DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-825 (SE5-032)
Drug Name:	GEODON® (ziprasidone HCl) Capsules
Indication:	Pediatric Bipolar Disorder
Applicant:	Pfizer Inc
Dates:	Date of Document: 10/21/2008
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Review Priority:	Priority
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The efficacy of ziprasidone in treating children and adolescents with Bipolar I disorder has been demonstrated. The patients with weight less than 45 kg appeared to show much less improvement numerically than the patients with weight at least 45 kg. Although the statistically insignificant results in the '< 45 kg' subgroup could be due to the lack of power and the patients in the two different weigh groups were dosed differently, it is unclear whether the weight effect is completely confounded with the dose effect.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Per the FDA's Pediatric Written Request (PWR) and also under the Pediatric Research Equity Act (PREA), the sponsor submitted a single efficacy study (Study A1281132) to demonstrate the efficacy of ziprasidone as a treatment of Bipolar I disorder with manic or mixed episodes in children and adolescents.

Study A1281132 was a 4-week, randomized, double-blind, placebo-controlled trial, where ziprasidone was titrated over the first 1-2 weeks of treatment and flexibly dosed through weeks 3 and 4. Ziprasidone was titrated from a starting dose of 20 mg/day with dose increases of 20 mg/day every other day up to a target dose of 120-160 mg/day for subjects weighing greater than or equal to 45 kg. For children weighing less than 45 kg, the target dose was only 60-80 mg/day. The primary efficacy endpoint of the study was change from baseline to Week 4 in YMRS total score. Based on the sponsor's analysis results, they concluded that oral ziprasidone was shown to be effective in the treatment of children and adolescents with Bipolar I disorder (manic or mixed).

1.3 STATISTICAL ISSUES AND FINDINGS

This statistical reviewer confirmed all of the sponsor's efficacy results and agreed that Ziprasidone's overall efficacy was demonstrated in both children and adolescents as a treatment of Bipolar I disorder with manic or mixed episodes. However, it was noted that the patients with weight less than 45 kg appeared to show much less improvement in comparison with the patients with weight at least 45 kg.

2. INTRODUCTION

2.1 OVERVIEW

The sponsor submitted this NDA to support a new indication, and associated prescribing information for the use of ziprasidone HCl in pediatric and adolescent patients aged 10-17 years with Bipolar I Disorder (manic or mixed episodes) in accordance with a commitment under the Pediatric Research Equity Act (PREA) per the 19 August 2004 approval letter for this indication in adults and per the development considerations contained in the 2003 Pediatric Written Request (PWR), and amended. In accordance

with the PWR, FDA agreed that a single positive study in pediatric patients aged 10-17 would support the bipolar indication in this new population.

The study drug, ziprasidone was initially approved in 2001. Oral formulations (capsule and oral suspension) are presently approved for treatment of schizophrenia and of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features, but only for adult population. FDA issued a PWR in February 2003 describing requirements for pediatric studies in both indications. In addition, there is a PREA Phase 4 commitment associated with the bipolar capsule approval for this indication. Studies proposed under the PREA requirement have been designed by Pfizer to meet the terms of the PWR.

The sponsor's clinical development program for ziprasidone consisted of three key studies (Studies A1281132, A1281123 and A1281133) in children and adolescents between the ages of 10 and 17 years. Study A1281132 was the only double-blind well-controlled study which supports the efficacy and safety of flexibly dosed ziprasidone in the treatment of Bipolar I disorder in pediatric patients. It was flexibly titrated over a 2-week period from a starting dose of 20 mg/day given in the evening with dose increases of 20 mg/day every 2nd day up to a target dose of 120-160 mg/day for subjects weighing ≥45 kg or 60-80 mg/day for subjects weighing <45 kg. The target dose was to be obtained by day 14. The dose was increased above 120 mg/day only in subjects who tolerated 120 mg/day. The study duration was 4 weeks. The primary endpoint was change from baseline to week 4 in YMRS total score. Per the FDA's requirement in the Written Request that at least 50% of subjects assigned to the active drug complete to the nominal endpoint for the study to be considered a completed trial, Study 1281132 was determined a completed study with 65.1% of total patients enrolled completed the 4 weeks of dosing. Based on statistically significant results in the primary endpoint and secondary endpoints for Study 1281132, the sponsor concluded that oral ziprasidone (120-160 mg/day) is efficacious in the treatment of manic or mixed episodes associated with Bipolar I Disorder in children and adolescents 10-17 years.

2.2 DATA SOURCES

The electronic submission for this NDA, including the clinical study report and the data sets, were stored in the following directory: **\\CDSESUB1\EVSPROD\NDA020825\0030** of the CDER electronic document room.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study A1281132

This study was titled "Four Week, Double-Blind, Placebo Controlled Phase III Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Flexible Doses of Oral Ziprasidone in Children and Adolescents with Bipolar I Disorder (Manic or Mixed)." It

was conducted in 36 centers in the United States (US).

3.1.1.1 Study Objective

Primary Objectives:

1. To establish efficacy of oral ziprasidone compared with placebo in the treatment of children and adolescents with Bipolar I disorder (manic or mixed); as measured by the change from baseline to Week 4 in Young Mania Rating Scale (YMRS) total score.

2. To evaluate the safety and tolerability of oral ziprasidone over 4 weeks in the treatment of children and adolescents with Bipolar I disorder (manic or mixed).

Secondary Objectives:

1. To evaluate efficacy of oral ziprasidone as compared with placebo in the treatment Of children and adolescents with Bipolar I disorder (manic or mixed), as measured by

   • Change from baseline in Clinical Global Impression of Severity (CGI-S) score.
   • Clinical Global Impression of Improvement (CGI-I) score.

2. To characterize the population pharmacokinetics and pharmacokinetics/ pharmacodynamics (PK/PD) of oral ziprasidone in children and adolescents with Bipolar I disorder (manic or mixed), including PK/PD analysis for safety (corrected QT interval [QTc]) measurements.

3.1.1.2 Study Design

This was a 4-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of flexibly dosed ziprasidone as compared with placebo for the treatment of Bipolar I disorder (manic or mixed) in children and adolescents. Ziprasidone was administered as oral capsules given twice daily (BID) with meals. Ziprasidone was titrated over the first 1-2 weeks of treatment, and flexibly dosed through Weeks 3 and 4.

Approximately 222 subjects (148 ziprasidone, 74 placebo) were to be recruited at approximately 70 US and Canadian sites. It was estimated that at least 318 subjects would be needed to be screened to account for a screen failure rate of approximately 30%. The completion rate of randomized subjects was 65.1%, which met the FDA's requirement.

Upon completion of the screening procedures, eligible subjects were allowed to begin a 1-10 day period to allow for washout of exclusionary medications. The qualified subjects were to be randomized in a 2:1 ratio at baseline to receive either double-blind oral ziprasidone or placebo, respectively.

During the 4 weeks of study, the first two weeks was the dose titration period. Following the titration, double-blind dosing continued to Week 4, during which time further dosing adjustments could be made if necessary within the range of 80-160 mg/day for subjects with a body weight of 45 kg or greater, or between 40-80 mg/day for subjects weighing less than 45 kg.

Subjects who demonstrated insufficient treatment response 1 week after completing their titration, and who reached their maximum tolerated dose, were to be discontinued from the study and could be eligible to enroll in the open-label extension trial (with active ziprasidone) provided there were no safety concerns. Subjects who could not tolerate the dose ranges cited above also were to be discontinued from the double-blind study and could be eligible to enter the extension trial. In addition, subjects requiring concomitant medications disallowed by the protocol could be discontinued and could enroll in the open-label extension if the concomitant medication(s) was/were allowed. Subjects who did not enter the open extension returned for a post-treatment follow-up clinic visit at Week 5.

Reviewer's Note: An interim analysis was originally planned to stop the trial for both efficacy and futility. Since this trial was conducted for seeking pediatric exclusivity, FDA recommended earlier that the sponsor forgo the interim analysis for futility. At the end, the interim analysis was not performed.

3.1.1.3 Efficacy Endpoint and Analysis

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

The analysis of change from baseline in the YMRS score was performed using SAS PROC MIXED to fit a mixed model repeated measures analysis of covariance (ANCOVA) with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate. The estimation method used was restricted maximum likelihood. The covariance structure among repeated measures was assumed to be adequately modeled using a first order autoregressive structure. Other covariance structures could be examined if indicated by model diagnostics. The EMPIRICAL option was specified to compute the estimated variance-covariance matrix of the fixed-effects parameters. Type III sums of squares were used to test both main effects and interactions. The primary comparison was between ziprasidone and placebo at Week 4, conducted as a 2-sided test at 5% level of significance. Based on the specified model, the point estimate and 95% confidence interval (CI) for the difference in means between the 2 treatments were constructed using the least squares means and appropriate standard errors.

For change from baseline in the CGI-S score, analyses were conducted using SAS PROC MIXED to fit a mixed model repeated measures ANCOVA with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

For the raw CGI-I score, analyses were conducted using SAS PROC MIXED to fit a mixed model repeated measures analysis of variance (ANOVA) with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects.

For all the above analyses, the estimation method used was restricted maximum likelihood. The covariance structure among repeated measures was assumed to be adequately modeled using a first order autoregressive structure. Other covariance structures could be examined if indicated by model diagnostics. The EMPIRICAL option was specified to compute the estimated variance-covariance matrix of the fixed-effects parameters. Type III sums of squares were used to test both main effects and interactions. The point estimates and 95% CIs for the difference in means between the 2 treatments were constructed using the least squares means and appropriate standard errors.

3.1.2 Patient Disposition and Demography and Baseline Characteristics

Table 3.1 shows patient disposition and Table 3.2 summaries patient demographics. A total of 327 patients were screened and 238 were randomized to treatment. Of these patients, 237 took study medication. The percentage of patients who completed the study was 65% in the ziprasidone group and 58% in the placebo group. Nevertheless, the ITT population only included 229 patients where 143 patients were randomized to ziprasidone and 86 patients to placebo. As shown in Table 3.2, treatment groups were comparable with regard to demography and baseline characteristics. Patients ranged in age from 10 to 18 years with an overall mean age of 13.6 years in the ziprasidone group and 13.7 years in the placebo group. The majority of patients were white males of non-Hispanic/Latino ethnicity.

Table 3.1 Patient Disposition for Study A1281132

	Ziprasidone	Placebo
Number (%) of subjects:		
Screened: N=327		
Assigned to study treatment: N=238		
Treated	149	88
Completed	97 (65.1)	51 (58.0)
Discontinued	52 (34.9)	37 (42.0)
Reason for discontinuation:		
Related to study drug:	14 (9.4)	3 (3.4)
Adverse event	13 (8.7)	3 (3.4)
Laboratory abnormality	1 (0.7)	0 (0)
Not related to study drug:	38 (25.5)	34 (38.6)
Adverse event	5 (3.4)	10 (11.4)
Lost to follow-up	8 (5.4)	1 (1.1)
Other	16 (10.7)	21 (23.9)
Subject no longer willing to participate	9 (6.0)	2 (2.3)
Analyzed for efficacy:		
Intent-to-treat	143 (96.0)	86 (97.7)
Per protocol	103 (69.1)	66 (75.0)
Analyzed for safety:		
Adverse events	149 (100)	88 (100)
Laboratory data	134 (89.9)	84 (95.5)

Source: Table 4 of Sponsor's CSR.

Table 3.2 Patient Demographics for Study A1281132

	Ziprasidone			Placebo		
	Male N=84	Female N=65	Total N=149	Male N=47	Female N=41	Total N=88
Age (years)						
10-13	47 (56.0)	27 (41.5)	74 (49.7)	19 (40.4)	16 (39.0)	35 (39.8)
14-17	36 (42.9)	38 (58.5)	74 (49.7)	28 (59.6)	25 (61.0)	53 (60.2)
≥18	1 (1.2)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)
Mean	13.2	14.1	13.6	13.5	14.0	13.7
SD	2.4	2.0	2.2	2.0	1.9	2.0
Range	10-18	10-17	10-18	10-17	10-17	10-17
Race						
White	66 (78.6)	55 (84.6)	121 (81.2)	38 (80.9)	34 (82.9)	72 (81.8)
Black	15 (17.9)	6 (9.2)	21 (14.1)	8 (17.0)	6 (14.6)	14 (15.9)
Asian	0 (0)	1 (1.5)	1 (0.7)	0 (0)	0 (0)	0 (0)
Other	3 (3.6)	3 (4.6)	6 (4.0)	1 (2.1)	1 (2.4)	2 (2.3)
Ethnicity						
Hispanic/Latino	5 (6.0)	6 (9.2)	11 (7.4)	2 (4.3)	5 (12.2)	7 (8.0)
Not Hispanic/Latino	79 (94.0)	59 (90.8)	138 (92.6)	45 (95.7)	36 (87.8)	81 (92.0)
Weight (kg)						
Mean	55.9	58.8	57.2	61.3	58.5	60.0
SD	16.3	11.5	14.4	17.9	13.4	16.0
Range	28.0-88.0	34.1-94.4	28.0-94.4	29.0-109.4	32.1-87.1	29.0-109.4
Height (cm)						
Mean	160.3	158.1	159.3	163.4	157.1	160.5
SD	14.1	8.0	11.9	13.8	8.1	11.9
Range	128-188	134-174	128-188	137-193	133-170	133-193

Source: Table 7 of Sponsor's CSR.

3.1.3 Sponsor's Efficacy Analysis Results

3.1.3.1 Sponsor's Results for Primary Endpoint

Table 3.3 summarizes the sponsor's primary analysis results for change from baseline to Week 4 in the YMRS total score. As shown in the table, the estimated least square (LS) means for ziprasidone and placebo for the change from baseline to Week 4 in YMRS total score were -13.83 and -8.61, respectively. The estimated LS means and the 95% CI for placebo-adjusted scores for ziprasidone were -5.22 [-8.12, -2.31]. This difference in treatment effect was statistically significant (p=0.0005). The sponsor noted that results from the primary analysis using the PP analysis set also indicated a statistically significant treatment effect (p=0.0004) in favor of ziprasidone.

Table 3.3 Sponsor's Analysis Results for Change from Baseline in Young Mania Rating Scale (YMRS) at Week 4 Repeated Measures for ITT Population for Study A1281132

	Ziprasidone N=133	Placebo N=85
LS Mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from Placebo LS Mean (SE)	-5.22 (1.48)	
95% CI for the difference from Placebo	[-8.12, -2.31]	
P-value	0.0005	

Sponsor's Table 10 of CSR.

Table 3.4 presents descriptive statistics for YMRS total score at baseline and change from baseline to each visit for the ITT populations. Since the 95% confidence intervals ruled out zero from Week 1 to Week 4, the sponsor concluded that the active and placebo groups separated as early as at Week 1 for the change from baseline in YMRS total score. Nevertheless, we should note that this conclusion was drawn without any prospective analysis plan for adjusting the overall type I error rate due to multiple comparisons.

Table 3.4 Sponsor's Descriptive Statistics for YMRS Total Score at Baseline and Change from Baseline by Treatment Group and Visit for Study A1281132

	Ziprasidone			Placebo		
Visit	N	Mean (SD)	95% C.I.	N	Mean (SD)	95% C.I.
Baseline	143	26.2 (6.6)	(25.08, 27.26)	86	27.0 (6.6)	(25.59, 28.43)
Week 1	131	-9.3 (7.5)	(-10.63, -8.04)	85	-6.3 (7.1)	(-7.86, -4.80)
Week 2	120	-11.5 (8.7)	(-13.07, -9.92)	81	-8.1 (7.9)	(-9.88, -6.40)
Week 3	108	-13.0 (8.1)	(-14.51, -11.42)	65	-9.0 (7.3)	(-10.82, -7.21)
Week 4	97	-13.8 (7.8)	(-15.32, -12.18)	51	-9.9 (7.7)	(-12.03, -7.70)
Week 4-LOCF	133	-12.8 (8.4)	(-14.27, -11.37)	85	-7.1 (7.8)	(-8.74, -5.40)

Source: Sponsor's Table 13.4.2.1 of CSR.

3.1.3.2 Sponsor's Results for Secondary Endpoints

One secondary efficacy endpoint for this study was the change from baseline in CGI-S score. Table 3.5 summarizes the statistical analysis for change from baseline to Week 4 in CGI-S total score. The estimated LS means for ziprasidone and placebo for the change from baseline to Week 4 (repeated measures) in CGI-S score was -1.43 and -0.74, respectively. The estimated LS means and 95% CI for placebo-adjusted scores for ziprasidone were -0.69 [-1.03, -0.34]. The difference in treatment effect was statistically significant (p=0.0001). The sponsor noted that this secondary analysis further supports the efficacy of oral ziprasidone in children and adolescents with Bipolar I disorder (manic or mixed). Results from the statistical analysis using the PP analysis set also indicated a significant treatment effect (p=0.0003) in favor of ziprasidone.

Table 3.5 Sponsor's Analysis Results for Change from Baseline in CGI-S Total Score at Week 4 for ITT Population for Study A1281132

	Ziprasidone N=133	Placebo N=85
LS Mean (SE)	-1.43 (0.13)	-0.74 (0.13)
Difference from Placebo LS Mean (SE)	-0.69 (0.18)	
95% CI for the difference from Placebo	[-1.03, -0.34]	
P-value	0.0001	

Source: Sponsor's Table 11 of CSR.

CGI-I score was another secondary efficacy endpoint. Table 3.6 summarizes the statistical analysis for change from baseline to Week 4 in CGI-I score. The estimated LS means for ziprasidone and placebo for the change from baseline to Week 4 in CGI-I score were 2.30 and 3.06, respectively. The estimated LS mean and 95% CI for placebo-adjusted scores for ziprasidone were -0.76 [-1.18, -0.34]. The difference in treatment effect was statistically significant (p=0.0004).

Table 3.6 Sponsor's Analysis Results for Change from Baseline in CGI-I Score at Week 4 for ITT Population for Study A1281132

	Ziprasidone N=132	Placebo N=85
LS Mean (SE)	2.30 (0.13)	3.06 (0.16)
Difference from Placebo LS Mean (SE)	-0.76 (0.21)	
95% CI for the difference from Placebo	[-1.18, -0.34]	
P-value	0.0004	

Source: Sponsor's Table 12 of CSR.

3.1.4 Statistical Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints. She agrees that the efficacy of ziprasidone has been demonstrated. However, she noted that ziprasidone seems to perform distinctly on two types of weight groups of patients. Patients with weights less than 45 kg showed much less improvement than patients with weight at least 45 kg. Since the dosing mechanism depends on weight of patients, it is unclear whether weight effect is completely confounded with the dose effect.

2. The change from baseline in CGI-S score was designated as a 'key' secondary efficacy endpoint in the clinical study report. In fact, none of secondary endpoints was pre-specified as a key secondary endpoint.

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Tables 3.7 to 3.9 showed the sponsor's subgroup analysis for gender, race and age on the primary endpoint YMRS total score and the secondary endpoint, CGI-S respectively. Except the category of other in race subgroups, numerically, ziprasidone showed larger change from baseline values than placebo in all other subgroups. The statistical reviewer confirmed all of the sponsor's subgroup analysis results.

Table 3.7 Sponsor's Analysis Results for Gender Subgroups for Study A1281132

	Male		Female	
YMRS Total	Ziprasidone N=74	Placebo N=44	Ziprasidone N=59	Placebo N=41
LS Mean of Change (SE)	-13.41 (1.12)	-6.50 (1.48)	-14.44 (1.15)	-10.70(1.45)
Difference from placebo LS Mean (SE)	-6.91 (1.72)		-3.74 (1.85)	
95% CI for the difference from placebo	(-10.28, -3.53)		(-7.38, -0.09)	
P value	<0.0001		0.0445	

	Male		Female	
CGI-S Score	Ziprasidone N=74	Placebo N=44	Ziprasidone N=59	Placebo N=41
LS Mean (SE)	-1.36 (0.14)	-0.63 (0.18)	-1.54 (0.15)	-0.80 (0.18)
Difference from placebo LS Mean (SE)	-0.73 (0.21)		-0.74 (0.21)	
95% CI for the difference from placebo	(-1.14, -0.32)		(-1.16, -0.32)	
P value	0.0005		0.0006	

Source: Sponsor's Table 5 of Clinical-Overview and Table 13.4.3.3.1 of Email to FDA on 2/17/2009

Table 3.8 Sponsor's Analysis Results for Race Subgroups for Study A1281132

YMRS Total Score (Change from Baseline)

White	**Ziprasidone**	**Placebo**
N	112	69
LS Mean of Change (SE)	-13.98 (0.95)	-7.68 (1.21)
Difference from Placebo LS Mean (SE)	-6.29 (1.37)	
95% CI for the Difference from Placebo	(-8.98, -3.61)	
p-value	<0.0001	
Black	15	14
N	-12.44 (2.30)	-11.38 (2.51)
LS Mean of Change (SE)	-1.06 (3.26)	
Difference from Placebo LS Mean (SE)	(-7.55, 5.34)	
95% CI for the Difference from Placebo	0.7461	
p-value		
Other		
N	5	2
LS Mean of Change (SE)	-11.96 (2.62)	-17.54 (4.01)
Difference from Placebo LS Mean (SE)	5.59 (4.80)	
95% CI for the Difference from Placebo	(-4.71, 15.89)	
p-value	0.2640	

CGI-S Score (Change from Baseline)

White	**Ziprasidone**	**Placebo**
N	112	69
LS Mean of Change (SE)	-1.51 (0.12)	-0.68 (0.15)
Difference from Placebo LS Mean (SE)	-0.83 (0.17)	
95% CI for the Difference from Placebo	(-1.15, -0.50)	
p-value	<0.0001	
Black	15	14
N	-0.83 (0.23)	-0.71 (0.25)
LS Mean of Change (SE)	-0.12 (0.34)	
Difference from Placebo LS Mean (SE)	(-0.80, 0.55)	
95% CI for the Difference from Placebo	0.7156	
p-value		
Other		
N	5	2
LS Mean of Change(SE)	-1.53 (0.51)	-2.50 (0.73)
Difference from Placebo LS Mean (SE)	0.97 (0.89)	
95% CI for the Difference from Placebo	(-0.93, 2.86)	
p-value	0.2947	

Source: Sponsor's Table 7 of Clinical-Overview and Table 13.4.3.3.3 of Email to FDA on 2/17/2009

Table 3.9 Sponsor's Analysis Results for Age Subgroup for Study A1281132

	<14 years		≥14 years	
YMRS Total	Ziprasidone N=66	Placebo N=35	Ziprasidone N=67	Placebo N=50
LS Mean of Change (SE)	-12.44 (1.12)	-8.57 (1.17)	-15.36 (1.15)	-8.33(1.31)
Difference from placebo LS Mean (SE)	-3.88(1.98)		-7.03 (1.62)	
95% CI for the difference from placebo	(7.77, 0.02)		(-10.22, -3.84)	
P value	0.0510		<0.0001	
CGI-S Score	Ziprasidone N=66	Placebo N=35	Ziprasidone N=67	Placebo N=50
LS Mean of Change (SE)	-1.45 (0.14)	-0.77 (0.21)	-1.40 (0.15)	-0.69 (0.17)
Difference from placebo LS Mean (SE)	-0.68 (0.24)		-0.71 (0.19)	
95% CI for the difference from placebo	(-1.15, -0.21)		(-1.09, -0.33)	
P value	0.0045		0.0003	

Source: Sponsor's Table 6 of Clinical-Overview and Table 13.4.3.3.2 of Email to FDA on 2/17/2009

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Since patients were dosed according to their weight, we are interested in exploring whether treatment effects are different in two weight groups. Table 3.10 shows the sponsor's subgroup analysis results for the weight category. As seen in the tables, ziprasidone seems to show different effect for patients in two weight groups. The significant efficacy findings appear to be mainly from patients whose weights are greater than 45 kg although we should note that only about 20% of patients whose weights are less than 45 kg.

Table 3.10 Sponsor's Analysis Results for Weight Subgroups for Study A1281132

	Weight <45 kg		Weight ≥45 kg	
YMRS Total Score	Ziprasidone N=31	Placebo N=14	Ziprasidone N=101	Placebo N=71
LS Mean of Change (SE)	-12.83 (1.86)	-10.97 (2.92)	-14.15 (0.90)	-8.21 (1.11)
Difference from placebo LS Mean (SE)	-1.86 (3.22)		-5.93 (1.36)	
95% CI for the difference from placebo	(-8.24, 4.51)		(-8.61, -3.25)	
P value	0.56		<0.0001	
CGI-S Score	Ziprasidone N=31	Placebo N=14	Ziprasidone N=101	Placebo N=71
LS Mean of Change (SE)	-1.32 (0.20)	-1.03 (0.32)	-1.48 (0.12)	-0.70 (0.15)
Difference from placebo LS Mean (SE)	-0.28 (0.35)		-0.78 (0.17)	
95% CI for the difference from placebo	(-0.97, 0.40)		(-1.10, -0.45)	
P value	0.4122		<0.0001	

Source: Sponsor's Tables 13.4.2.23.1 and 13.4.3.3.4 from Sponsor's email to FDA on 2/28/2009

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This statistical reviewer confirmed all of the sponsor's efficacy analysis results and agreed that Ziprasidone's overall efficacy was demonstrated in both children and adolescents as a treatment of Bipolar I disorder with manic or mixed episodes. However, it was noted that the patients with weight less than 45 kg appeared to show much less improvement in comparison with the patients with weight at least 45 kg.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The efficacy of ziprasidone in treating children and adolescents with Bipolar I disorder has been demonstrated. The patients with weight less than 45 kg appeared to show much less improvement numerically than the patients with weight at least 45 kg. Although the insignificant results in the < 45 kg subgroup could be due to the lack of power and the patients in the two different weigh groups were dosed differently, it is unclear whether the weight effect is completely confounded with the dose effect.

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HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

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