reported 2135 pediatric adverse events from 809 pediatric cases, which represented 6.7% of the total ziprasidone AE reports in the MAH database (total=12,073). Of these reports, 85% were reported by healthcare professionals. Approximately 83% of the pediatric AE cases were from US sources, followed by Germany (3%), Brazil (2%), Denmark and Norway (<2% respectively).

Although the majority of the pediatric AE cases occurred in patients with an unknown indication, pediatric AEs were reported most frequently in patients with a bipolar indication when compared to other psychiatric indications (13% vs. 12% for schizophrenia/psychotic disorders and schizoaffective combined).

Deaths
There were eight (8) reported pediatric deaths reported in the post marketing database during the time of reporting. The following table adapted from the sponsor's submission delineates these cases:

Case Number Age (yrs) /Gender Source	Daily Dose/Duration of Therapy	Indication/Relevant Medical History	Cause of Death	Adverse Events (Preferred Terms)	Comments
2004045603 8/Male Spontaneous non-Health professional	Unknown/Unknown	Autism/Unknown	Asphyxia	Asphyxia Drug toxicity	Death ruled a homicide by suffocation 'due to external chest compression' while being restrained; Medical examiner stated 'toxic blood levels' of brompheniramine and ziprasidone were present.
2005087572 13/Female Spontaneous Health professional	40mg/ < 1 month	Bipolar disorder/ Irritability, Oppositional defiant disorder, Weight increased	Gunshot wound	Completed suicide Belligerence Irritability Oppositional defiant disorder	Comcomitant medication includes risperidone; no history of active suicidal ideation or attempts; reporting physician stated subject was being tapered off risperidone and onto ziprasidone when patient became irritable and defiant (consistent with past behavior); patient shot herself in the head unexpectedly 2 days later.
2006086834 Child/Unknown Spontaneous Health professional	Unknown/Unknown	Unknown/Neuroleptic malignant syndrome	Neuroleptic malignant syndrome	Dystonia	Treated with methylphenidate prior to his or her death.
2006123196 Adolescent/Unknown Spontaneous Health professional	Unknown/Unknown	Unknown/Unknown	Unknown	Death	No other information.

Case Number Age (yrs) /Gender Source	Daily Dose/Duration of Therapy	Indication/Relevant Medical History	Cause of Death	Adverse Events (Preferred Terms)	Comments
2006127055 13/Male Spontaneous non-Health professional	Unknown/Unknown	Autism/Unknown	Unknown	Cerebrovascular accident Aggression Convulsion Decreased appetite Erection increased Haematoma Hydrocele Migraine Ocular hyperaemia Pain Testicular disorder Testicular swelling	Subject's mother reported that her son died of a 'stroke' in a local hospital; no other information available.
2007002612 16/Unknown Spontaneous Health professional	160 mg/1 year	Schizophrenia/Unknown	Cardiopulmonary failure	Cardiac failure Respiratory failure	Concomitant medications include quetiapine, sertraline, and topiramate; reporting physician did not suspect death related to ziprasidone.
A109864 17/Male Spontaneous Health professional	20 mg/ < 1 month	Autism, aggressive behavior/ seizures, mental retardation	Aspiration	Convulsion Loss of consciousness Nausea Vomiting	Following breakfast, became nauseous vomited and experienced a seizure; lost consciousness and never regained it.
A116732 17/Female Spontaneous Health professional	Unknown/Unknown	Ill-defined disorder/Unknown	Unknown	Death Mania	Concomitant medications include lorazepam and valproate; no cardiac history; subject was consuming alcohol and unknown drug (suspected to be marijuana and heroin) when she collapsed.

Adverse Events by System organ Classes

The top five system organ classes by number of pediatric adverse events were (in descending order): Nervous system, psychiatric, general disorders, investigations and gastrointestinal. There were no differences in rankings between the top five pediatric vs. non-pediatric AEs. In general, there were more nervous system adverse events reports in the pediatric population vs. non-pediatric patients.

Adverse Events by Preferred Term

For those adverse events that were reported in a proportion of $\geq$2% or greater, dystonia was noted to be reported at a rate of greater than 3 fold in the pediatric population (10.4% vs. 2.9% respectively) as compared to those in the non-pediatric population. Adverse events reports of somnolence were reported at a rate of greater than 2 fold in the pediatric group vs. non-pediatric patients (9.8% vs. 4.7%).

Of note, AE reports of convulsions were reported in 2.1% of pediatric patients. Extrapyramidal disorder AEs were reported more frequently in kids vs. non-pediatric patients, though less than a two-fold increase (5.9% vs. 3.5%). Adverse event reporting rates of Akathesia (2.6% vs. 3%), dyskinesia(3.8% vs. 2.4%), tardive dyskinesia (3% vs.3.1%) and tremor (4.8% vs. 3.7%) were generally similar between pediatric and non-pediatric populations.

Suicidality

Using a broad search strategy involving MedDRA preferred terms for suicide and suicide related events, the sponsor identified 27 cases (3% of total dataset) of suicidality-related adverse events. The vast majority (24) occurred in patients aged 13-17 years old taking ziprasidone for unknown

(10) or multiple indications (5). Most patients were receiving concomitant psychiatric medications as well.

There was one completed suicide (patient 2005087572) as seen in the table above. The remaining cases were classified as: suicidal ideation and suicide attempt (9 cases each respectively),intentional self-injury (2), and self-injurious ideation and suicidal behavior (1 case each). Four other cases were intentional overdoses. Compared to non-pediatric AE post marketing reports, the proportion of patients with suicidal ideation and attempts are generally similar between the groups.

Table 49: MedDRA classification of suicidality reports
Pediatric and non-pediatric reports

PREFERRED TERM	NO. OF EVENTS IN NON-PEDIATRIC CASES (N=11264)	NO. OF EVENTS REPORTED IN PEDIATRIC CASES (N=809)
Completed suicide	82 (<1%)	1 (<1%)
Intentional Self Injury	7 (<1%)	2 (<1%)
Self-injurious behavior	7 (<1%)	-
Self-injurious ideation	6 (<1%)	1(<1%)
Suicidal behavior	13(<1%)	1(<1%)
Suicidal ideation	114 (1%)	9 (1%)
Suicide attempt	90 (<1%)	9 (1%)
Total	319	23

QT related Events

There were 44 cases identified as QT prolongation AE, with 21 cases reported as syncope or loss of consciousness and considered not QT-related by the sponsor. Out of the 23 cases that were considered to be a QT-related event, 20 cases were reported as ECG prolonged. Of note, one patient (2007002612, AERS No 5259176), was a 16 yo male patient who was taking Geodon® 80mg BID X 1 year, in addition to Topomax, Zoloft and Aeroquip, when he collapsed and died. Autopsy results were inconclusive with cardiopulmonary failure noted as the cause of death and not related to death from any drug. This patient had no history of cardiac disease or suspicion of an arrhythmia.

There were no cases of torsades de pointes reported in the sponsor's database.

Nervous System events

There were 426 cases reporting nervous system disorder post marketing AEs. As stated before, dystonia was the only event with a post-marketing reporting proportion greater than 3 fold than that of non-pediatric patients, suggesting that the pediatric population may be more susceptible to dystonic reactions with ziprasidone use as compared to non-pediatric patients.

A total of 84 dystonic pediatric cases were reported, with 37 cases reported in children aged 2-11 years of age. Dystonic reactions were most commonly reported in patients with bipolar disorder (10) when an indication was reported, as well as with the 40mg dose (18 cases), when the dosing data was provided in the reports however 40mg was the most commonly reported dose in the database associated with nervous system AEs.

Pediatric Pregnancy use/Lactation

The sponsor identified 15 pediatric cases of in Utero exposure with ziprasidone. Out of the 15 cases, there were 11 live births, 1 spontaneous abortion and unknown information regarding the remaining three cases.

Of the 11 live births, seven (7) babies were reported as normal healthy infants, three were born with serious adverse events:

Case 2005079138 was reported in the literature (*Journal of Investigative Medicine Jan 2006*) and involved a congenital anomaly (46XY and 550 bands) of a 34 week gestational infant born to a 28 yo schizophrenic mother who continued treatment with ziprasidone. The infant was small for gestational age, phalange hypoplasia, nail deformity, dysmorphism, and nose deformity and finger hypoplasia.

Case 2006072812 involved a neonatal infection that occurred after birth to an uncomplicated delivery in a 33 yo mother for schizophrenic psychosis.

Case 2008034681 involved a case of neonatal pulmonary arterial hypertension in an infant whose mother received ziprasidone at some point during her pregnancy. No additional data is available for this case.

Drug Overdose

There were 17 cases of pediatric overdoses reported as AEs. For three of the cases, the patients received ziprasidone over the recommended amount for an unspecified period of time. One case developed parkinsonism, while a second of these three cases (200mg/day) developed tardive dyskinsia and serotonin syndrome. No AEs were reported for the third case.

In five cases where a single overdose was reported (200 to 2400mg), two cases were suicide attempts with three of the cases reporting prolonged QT intervals. All subjects recovered.

Drug abuse, misuse, dependence

There was one case of abuse reported (no information available) and eight (8) cases of misuse. One case of misuse, case 2004045603, involved the asphyxiation and death of an 8 year old boy who died during a “prayer session”. Toxicology results at autopsy revealed toxic levels of ziprasidone and another drug in the boy’s system.

Six (6) cases of intentional misuse were reported. One patient was described as snorting ziprasidone powder from his capsule, whereas another patient (17 yo with a record of homicide while "high" on lorazepam, committed homicide after skipping one of his daily doses of ziprasidone.

No cases of drug dependence were noted.

IM administration events

There were six cases reporting post marketing AEs associated with IM ziprasidone use, of which four (4) were considered serious. Aggression, circulatory collapse,dystonia, EPS, fatigue, hypersensitivity, orthostatic hypotension, resp. disorder, sedation, somnolence and syncope (1 case each respectively) were reported with IM use.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Pursuant to the Written Request for studies of bipolar in adolescent patients, 237 patients (149 ziprasidone vs. 88 placebo) in the placebo controlled study A1281132 were exposed to four weeks of study medication, with 162 patients participating in a 6-month open label extension safety study A1281133 [67 patients (41%) completed entire study]. For study A1281123, an initial 3 week, open-label, flexible dose titration study (46 patients, bipolar only) with a 6 month long term extension in patients with bipolar (39 patients) and schizophrenia or schizoaffective disorder (17 patients) with ziprasidone was performed. In total, 405 patients were exposed to flexible doses (maximum doses determined by weight of patients) vs. 88 placebo patients during the adolescent bipolar program. This is delineated below:

Table 50: Delineation of pediatric bipolar patients enrolled by study and treatment received

STUDY	ZIPRASIDONE PATIENTS TREATED	PLACEBO SUBJECTS TREATED	ALL SUBJECTS TREATED
A1281123 PERIOD 1 (3 week titration bipolar only)	46		46

A1281123 PERIOD 2 (6 month extension study of 1123-bipolar only	39		39
A1281132 (4 week, double blind, placebo controlled study)	149	88	237
A1281133 (6 month extension study of A1281132)	162		162
A1281123 + A1281133 (6 month studies combined-ISS)	201		201
Total Exposed	405	88	

For all bipolar patients enrolled in the 6 month open label studies, only 73 patients completed at least 5 months of ziprasidone treatment up to 160m/day out of 188 patient's total.

	Ziprasidone Dosage Group (mg/d)					
Days	≤40 n=18	>40–≤80 n=54	>80–≤120 n=29	>120-≤160 n=87	>160 n=13	All subjects ≤160 n=188
Mean Duration	72.5	103.7	101.7	116.5	111.5	106.3
Median Duration	39	98	82	135	148	102.5
Range	3-169	6-189	7-185	8-190	16-189	3-190
	No. of Subjects					
Duration Category (Days)						
1-<7	4	2	0	0	0	6
7-<14	5	3	2	3	0	13
14-<21	0	2	3	8	2	13
21-<30	0	2	1	2	0	5
30-<60	0	10	3	11	3	24
60-<90	2	7	6	11	1	26
90-<120	1	4	1	5	0	11
120-<150	1	2	2	6	1	11
150-<180	5	13	7	23	4	48
≥180	0	9	4	18	2	31

Source: Table 2.1.5
Note: The duration is defined as the total number of actual dosing days from first to and including last day of study treatment.

7.2.1.2 Demographics

Please refer to section 6.1.4 for a review of the demographics of patient's enrolled in the placebo controlled study. The review in this section will focus on the combined demographic characteristics of patients enrolled in the open label studies A1281123 and A1281133.

The following table delineates the demographic characteristics of patients exposed to 6 months of open label ziprasidone.

Table 51: Demographics of patients in open label pediatric bipolar trials by dose

METRIC	≤40MG/DAY N=18	>40 TO ≤80MG/DAY N=54	80 TO ≤120MG/DAY N=29	>120 TO ≤160MG/DAY N=87	160MG/DAY N=13
Male	50%	61%	45%	61%	62%
Age					
10-13 years	56%	59%	48%	48%	46%
Race					
White	89%	85%	97%	83%	77%
Black	11%	13%	3%	12%	8%
Weight (kg) ± SD	53.3 (13.3)	53.6 (17.3)	61.7 (14.9)	58.5 (14.3)	61.7 (11)
Height (cm) ± SD	156.2 (11.9)	155.4 (12.4)	162.2 (10.2)	159.7 (11.4)	160.6 (5.5)

Concomitant Medications and therapy

Excluding the 13 patients who received doses of ziprasidone >160mg/day, eighty percent (80%-151/188) of patients in the open label trials received at least one concomitant medication, with paracetamol (19%), ibuprofen (18%) and lorazepam (15%) being the top three concomitant medications taken. Approximately 10% of patients (18/188) also received psychotherapy during treatment in the open label trials.

7.2.1.3 Extent of exposure (dose/duration)

For the placebo controlled study, there was a total of 9.37 person-years exposure to ziprasidone during the trial. The mean duration of exposure during the double-blind trials was 22.9 days vs. 23.7 for placebo. The mean daily dose during weeks 3, 4 and early termination in patients ≥ 45kg was 118.8 mg, with a mean modal dose of 69.23 for patients <45kg.

The duration of exposure in the combined open label studies A1281123 and A1281133 for bipolar patients only was 58.73 person-years exposure. If the schizophrenia patients enrolled in study A1281123 were included, a total of 65.45 person-years exposure to ziprasidone.

Bipolar only patients enrolled in studies A1281123 and A1281133 had a mean duration of treatment of 106.3 days with a median of 102.5 days. Including the schizophrenia patients, the mean duration of treatment was 109.5 days with a median of 125 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The sponsor also submitted clinical data from the following pediatric studies. Pertinent safety findings are discussed below.

Table 52: Other pediatric ziprasidone studies submitted with this application

STUDY	ZIPRASIONE PATIENTS TREATED	PLACEBO PATIETNS TREATED	TOTAL PATEITNS TREATED
128-044- Phase 1 single dose pharmacokinetic study in patients with Tourettes Syndrome (TS)	24	0	24
128-122-phase II double-blind, placebo controlled 8 week study in patients with TS	16	12	28
IIR studies			
20010457-Autism-6 week open label	8	0	8
20020012- 1 year open label study in patients aged 8-18 with early onset schizophrenia	40	0	40
20020501-Pediatric Bipolar open label monotherapy 8 week study	21	0	21
20020516-Retrospective pediatric safety study with ziprasidone for various psychiatric disorders	36	0	36
20030094-Pediatr bipolar open label study	30	0	30

7.2.2.1.1 Studies 128-044 and 128-122

Both of these studies of ziprasidone use in patients with Tourette's Syndrome took place before the approval of the original NDA for ziprasidone. In the open label study 044, twenty four (24) patients aged 7-16 years of age with a diagnosis of TS or chronic tic disorder were given single oral doses of 20mg (>60kg), 10mg (31-60kg) or 5mg ziprasidone. At the conclusion of this study, no deaths or SAEs were noted. 71% of patients experienced an adverse event, with somnolence being the most often complaint. No significant changes in laboratory, vital signs or ECGs were recorded.

For the 56-day double-blind study 128-122, twenty eight (28) patients aged 7-16 years of age with a diagnosis of TS or chronic tic disorder were given flexible, escalating daily doses of ziprasidone (5mg/day initial) to a maximum dose of 20mg po BID or placebo. The primary efficacy endpoint was the change from baseline score using the global severity and total tic scores of the Yale Global Tic Severity Scale (YGTSS) and the CGI-S scale for Tourette's Syndrome. There were no deaths or serious adverse events noted in this study. Four (4) subjects were prematurely discontinued from the study (3-placebo, 1-ziprasidone, withdrew consent). Eleven (11) of 15 patients randomized to ziprasidone required dose reductions due to mild-moderate sedation. All patients randomized to ziprasidone experienced at least one nervous system adverse event, with the majority being somnolence. There were no sustained clinically significant changes in laboratory, vital signs or ECG recordings noted for this study.

Although the efficacy results from this study will not be fully reviewed at this time, it is worth noting that ziprasidone treated patients achieved a significant reduction in tic severity and total tic score as compared to placebo patients. However a statistically significant reduction on one of three co-primary endpoints (CGI-TS) was not achieved.

TABLE 53: Summary Efficacy results from Study 128-055, LOCF approach

EFFICACY VARIABLE	**ZIPRASIDONE N=16**		**PLACEBO N=11**		**P-VALUE**
	Baseline	*Mean change from Baseline*	*Baseline*	*Mean change from baseline*	
YGTSS Global severity (SD)	46.9 (13.8)	-18.25	46.9 (17.7)	-7.64	0.0155
YGTSS Total Tic score (SD)	24.7 (6.8)	-8.56	24.6 (9.6)	-1.73	0.0080
CGI-TS current score (SD)	4.6 (0.9)	-1.37	4.5 (1.0)	-0.73	0.1067

7.2.2.1.2 Phase IIR studies

Most of the submitted safety data from these studies were abstracts of study results. For the open label schizophrenia study 2002-0012, the sponsor noted that 27 of 40 patients completed at least 8 weeks of open label treatment. Only 10 subjects completed the entire 52 week course. The mean final dose was 117.8mg. From a safety standpoint, 17 patients had notable activation including 9 patients who developed frank mania or hypomania. A mean QTc prolongation of 5msec was also noted.

For the remaining studies listed above, very limited information was provided to full address the safety findings from these studies. However no deaths were noted from the information provided by the sponsor for these studies.

7.2.2.2 Post marketing experience

Please refer to the review in section 7.1.17 for a full review of the sponsor's post-marketing analysis of their global database.

7.2.2.3 Literature

The sponsor conducted a medical literature review from February 5, 1998 through April 30, 2008 as part of the sponsor's post marketing database review and analysis. The results of the medical literature search have been reviewed in section 7.1.17.

7.2.3 Adequacy of Overall Clinical Experience

Overall, the clinical development program for pediatric bipolar disorder is adequate to support the acute use of ziprasidone in the treatment of pediatric bipolar disorder. In this reviewer's opinion, there is sufficient efficacy and safety data from study A1281132 to adequately assess the acute efficacy and safety risks associated with pediatric ziprasidone use.

However, with only 73 pediatric patients (out of 188 total) completing a 5 month course of ziprasidone therapy, there is insufficient data from which to draw any long term safety risks or conclusions with pediatric use of ziprasidone at this time. A full assessment of the long term safety of pediatric ziprasidone use will take place once the long term studies of at least 6 months in duration that are currently underway in the pediatric schizophrenia program are completed and submitted to the agency.

7.2.4 Adequacy of Special Animal and/or *In vitro* Testing

No animal or *in vitro* testing studies were performed or required as part of the Written Request. In addition, the current labeling for ziprasidone has information from previous preclinical and *in vitro* testing of ziprasidone included.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal metabolic, clearance or drug interaction data or information was required or performed pursuant to the Written Request. In addition, this information is currently available as part of the current labeling for ziprasidone.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The pediatric studies conducted under this NDA were adequate to evaluate acute pediatric adverse events associated with ziprasidone use. The long term adverse events of pediatric ziprasidone use cannot be assessed at this time due to lack of long term safety data. ECG monitoring was adequate to detect acute changes in any QTc prolongation associated with ziprasidone use, although the long term QTc risks cannot be assessed at this due to lack of long term safety data.

7.2.8 Assessment of Quality and Completeness of Data

Review of case report forms, narrative and adverse event line listings for each of the patients listed below in Table 54 was conducted. Consistent reporting was noted in adverse events between all databases with no errors noted for studies A1281132, A1281123 and A1281133.

TABLE 54: GEODON® CRF AUDIT

PID (UNIQUE ID)	CASE REPORT FORM AE'S	SUMMARY
A1281132/10261001	Dystonia, Overdose	OK
A1281132/10401022	Liver Function Tests Abnormal	OK
A1281132/11241002	Hallucination, Paranoia, Aggression	OK
A1281123/10021008	Exacerbation of Bipolar Symptoms	OK
A1281123/10151012	Mania Aggravated	OK
A1281133/11011002	Hallucination, Conversion disorder, Self injurious behavior	OK
A1281133/10131002	Depressive Symptom, Drug Ineffective, Sedation	OK
A1281133/10401016	Suicidal ideation	OK

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7.2.9 Additional Submissions, Including Safety Update

After discussions with the Agency, the sponsor was unable to submit the results of the pediatric schizophrenia studies at this time due to significant lack of recruitment for these studies. As a result, the Written Request was modified to allow the sponsor sufficient time (based on the sponsor's projected recruitment rates) to complete submit all pediatric schizophrenia studies as a separate amendment to this NDA by 2011.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Sedation, dystonia and extrapyramidal symptoms appear to be frequently noted in the pediatric population. A closer analysis of the adverse events by patient weight revealed that patients who weighed less than 45kg were most likely to report EPS, tremor and abdominal pain adverse events in the double-blind trials.

The sponsor also conducted a concentration-QTcF analysis from concentration-QTcF data points obtained from 4 pediatric trials and from 21 adult trials. The result showed a linear concentration-dependent increase in QTcF prolongation in both the pediatric and adult population. Of particular concern is that the pediatric population overall had a 58% increase in concentration dependant QTcF prolongation rates at any given concentration when compared to the adult population. The results showed that the pediatric dataset exhibited a steeper slope to the regression line as compared to the adult dataset, suggesting that the pediatric population is at least as sensitive to the concentration-dependant QTcF prolongation effects of ziprasidone administration as compared to adults or potentially may be at more at risk for QTc related cardiac arrhythmias. Despite the absence of reports or adverse events of torsades de pointes seen in the pediatric clinical trials and post-marketing reports thus far, this reviewer recommends that the QTc warning language be re-worded to include children as being potentially at risk for QTc related adverse events associated with ziprasidone use.

A review of the post-marketing reports revealed 8 pediatric deaths from the sponsor's database, including one case of cardiac failure after receiving 160mg/day of ziprasidone for over 1 year. A review of the Agency post-marketing database (please see section 8.8 for details) concluded that the safety profile of ziprasidone in the pediatric population is similar to the adult population, including QTc-related events. Thus the Office of Surveillance and Epidemiology recommends enhancing the Warnings section of the current ziprasidone label to include the risk of QT prolongation for both adult and pediatric patients.

Although post marketing data is subject to many limitations from which to draw firm regulatory conclusions, reports of cardiovascular deaths in patients who received ziprasidone is of concern to this reviewer in light of the more prominent concentration dependant QTcF prolongation seen in pediatric patients as compared to the adult population. This reviewer therefore recommends that there is sufficient evidence to warrant a change in the current Warnings section of the QT

prolongation to include children as being at risk for QT prolongation-related adverse events with ziprasidone use.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Safety data only from the placebo controlled study was reviewed to determine mean change from baseline differences in laboratory and vital sign data for ziprasidone. The safety data from the open label studies A1281123 and A1281133 were pooled and reviewed in response to the specific additional long term safety requirement as delineated in the Written Request.

Efficacy data was only reviewed from the placebo controlled, double blind study.

7.4.1.2 Combining data

Safety data from the two open label studies were combined with an analysis performed via a separate Integrated Safety Study. In addition, those patients with a diagnosis of schizophrenia and schizoaffective disorder who took part in study A1281123 were also pooled with study A1281133 to fully examine the long term safety of pediatric ziprasidone use.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Due to the flexible dose study design form the placebo controlled study, an analysis of dose related adverse events cannot be performed.

7.4.2.2 Explorations for time dependency for adverse findings

Time dependent studies were not performed as there were no long term controlled data that was collected during the clinical development program.

7.4.2.3 Explorations for drug-demographic interactions

Please see section 7.1.5.6 for review of adverse events as related to patient weight.

7.4.2.4 Explorations for drug-disease interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.4.2.5 Explorations for drug-drug interactions

There were no explorations done to examine drug-drug interactions in the clinical development program.

7.4.3 Causality Determination

In this review, causality was determined if an adverse event occurred in 5% or greater of patients taking ziprasidone compared to placebo AND that the adverse event reporting rate in patients taking drug was at least twice the rate in placebo patients.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Based on the three week dose titration results from study A1281123-period 1, the sponsor employed a maximum dose limit based on patient weight as to limit the maximum exposure of ziprasidone to patients who weighed <45kg.

8.2 Drug-Drug Interactions

There are no further recommendations at this time for dose adjustments for ziprasidone in pediatric patients taking concomitant medications. Discuss

8.3 Special Populations

Dosing for the pediatric studies utilized patient weight as a basis to limit overall exposure of ziprasidone in these trials. As a result, the sponsor has proposed language for labeling that is consistent with the dosing regimens used for dosing in the pediatric bipolar trials submitted under this NDA.

8.4 Pediatrics

The clinical development program was conducted pursuant to the Agency's Written Request.

8.5 Advisory Committee Meeting

An advisory committee meeting is scheduled for June 2009 to review the results of the clinical development program for pediatric bipolar disorder. The

8.6 Literature Review

Relevant reviews of the literature that are pertinent to this review have been cited throughout the review and in the references section of this NDA.

8.7 Post marketing Risk Management Plan

Not applicable at this time.

8.8 Other Relevant Materials

An FDA review of AERS post marketing data was completed by the Office of Surveillance and Epidemiology (OSE) on March 24, 2009 by Ida-Lina Diak, PharmD for the time period of initial market approval until January 14, 2009 for patients aged 0-17 years of age. For an in-depth review, the reader is referred to the March 24, 2009 review for details.

Ten (10) reports of death associated with ziprasidone in patients aged 3-17 years old were reviewed by OSE. Four of the deaths were of an unspecified cause, two were completed suicides and the remaining cases were deaths attributed to different causes. Overall the adverse events that led up to death in the pediatric cases were consistent with the pattern seen with the adult use of ziprasidone.

There were 24 suicide-related events associated with ziprasidone use, along with 24 cases describing QT-related events (3 cases as a result of intentional overdoses and two reports of accidental exposure). Again the cases that were reviewed occurred in a similar manner as reported in the adult population.

A comparison of adverse events reported with a proportion >= 2% by MedDRA system organ class (SOC) and by preferred term between adults and pediatric patients was also performed. For the system organ class comparison, the reports were generally similar between the two populations. However, for the preferred term, the top 5 adverse events reported by preferred term differed between the two populations. For the pediatric population, the top 5 adverse events (in descending order) were: Dystonia (11%), ECG QT prolonged (8%), Extrapyramidal disorder (8%), sedation (7%) and dyspnea (6%). For adults, ECG QT prolongation (7%), insomnia (6%), tremor (6%), agitation (5%) and anxiety (5%) were frequently reported.

9 OVERALL ASSESSMENT

9.1 Conclusions

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.2 Recommendation on Regulatory Action

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3 Recommendation on Post marketing Actions

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3.1 Risk Management Activity

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3.2 Required Phase 4 Commitments

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3.3 Other Phase 4 Requests

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.4 Labeling Review

A formal review of the submitted labeling for this application will occur after a full review of discussions and recommendations of advisory committee proceedings have been accomplished by this reviewer and division at the conclusion of the June 9-10th Advisory committee meeting.

However this reviewer recommends data table 29 of this review be included in final labeling as part of the pediatric trial safety results. Also, there appears to be sufficient evidence from both the post-marketing database reviews and the concentration dependant increase in QTcF seen with ziprasidone use in both adults and children to warrant a change in the Warnings section of final labeling to extend the risk of QT prolongation adverse events associated with ziprasidone use to children and adults.

9.5 Comments to Applicant

Comments to the applicant are being deferred until a full review of discussions and recommendations of advisory committee proceedings have been accomplished by this reviewer and division at the conclusion of the June 9-10th Advisory committee meeting.

10 APPENDICES

10.1 Review of Individual Study Reports

Please refer to section 6 for a full review of the protocol for the double-blind, placebo controlled study.

10.2 Line-by-Line Labeling Review

Deferred at this time.

REFERENCES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Ritter
4/28/2009 11:33:29 AM
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