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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Geodon® / Zeldox® / Ziprasidone hydrochloride

PROTOCOL NO.: A1281137

PROTOCOL TITLE: A Phase 3, Randomized, 6-Month, Double Blind Trial in Subjects With Bipolar I Disorder to Evaluate the Continued Safety and Maintenance of Effect of Ziprasidone Plus a Mood Stabilizer (vs Placebo Plus a Mood Stabilizer) Following a Minimum of 2 Months of Response to Open-Label Treatment With Both Agents

Study Centers: A total of 89 centers took part in the study and randomized subjects; 57 in United States, 6 in India, 4 each in Germany and Italy, 3 each in Chile, France, and Spain, 2 each in Mexico, Venezuela, and Russian Federation, and 1 each in Taiwan, Guatemala, and Hong Kong.

Study Initiation Date and Final Completion Date: 27 December 2005 to 23 May 2008

Phase of Development: Phase 3/4

Study Objectives: Primary Objective: To achieve a long-term maintenance indication for bipolar disorder by comparing the Time to Intervention for a Mood Episode (TIME) in subjects receiving double-blind ziprasidone plus a mood stabilizer versus (vs) subjects receiving placebo plus a mood stabilizer.

Secondary Objective: Evaluate time to discontinuation for any reason and changes in Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), Mania Rating Scale (MRS), Montgomery Asberg Depression Rating Scale (MADRS) and Positive and Negative Syndrome Scales (PANSS).

METHODS

Study Design: This was a double-blind, placebo-controlled trial to evaluate the maintenance of effect of ziprasidone plus adjunctive lithium or valproic acid in symptomatic subjects with a recent or current manic or mixed episode of Bipolar I Disorder.

The trial consisted of an open-label stabilization period (Period 1) followed by a 6 month, double-blind maintenance period (Period 2). In the stabilization period, open-label ziprasidone (80-160 mg daily) was added to a therapeutic blood level of lithium (0.6-1.2 mEq/L) or valproic acid (50-125 µg/mL) after the mood stabilizer had been maintained for at least 2 weeks. Subjects who achieved stability for 8 consecutive weeks on the adjunctive regimen (as assessed by the CGI-I scale and the establishment of a stable

treatment regimen) were randomized into Period 2 in a 1:1 ratio to ziprasidone plus the mood stabilizer or placebo plus the mood stabilizer to evaluate the maintenance of effect for up to an additional 6 months. Table 1 and Table 2 describe trial activities.

Table 1. Schedule of Events – Screening and Open-Label Stabilization Period 1

Event	Scr	Open-Label Stabilization Visits									
		BL	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10[a]	Week 12[a]	Week 14[a]	Week 16/ET[a]
ICD	X										
Medical history	X										
Physical exam and height	X										X
SCID-I	X										
Body weight and waist circumference	X	X			X		X		X		X
Blood pressure/pulse rate	X	X	X		X		X		X		X
Electrocardiogram	X	X[b]	X		X		X		X		X
Labs	X	X[c]			X				X		X
T4 and TSH	X				X				X		X
Prolactin	X				X						X
Lithium or VPA[d]	X	X		X	X		X		X		X
Pregnancy test[e]	X	X			X		X		X		X
UDS[e]	X	X			X				X		X
Pharmacogenomics sample[f]		X									
SADS-CB (MRS), MADRS	X	X	X	X	X		X		X		X
CGI-S	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X
PANSS		X			X		X		X		X
Cognition	X	X					X				X
Q-LES-Q, SDS, CSFQ[g]		X					X				X
S-ARS, BARS, AIMS		X			X		X				X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X

AIMS = Abnormal Involuntary Movement Scale; BARS = Brief Agitation Rating Scale; BL = Baseline; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CSFQ = Changes in Sexual Functioning Questionnaire; ET = end of therapy; ICD = informed consent document; IEC = independent ethics committee; IRB = institutional review board; MADRS = Montgomery Asberg Depression Rating Scale; MRS = Mania Rating Scale; PANSS = Positive and Negative Syndrome Scales; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; S-ARS = Simpson-Angus Scale; SADS-CB = Schedule for Affective Disorders and Schizophrenia-Change Bipolar; scr = screening; SCID-I = Structured Clinical Interview for DSM-IV; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition; SDS = Sheehan Disability Scale; T4 = thyroxine; TSH = thyroid stimulating hormone; UDS = urine drug screens; VPA = Divalproex Sodium.

a. Performed Week 16 assessments if subject qualified for randomization at Weeks 10, 12 or 14; otherwise, performed only assessments indicated for that visit. Visits 12-16 of open-label were performed, only as needed, for subjects to meet stabilization criteria after Week 10.
b. Performed in triplicate at Baseline.
c. Performed at Baseline only for subjects who started the mood stabilizer at the Screening visit. Screening labs were also performed for these subjects.
d. Performed as needed between Screening and Baseline visits for subjects initiating mood stabilizer at the Screening visit. Subjects had to be within documented therapeutic range for 2 weeks prior to entering open-label.
e. At Investigator's discretion, test could have been performed as needed between visits.
f. Optional and subject to IRB/IEC approval.
g. CSFQ was not performed during Period 2.

Table 2. Schedule of Activities – Double-Blind Maintenance Period 2

Event	Double-Blind Randomization Visits							
	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Physical exam and height					X			X
Body weight and waist circumference			X	X	X	X	X	X
Blood pressure / pulse Rate			X	X	X	X	X	X
Electrocardiogram			X	X	X	X	X	X
Labs			X		X			X
T4 and TSH			X		X			X
Prolactin			X					X
Lithium or VPA		X	X	X	X	X	X	X
Pregnancy test[a]			X	X	X	X	X	X
UDS[a]			X		X			X
SADS-CB (MRS) MADRS	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X
CGI-I	X	X	X	X	X	X	X	X
PANSS			X	X	X	X	X	X
Cognition			X	X		X		X
Q-LES-Q, SDS			X	X		X		X
S-ARS, BARS, AIMS				X		X		X
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X

AIMS = Abnormal Involuntary Movement Scale; BARS = Brief Agitation Rating Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; MADRS = Montgomery Asberg Depression Rating Scale; MRS = Mania Rating Scale; PANSS = Positive and Negative Syndrome Scales; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; S-ARS = Simpson-Angus Scale; SADS-CB = Schedule for Affective Disorders and Schizophrenia-Change Bipolar; SDS = Sheehan Disability Scale; T4 = thyroxine; TSH = thyroid stimulating hormone; UDS = urine drug screens; VPA = Divalproex Sodium.

a. At Investigator's discretion, test could have been performed as needed between visits.

Number of Subjects (Planned and Analyzed): It was planned to screen 1278 subjects with the expectation that 767 would be enrolled into the open-label period of the trial. An estimated 230 subjects were required for analysis.

A total of 584 subjects were treated in the open-label period; all 584 subjects were analyzed for adverse events (AEs) and laboratory data were analyzed in 482 subjects. A total of 239 subjects were treated in the double-blind period (127 subjects with ziprasidone and 112 subjects with placebo); 238 subjects were analyzed for efficacy, 239 subjects were analyzed for AEs, and laboratory data were analyzed in 230 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 years and older with a primary diagnosis of schizophrenia as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for bipolar I disorder

(presented with manic or mixed symptoms). Subjects suffering from ultra-fast rapid cycling or with significant cardiovascular disease including history of QT prolongation and/or congenital long QT syndrome were excluded.

Study Treatment: Ziprasidone (or matching placebo) was supplied as 20, 40, 60, and 80 mg capsules and was administered orally on a twice a day (BID) schedule with meals (preferably breakfast and supper).

Throughout the trial, subjects had to be maintained within the therapeutic serum concentration of lithium or valproic acid. On Day 1 of Period 1, open-label ziprasidone, 40 mg BID (80 mg/day), was added to the existing mood stabilizer. It was then increased to 60 mg BID or 80 mg BID on Day 2. Thereafter, the dose could be adjusted within the range of 40-80 mg BID on the basis of toleration and efficacy.

No dosage adjustments could be made to ziprasidone or the mood stabilizer during the 4 weeks prior to randomization, except for documented safety reasons. In addition, an adjustment to the mood stabilizer to maintain the therapeutic range could occur if the level went below or above the required therapeutic range or if the plasma concentrations of lithium or valproic acid changed by at least 0.2 mEq/L or 25 μg/mL, respectively, from previous therapeutic levels.

Subjects who were randomized in Period 2 to ziprasidone plus mood stabilizer remained on the dose level they received during the last 4 weeks of the open-label period. Subjects who were randomized to placebo plus the mood stabilizer were tapered off ziprasidone and onto matching placebo; the level of ziprasidone was decreased 20 mg BID every 2 days. The blind of the trial was maintained. After randomization, no adjustments to the treatment regimen were permitted for efficacy or symptom control; however, a down titration could have occurred for documented safety reasons.

Efficacy Endpoints: Primary Endpoint: TIME during the double-blind maintenance period.

Secondary Endpoints:

- Time to discontinuation for any reason during the double-blind period (key-secondary).
- Modified TIME during the double-blind period.
- Change from Baseline in the MRS.
- Change from Baseline in the CGI-S Score.
- CGI-I score.
- Change from Baseline in the MADRS.
- Change from Baseline in the PANSS Total score.
- Change from Baseline in the PANSS Positive Symptoms score.

- Change from Baseline in the PANSS Negative Symptoms score.

Modified TIME was a time to event variable similar to the primary and key secondary endpoint. In addition to discontinuations due to a mood episode requiring intervention, other discontinuations related to lack of persistent satisfactory treatment effect were included. These other events include discontinuations due to treatment related AEs, death due to treatment, or death due to disease under study. Modified TIME may be thought of as an endpoint covering the ground between the primary variable and the key secondary variable.

Safety Evaluations: AEs, clinical laboratory results, physical examination findings, blood pressure and pulse rate, height and body weight, body mass index, waist circumference, electrocardiogram results, movement disorder ratings on Simpson-Angus Rating Scale , Barnes Akathisia Rating Scale , and Abnormal Involuntary Movement Scale were evaluated.

Statistical Methods: The full analysis set consisted of the intent-to-treat (ITT) population, defined as those subjects randomly assigned to treatment in the double-blind period who took at least 1 dose of double-blind medication and who had at least 1 post randomization observation. The Per-Protocol (PP) analysis set included all subjects in the full analysis set who did not have major protocol violations. The safety population was defined as all subjects who received at least 1 dose of adjunctive ziprasidone (for the open-label period) and all subjects who received at least 1 dose of double-blind medication (for the double-blind period).

The primary endpoint (TIME during the double-blind maintenance period) analysis was based on the Kaplan-Meier product-limit estimator. P-values were obtained from the log-rank test for equality of survival curves over treatment groups. Kaplan-Meier survival curves were presented. The number of subjects at risk, number of events and number of censored observations were summarized, by treatment, at each visit. The relative risk of intervention through 3 and 6 months and the percentage of subjects maintained to 3 and 6 months post randomization were presented. The analyses on the primary endpoint (including sensitivity) were done using both the ITT and PP analysis sets.

The key secondary efficacy endpoint (time to discontinuation for any reason during the double-blind period), was analyzed using Kaplan-Meier product-limit estimator similar to that of the primary endpoint (the Modified TIME during the double-blind period was also analyzed in the same way as the key secondary endpoint).

P-values for survival analyses were obtained from the log-rank test for equality of survival curves over treatment groups.

Analysis of change during the double-blind period from the final visit in the open-label period in each of the following rating scales, the MRS, MADRS, CGI-S and PANSS (total score, positive symptom score and negative symptom score) was conducted using SAS PROC MIXED to fit a mixed model, repeated measures (MMRM) analysis of covariance with center and subject-within-center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects, and Baseline score (final open-label visit) as a covariate. Analysis during the double-blind period of CGI-I scores was conducted using

SAS PROC MIXED to fit a MMRM analysis of variance with center and subject-within-center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects.

RESULTS

Subject Disposition and Demography: Table 3 summarizes subject disposition. A total of 584 subjects were treated in the open-label stabilization period. In the double-blind randomization period, 127 subjects were treated with ziprasidone and 112 subjects were treated with placebo.

Table 3. Subject Disposition

Number (%) of Subjects	Open-Label Period	Double-Blind Period	
	Total	Ziprasidone	Placebo
Screened 1088			
Assigned to study treatment[a]	586	127	113
Treated	584	127	112
Completed	241 (41.3)	84 (66.1)	54 (48.2)
Discontinued	343 (58.7)	43 (33.9)	58 (51.8)
Reason for discontinuation			
Related to study drug	158 (27.1)	15 (11.8)	28 (25.0)
Lack of efficacy	31 (5.3)	9 (7.1)	22 (19.6)
Laboratory abnormality	1 (0.2)	1 (0.8)	0
Adverse event	126 (21.6)	5 (3.9)	6 (5.4)
Not related to study drug	189 (32.4)	28 (22.0)	30 (26.8)
Other	54 (9.2)	10 (7.9)	6 (5.4)
Laboratory abnormality	2 (0.3)	-	-
Adverse event	22 (3.8)	6 (4.7)	9 (8.0)
Lost to follow-up	35 (6.0)	3 (2.4)	6 (5.4)
Subject no longer willing to participate in study	76 (13.0)	9 (7.1)	9 (8.0)
Analyzed for efficacy			
Intent-to-treat	NA	127 (100)	111 (99.1)
Per protocol set	NA	99 (78.0)	90 (80.4)
Analyzed for safety			
Adverse events	584 (100.0)	127 (100.0)	112 (100.0)
Laboratory data	482 (82.5)	123 (96.9)	107 (95.5)

NA = not applicable; ITT = intent-to-treat, PP = per protocol.

a. One subject was randomized into the double-blind phase at 2 sites; therefore, the data associated with the corresponding subject were excluded from this summary, the ITT, PP, and safety analysis sets.

Table 4 below provides the demographics for subjects randomized to ziprasidone and placebo in the double-blind period. There were no apparent differences between the ziprasidone and placebo treatment groups in age, race, ethnicity, or weight and height distributions. The ziprasidone treatment group had a higher proportion of female subjects (about 60%) compared to the placebo treatment group (approximately 47%).

Table 4. Subject Demographics

Number (%) of Subjects	Ziprasidone			Placebo		
	Male N=51	Female N=76	Total N=127	Male N=60	Female N=53	Total N=113
Age (years)						
18-44	34 (66.7)	45 (59.2)	79 (62.2)	41 (68.3)	40 (75.5)	81 (71.7)
45-64	17 (33.3)	31 (40.8)	48 (37.8)	19 (31.7)	12 (22.6)	31 (27.4)
≥65	0	0	0	0	1 (1.9)	1 (0.9)
Mean	38.9	40.1	39.6	38.5	37.4	38.0
SD	13.2	11.7	12.3	11.3	11.9	11.6
Range	18-62	18-64	18-64	19-63	18-71	18-71
Race						
White	29 (56.9)	53 (69.7)	82 (64.6)	39 (65.0)	28 (52.8)	67 (59.3)
Black	0	5 (6.6)	5 (3.9)	1 (1.7)	5 (9.4)	6 (5.3)
Asian	20 (39.2)	11 (14.5)	31 (24.4)	18 (30.0)	11 (20.8)	29 (25.7)
Other	2 (3.9)	7 (9.2)	9 (7.1)	2 (3.3)	9 (17.0)	11 (9.7)
Ethnicity						
Hispanic/Latino	5 (9.8)	15 (19.7)	20 (15.7)	6 (10.0)	14 (26.4)	20 (17.7)
Not Hispanic/ Latino	46 (90.2)	61 (80.3)	107 (84.3)	54 (90.0)	39 (73.6)	93 (82.3)
Weight (kg)						
Mean	83.8	74.8	78.4	84.5	73.7	79.4
SD	22.0	16.1	19.1	23.2	23.6	23.9
Range	40.0–133.6	45.0–115.0	40–133.6	42.0–150.0	35.0–140.6	35.0–150.0
N	51 (100.0)	76 (100.0)	127 (100.0)	60 (100.0)	53 (100.0)	113 (100.0)
Height (cm)						
Mean	172.7	161.7	166.1	175.3	160.2	168.3
SD	9.4	9.7	11.0	9.4	8.2	11.6
Range	155.0–192.0	132.0–180.0	132.0–192.0	155.0-198.0	133.0–77.8	133.0–198.0
N	51 (100.0)	76 (100.0)	127 (100.0)	60 (100.0)	53 (100.0)	113 (100.0)

N = number of subjects; SD = standard deviation.

Efficacy Results: Based on the primary analysis, the log-rank test for equality of survival curves across treatment groups, the TIME was statistically significant in favor of ziprasidone (p=0.0104), during 6 months of double-blind treatment. Only 19.7% (25/127) of the ziprasidone subjects required intervention for a mood episode compared with 32.4% (36/111) of the placebo subjects. Table 5 below summarizes the results from the primary analysis for the TIME for subjects in the double-blind period.

Table 5. Primary Analysis – Log-Rank Test for Time to Intervention for Mood Episode (ITT Analysis—Double-Blind)

Variable	Ziprasidone N=127	Placebo N=111
Subjects censored (%)	102 (80.3)	75 (67.6)
Subjects with intervention for mood episode (%)	25 (19.7)	36 (32.4)
25th percentile (95% CI)	- (146.0, -)	82.00 (27.0, 140.0)
50th percentile (95% CI)[a]	-	-
75th percentile (95% CI)	-	-
Mean survival time (days)	172.2	143.1
Treatment effect vs. placebo (p-value)[b]	0.0104	-

CI = confidence interval; ITT = intent-to-treat, N = total number of subjects; vs = versus.
a. 50th percentile is the median Time to Intervention for a Mood Episode.
b. p-value was calculated from a log-rank test at a 0.05 level of significance.

Secondary Analyses:

Time to Discontinuation: Based on the log-rank test for equality of survival curves across treatment groups, the time to discontinuation for any reason (the key secondary endpoint) was statistically significant in favor of ziprasidone (p=0.0047) during 6 months of double-blind treatment. While 33.9% (43/127) of the ziprasidone subjects discontinued for any reason, 51.4% of the (57/111) placebo subjects discontinued for any reason. Table 6 below, summarizes the results from the key secondary analysis for the time to discontinuation for any reason in the double-blind period (ITT).

Table 6. Log-Rank Test for Time to Discontinuation for Any Reason During Double-Blind Period (ITT Analysis Set)

Variable	Ziprasidone N=127	Placebo N=111
Subjects censored (%)	84 (66.1)	54 (48.6)
Subjects discontinued for any reason (%)	43 (33.9)	57 (51.4)
25th percentile (95% CI)	88.0 (56.0, 165.0)	29.00 (25.0, 65.0)
50th percentile (95% CI)[a]	-	160.00 (103.0, -)
75th percentile (95% CI)	-	-
Mean survival time (days)	153.5	123.3
Treament effect vs. placebo (p-value)[b]	0.0047	-

CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; vs = versus.
a. 50th percentile is the median time to discontinuation.
b. p-value was calculated from a log-rank test at a 0.05 level of significance.

Modified TIME: Based on the log-rank test for equality of survival curves across treatment groups, the Modified TIME was statistically significant in favor of the ziprasidone group (p=0.0205, log-rank test, Table 7). Only 22.8% (29/127) of the ziprasidone subjects discontinued per the Modified TIME criteria compared with 34.2% of the (38/111) of the placebo subjects.

Table 7. Log-rank Test for Modified Time to Intervention for Mood Episode (ITT Analysis Set)

Variable	Ziprasidone (N=127)	Placebo (N=111)
Subjects censored (%)	98 (77.2)	73 (65.8)
Subjects with modified intervention for mood episode (%)	29 (22.8)	38 (34.2)
25th percentile (95% CI)	- (111.0, -)	63.00 (27.0, 114.0)
50th percentile (95% CI)[a]	-	-
75th percentile (95% CI)	-	-
Mean survival time (days)	168.1	140.3
Treatment effect vs. placebo (p-value)[b]	0.0205	-

Modified TIME variable was calculated considering discontinuations for treatment related adverse events, death due to drug, or death due to disease under study as events rather than as censored observations.
CI = confidence interval; ITT = intent-to-treat; N = total number of subjects, vs = versus.
a. 50th percentile is the median Modified Time to Intervention for a Mood Episode.
b. p-value was calculated from a log-rank test.

MRS Score and Change From Baseline: The descriptive statistics for the change from Baseline in MRS score by visit are summarized in Table 8. Results from the repeated measures mixed model for the change from Baseline in MRS score during the double-blind period are presented in Table 9. For all visits beginning at Week 12, the decrease from Baseline in MRS score for the ziprasidone group was statistically significantly superior to the placebo group, consistent with the maintenance of treatment effect in the ziprasidone treated group.

Table 8. MRS Score and Change From Baseline by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	4.5	4.7	3	(3.66, 5.33)	111	4.0	4.7	2	(3.09, 4.87)
Week 1	121	4.1	5.2	2	(3.16, 5.03)	106	4.6	5.3	3	(3.59, 5.65)
Week 1 Chg BL	121	-0.2	3	0	(-0.79, 0.29)	106	0.8	5.1	0	(-0.23, 1.75)
Week 2	116	4.1	5.1	2	(3.13, 5.01)	95	3.6	4.9	2	(2.59, 4.57)
Week 2 Chg BL	116	-0.4	4.2	0	(-1.17, 0.38)	95	-0.1	4.7	0	(-1.01, 0.91)
Week 4	117	3.8	5.1	2	(2.91, 4.77)	95	3.9	5.5	2	(2.79, 5.03)
Week 4 Chg BL	117	-0.6	3.7	0	(-1.28, 0.08)	95	0.2	5.4	0	(-0.87, 1.33)
Week 8	107	4.1	5.9	2	(2.96, 5.21)	79	4.2	6.1	2	(2.79, 5.54)
Week 8 Chg BL	107	-0.3	5.7	0	(-1.40, 0.77)	79	0.8	5.4	0	(-0.42, 2.01)
Week 12	98	3.2	4.7	1	(2.29, 4.18)	70	4.7	8.2	1	(2.70, 6.62)
Week 12 Chg BL	98	-1.0	4.3	-1	(-1.84, -0.12)	70	1.2	8.2	0	(-0.79, 3.13)
Week 16	94	2.7	4.0	1	(1.92, 3.57)	65	4.6	6.0	2	(3.08, 6.06)
Week 16 Chg BL	94	-1.4	4.3	-1	(-2.33, -0.56)	65	1.2	6.3	0	(-0.39, 2.76)
Week 20	84	2.9	5.7	1	(1.71, 4.17)	58	3.8	4.6	2	(2.55, 4.97)
Week 20 Chg BL	84	-1.1	6.5	-1	(-2.52, 0.30)	58	0.2	5.1	0	(-1.18, 1.52)
Week 24	85	2.9	4.8	1	(1.88, 3.96)	53	3.4	4.5	1	(2.19, 4.68)
Week 24 Chg BL	85	-1.1	5.5	-1	(-2.33, 0.07)	53	0.3	4.2	0	(-0.85, 1.45)
ET/OW	25	4.1	5.3	1	(1.91, 6.33)	24	10.9	11.0	9	(6.22, 15.53)
ET/OW Chg BL	25	-0.4	4.7	0	(-2.31, 1.59)	24	5.0	11.6	1	(0.12, 9.96)

Baseline was the last available observation from the open-label period.
Windowing is applied to all visits, including early termination, based on study day of treatment.
CI = confidence interval; Chg BL = change from Baseline; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; MRS = Mania Rating Scale; N = total number of subjects; SD = standard deviation.

Table 9. Secondary Analysis - Change in MRS Score During Double-Blind Period (ITT Analysis Set)

Visit	Ziprasidone		
	Difference From Placebo LS Mean (SE)	95% CI for the Difference From Placebo	p-value
Week 1	-0.85 (0.55)	(-1.93, 0.24)	0.1247
Week 2	-0.20 (0.62)	(-1.42, 1.02)	0.7515
Week 4	-0.63 (0.62)	(-1.84, 0.58)	0.3074
Week 8	-1.25 (0.71)	(-2.64, 0.13)	0.0758
Week 12	-1.98 (0.82)	(-3.59, -0.37)	0.0162
Week 16	-3.01 (0.83)	(-4.64, -1.38)	0.0003
Week 20	-2.21 (0.98)	(-4.13, -0.29)	0.0242
Week 24	-1.71 (0.71)	(-3.10, -0.32)	0.0161

Results were obtained from a mixed effects repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and Baseline score (final open-label visit) as a covariate.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CI = confidence interval; ITT = intent-to-treat; LS Mean = least squares mean; MRS = Mania Rating Scale; SE = standard error.

CGI-S Score and Change From Baseline: The descriptive statistics for the change from Baseline in CGI-S score by visit are summarized in Table 10. Results from the repeated measures mixed model for the change from Baseline in CGI-S score are presented in Table 11. Except for Week 1 when the ziprasidone-treated subjects had a significantly lower CGI-S severity score than the placebo-treated subjects (p=0.0088), there were no significant differences in the change from Baseline in CGI-S scores between the ziprasidone and placebo groups.

Table 10. CGI-S Score and Change From Baseline by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	2.2	0.9	2	(2.05, 2.36)	111	2.2	0.9	2	(2.07, 2.41)
Week 1	122	2.3	1.0	2	(2.10, 2.44)	106	2.5	1.1	3	(2.33, 2.77)
Week 1 Chg BL	122	0.1	0.7	0	(-0.06, 0.19)	106	0.3	1.0	0	(0.11, 0.50)
Week 2	117	2.4	1.0	2	(2.21, 2.58)	95	2.5	1.2	2	(2.24, 2.73)
Week 2 Chg BL	117	0.2	0.9	0	(-0.00, 0.31)	95	0.2	1.0	0	(0.02, 0.44)
Week 4	117	2.2	1.0	2	(2.03, 2.38)	95	2.3	1.1	2	(2.09, 2.54)
Week 4 Chg BL	117	-0.0	0.7	0	(-0.15, 0.11)	95	0.1	0.9	0	(-0.07, 0.30)
Week 8	107	2.2	1.0	2	(2.03, 2.42)	79	2.0	0.9	2	(1.82, 2.23)
Week 8 Chg BL	107	-0.0	0.8	0	(-0.17, 0.15)	79	-0.1	0.8	0	(-0.29, 0.08)
Week 12	98	2.1	1.0	2	(1.92, 2.32)	70	2.2	1.1	2	(1.91, 2.44)
Week 12 Chg BL	98	-0.1	0.9	0	(-0.29, 0.08)	70	0.0	1.1	0	(-0.23, 0.29)
Week 16	94	2.1	1.0	2	(1.92, 2.32)	65	2.2	1.0	2	(1.92, 2.42)
Week 16 Chg BL	94	-0.1	0.9	0	(-0.31, 0.07)	65	0.0	1.1	0	(-0.23, 0.32)
Week 20	83	2.0	0.9	2	(1.84, 2.26)	58	1.9	0.8	2	(1.69, 2.14)
Week 20 Chg BL	83	-0.1	0.9	0	(-0.33, 0.06)	58	-0.2	1.0	0	(-0.47, 0.05)
Week 24	85	2.1	1.0	2	(1.85, 2.26)	53	1.9	0.9	2	(1.67, 2.14)
Week 24 Chg BL	85	-0.2	1.0	0	(-0.38, 0.05)	53	-0.2	1.0	0	(-0.51, 0.02)
ET/OW	23	2.3	1.4	2	(1.71, 2.89)	21	3.0	1.7	3	(2.22, 3.78)
ET/OW Chg BL	23	0.0	1.5	0	(-0.64, 0.64)	21	1.0	1.9	0	(0.07, 1.83)

Baseline was the last available observation from the open-label period.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CI = confidence interval; CGI-S = Clinical Global Impression-Severity; Chg BL = change from Baseline; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; N = total number of subjects; SD = standard deviation.

Table 11. Secondary Analysis - Change in CGI-S Score During Double-Blind Period (ITT Analysis Set)

Visit	Ziprasidone		
	Difference From Placebo LS Mean (SE)	95% CI for the Difference From Placebo	p-value
Week 1	-0.24 (0.09)	(-0.41, -0.06)	0.0088
Week 2	-0.11 (0.13)	(-0.36, 0.13)	0.3677
Week 4	-0.18 (0.10)	(-0.39, 0.02)	0.0734
Week 8	-0.01 (0.11)	(-0.23, 0.21)	0.9166
Week 12	-0.14 (0.13)	(-0.41, 0.12)	0.2791
Week 16	-0.23 (0.16)	(-0.54, 0.08)	0.1460
Week 20	-0.05 (0.15)	(-0.35, 0.25)	0.7301
Week 24	-0.03 (0.14)	(-0.31, 0.24)	0.8162

Results were obtained from a mixed effects repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and Baseline score (final open-label visit) as a covariate.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CGI-S = Clinical Global Impression-Severity; CI = confidence interval; ITT = intent-to-treat;
LS Mean = least squares mean; SE = standard error.

CGI-I Score by Visit: The descriptive statistics for the CGI-I score by visit are summarized in Table 12. Results from the repeated measures mixed model for the CGI-I score are presented in Table 13. The CGI-I score for ziprasidone group was significantly lower (ie, indicating greater improvement) than the placebo group during Week 1 (p=0.0013), Week 4 (p=0.0188), and Week 16 (p=0.0085) of the double-blind period.

Table 12. CGI-I Score by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	1.8	0.8	2	(1.70, 1.97)	111	1.8	0.8	2	(1.65, 1.94)
Week 1	122	2.3	1.2	2	(2.08, 2.52)	106	2.8	1.6	2	(2.44, 3.06)
Week 2	117	2.4	1.4	2	(2.18, 2.68)	95	2.6	1.6	2	(2.28, 2.92)
Week 4	117	2.3	1.2	2	(2.04, 2.49)	95	2.5	1.5	2	(2.21, 2.82)
Week 8	107	2.3	1.4	2	(2.03, 2.55)	79	2.2	1.2	2	(1.89, 2.44)
Week 12	98	2.2	1.3	2	(1.93, 2.46)	70	2.2	1.4	2	(1.91, 2.58)
Week 16	94	2.3	1.4	2	(1.97, 2.56)	65	2.5	1.5	2	(2.11, 2.87)
Week 20	83	2.1	1.4	2	(1.85, 2.44)	58	2.1	1.4	2	(1.76, 2.52)
Week 24	85	2.2	1.3	2	(1.89, 2.47)	53	2.2	1.4	2	(1.83, 2.58)
ET/OW	23	2.6	1.9	2	(1.76, 3.37)	21	3.5	2.1	3	(2.58, 4.46)

Baseline was the last available observation from the open-label period.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CGI-I = Clinical Global Impression-Improvement; CI = confidence interval; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; N = total number of subjects; SD = standard deviation.

Table 13. Secondary Analysis - CGI-I Score During Double-Blind Period (ITT Analysis Set)

Visit	Ziprasidone		
	Difference From Placebo LS Mean (SE)	95% CI for the Difference From Placebo	p-value
Week 1	-0.48 (0.15)	(-0.77, -0.19)	0.0013
Week 2	-0.27 (0.17)	(-0.61, 0.07)	0.1167
Week 4	-0.40 (0.17)	(-0.73, -0.07)	0.0188
Week 8	-0.15 (0.16)	(-0.46, 0.16)	0.3413
Week 12	-0.18 (0.16)	(-0.49, 0.14)	0.2760
Week 16	-0.51 (0.19)	(-0.89, -0.13)	0.0085
Week 20	-0.27 (0.18)	(-0.62, 0.08)	0.1317
Week 24	-0.25 (0.18)	(-0.61, 0.11)	0.1666

Results were obtained from a mixed effects repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and Baseline score (final open-label visit) as a covariate.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CGI-I = Clinical Global Impression-Improvement; CI = confidence interval; ITT = intent-to-treat; LS Mean = least squares mean; SE = standard error.

MADRS Total Score and Change From Baseline by Visit: The descriptive statistics for the change from Baseline in MADRS total score by visit are summarized in Table 14. Results

from the repeated measures mixed model for the change from Baseline in MADRS score are presented in Table 15. Except for Week 1 when the ziprasidone treated subjects had a significantly (p=0.0023) lower total MADRS score than the placebo-treated subjects, there were no significant differences in the change from Baseline in MADRS total score between ziprasidone and placebo groups.

Table 14. MADRS Total Score and Change from Baseline by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	5.7	6.6	3	(4.56, 6.89)	111	4.7	6.1	3	(3.59, 5.89)
Week 1	121	5.5	5.9	4	(4.46, 6.57)	106	7.5	9.4	4	(5.70, 9.34)
Week 1 Chg BL	121	-0.2	4.9	0	(-1.06, 0.71)	106	2.7	7.3	0	(1.30, 4.11)
Week 2	117	7.0	8.5	4	(5.42, 8.53)	95	7.5	9.2	4	(5.61, 9.34)
Week 2 Chg BL	117	1.1	7.4	0	(-0.27, 2.44)	95	2.7	7.1	0	(1.25, 4.12)
Week 4	117	5.5	7.0	2	(4.22, 6.77)	95	6.0	8.3	2	(4.34, 7.70)
Week 4 Chg BL	117	-0.3	5.3	0	(-1.26, 0.68)	95	1.6	6.0	0	(0.42, 2.86)
Week 8	107	6.1	7.8	2	(4.62, 7.62)	79	4.6	7.0	2	(3.07, 6.22)
Week 8 Chg BL	107	0.4	5.9	0	(-0.72, 1.55)	79	0.4	5.3	0	(-0.75, 1.64)
Week 12	98	6.6	7.3	3	(5.11, 8.02)	70	4.4	6.2	2	(2.89, 5.83)
Week 12 Chg BL	98	1.1	5.9	0	(-0.12, 2.22)	70	0.6	5.4	0	(-0.64, 1.93)
Week 16	94	6.9	8.0	4	(5.27, 8.54)	65	4.3	6.0	2	(2.81, 5.77)
Week 16 Chg BL	94	1.2	6.3	0	(-0.09, 2.47)	65	0.4	3.9	0	(-0.53, 1.39)
Week 20	84	5.8	6.7	4	(4.31, 7.23)	58	3.5	5.5	1	(2.05, 4.95)
Week 20 Chg BL	84	0.5	5.6	0	(-0.77, 1.67)	58	-0.2	4.9	0	(-1.48, 1.11)
Week 24	85	5.7	7.5	2	(4.11, 7.35)	53	4.6	7.2	1	(2.61, 6.56)
Week 24 Chg BL	85	0.4	6.4	0	(-0.94, 1.84)	53	1.0	6.5	0	(-0.83, 2.76)
ET/OW	25	10.1	11.8	7	(5.22, 14.94)	26	8.5	7.8	7	(5.30, 11.62)
ET/OW Chg BL	25	2.9	13.4	0	(-2.59, 8.43)	26	2.5	6.3	2	(-0.09, 5.01)

Baseline was the last available observation from the open-label period.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CI = confidence interval; Chg BL = change from Baseline; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; MADRAS = Montgomery Asberg Depression Rating Scale; N = total number of subjects; SD = standard deviation.

Table 15. Secondary Analysis - Change in MADRS Total Score during Double-Blind Period (ITT Analysis Set)

Visit	Ziprasidone		
	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	p-value
Week 1	-2.29 (0.75)	(-3.76, -0.82)	0.0023
Week 2	-1.34 (0.91)	(-3.12, 0.45)	0.1412
Week 4	-1.49 (0.87)	(-3.19, 0.21)	0.0861
Week 8	-0.43 (0.82)	(-2.05, 1.18)	0.5992
Week 12	0.41 (0.76)	(-1.08, 1.90)	0.5873
Week 16	0.97 (0.78)	(-0.55, 2.49)	0.2116
Week 20	0.90 (0.68)	(-0.43, 2.23)	0.1847
Week 24	-0.00 (0.82)	(-1.62, 1.62)	0.9972

Results were obtained from a mixed effects repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and Baseline score (final open-label visit) as a covariate.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CI = confidence interval; ITT = intent-to-treat; MADRAS = Montgomery Asberg Depression Rating Scale; LS Mean = least squares mean; SE = standard error.

PANSS Total Score: The descriptive statistics for the change from Baseline in PANSS total score, PANSS positive symptom subscale scores and PANSS negative symptom subscale scores by visit are summarized in Table 16, Table 17 and Table 18, respectively. Results from the repeated measures mixed model for the change from Baseline in PANSS total score, PANSS positive symptom subscale scores and PANSS negative symptom subscale scores are presented in Table 19. There were no significant differences in the change from Baseline in PANSS total score, PANSS positive symptom subscale scores (except Week 16) or PANSS negative symptom subscale scores (except Week 8) between ziprasidone and placebo groups during any study visits.

Table 16. PANSS Total Score and Change From Baseline by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	38.4	9.3	35	(36.81, 40.08)	111	37.5	8.9	35	(35.84, 39.17)
Week 4	123	39.0	11.6	34	(36.90, 41.03)	98	38.6	8.9	35	(36.83, 40.42)
Week 4 Chg BL	123	0.4	8.7	0	(-1.16, 1.97)	98	1.5	6.9	0	(0.12, 2.88)
Week 8	107	38.5	12.4	33	(36.16, 40.92)	79	36.4	7.7	34	(34.64, 38.10)
Week 8 Chg BL	107	-0.1	8.3	0	(-1.72, 1.48)	79	-0.8	6.0	-1	(-2.19, 0.49)
Week 12	98	38.1	10.4	33	(35.98, 40.17)	70	37.3	9.7	33	(34.95, 39.59)
Week 12 Chg BL	98	-0.1	6.5	-1	(-1.39, 1.23)	70	0.3	9.4	-2	(-1.90, 2.56)
Week 16	94	38.0	10.7	34	(35.84, 40.22)	65	37.8	9.4	35	(35.49, 40.14)
Week 16 Chg BL	94	-0.0	7.1	-1	(-1.50, 1.42)	65	0.7	8.7	0	(-1.46, 2.84)
Week 20	84	37.5	9.0	34	(35.58, 39.49)	58	35.4	7.0	33	(33.54, 37.22)
Week 20 Chg BL	84	-0.2	7.4	-1	(-1.78, 1.42)	58	-1.0	6.1	-1	(-2.57, 0.64)
Week 24	85	36.5	9.0	33	(34.52, 38.42)	53	35.8	7.7	33	(33.73, 37.97)
Week 24 Chg BL	85	-0.6	8.0	-1	(-2.36, 1.09)	53	-0.9	7.4	-1	(-2.98, 1.10)
ET/OW	14	37.2	7.7	36	(32.78, 41.65)	25	45.7	13.9	43	(39.99, 51.45)
ET/OW Chg BL	14	-1.8	7.5	-3	(-6.10, 2.52)	25	5.9	12.8	4	(0.64, 11.20)

Baseline was the last available observation from the open-label period.
Windowing is applied to all visits, including early termination, based on study day of treatment.
Chg BL = change from Baseline; CI = confidence interval; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; N = total number of subjects; PANSS = Positive and Negative Syndrome Scales; SD = standard deviation.

Table 17. PANSS Positive Scale and Change From Baseline by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	8.4	2.2	7	(7.99, 8.78)	111	8.3	2.4	7	(7.90, 8.79)
Week 4	123	8.4	2.3	7	(8.01, 8.83)	98	8.3	2.1	7	(7.86, 8.71)
Week 4 Chg BL	123	0.0	1.6	0	(-0.27, 0.30)	98	0.1	1.4	0	(-0.22, 0.36)
Week 8	107	8.4	2.5	7	(7.89, 8.84)	79	8.2	2.1	7	(7.68, 8.62)
Week 8 Chg BL	107	-0.2	2.0	0	(-0.55, 0.23)	79	-0.2	1.9	0	(-0.60, 0.25)
Week 12	98	8.0	2.2	7	(7.59, 8.49)	70	8.6	3.3	7	(7.87, 9.42)
Week 12 Chg BL	98	-0.3	1.7	0	(-0.61, 0.06)	70	0.3	3.3	0	(-0.46, 1.12)
Week 16	94	7.9	1.7	7	(7.58, 8.29)	65	8.4	2.0	7	(7.88, 8.86)
Week 16 Chg BL	94	-0.4	1.8	0	(-0.72, -0.00)	65	0.0	2.1	0	(-0.50, 0.56)
Week 20	84	8.0	2.4	7	(7.50, 8.54)	58	8.1	2.2	7	(7.55, 8.69)
Week 20 Chg BL	84	-0.2	2.2	0	(-0.65, 0.31)	58	-0.1	2.1	0	(-0.61, 0.47)
Week 24	85	7.8	1.9	7	(7.43, 8.26)	53	8.3	2.1	7	(7.70, 8.86)
Week 24 Chg BL	85	-0.2	2.2	0	(-0.67, 0.29)	53	-0.1	2.1	0	(-0.72, 0.46)
ET/OW	14	8.1	1.4	7	(7.24, 8.90)	25	10.8	5.2	8	(8.62, 12.90)
ET/OW Chg BL	14	-0.7	2.3	0	(-2.06, 0.63)	25	1.9	5.0	0	(-0.16, 4.00)

Baseline was the last available observation from the open-label period.
Windowing was applied to all visits, including early termination, based on study day of treatment.
Chg BL = change from Baseline; CI = confidence interval; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; N = total number of subjects; PANSS = Positive and Negative Syndrome Scales; SD = standard deviation.

Table 18. PANSS Negative Scale and Change From Baseline by Visit During Double Blind Period (ITT Analysis Set)

Visit	Ziprasidone					Placebo				
	N	Mean	SD	Median	(95% CI)	N	Mean	SD	Median	(95% CI)
Baseline	127	8.8	2.8	7	(8.28, 9.25)	111	8.3	2.3	7	(7.87, 8.73)
Week 4	123	9.0	3.5	7	(8.39, 9.65)	98	8.6	2.5	7	(8.10, 9.11)
Week 4 Chg BL	123	0.2	3.1	0	(-0.33, 0.76)	98	0.4	2.2	0	(-0.08, 0.79)
Week 8	107	9.1	3.9	7	(8.33, 9.82)	79	8.1	1.9	7	(7.67, 8.51)
Week 8 Chg BL	107	0.2	3.2	0	(-0.37, 0.86)	79	-0.1	1.8	0	(-0.52, 0.27)
Week 12	98	9.0	3.1	7	(8.34, 9.60)	70	8.2	2.0	7	(7.72, 8.68)
Week 12 Chg BL	98	0.1	2.5	0	(-0.41, 0.59)	70	0.1	2.1	0	(-0.37, 0.62)
Week 16	94	9.1	3.7	7	(8.35, 9.89)	65	8.7	2.9	7	(8.00, 9.42)
Week 16 Chg BL	94	0.3	3.1	0	(-0.33, 0.95)	65	0.4	2.6	0	(-0.26, 1.03)
Week 20	84	8.8	2.8	7	(8.14, 9.36)	58	7.7	1.6	7	(7.33, 8.15)
Week 20 Chg BL	84	-0.0	2.3	0	(-0.54, 0.45)	58	-0.4	1.8	0	(-0.83, 0.11)
Week 24	85	8.6	2.9	7	(7.96, 9.19)	53	8.0	1.9	7	(7.44, 8.48)
Week 24 Chg BL	85	-0.1	2.6	0	(-0.62, 0.50)	53	-0.1	2.1	0	(-0.71, 0.45)
ET/OW	14	8.1	2.2	7	(6.86, 9.42)	25	9.5	3.7	8	(7.93, 11.03)
ET/OW Chg BL	14	0.0	1.1	0	(-0.64, 0.64)	25	0.7	3.3	0	(-0.63, 2.07)

Baseline was the last available observation from the open-label period.
Windowing was applied to all visits, including early termination, based on study day of treatment.
Chg BL = change from Baseline; CI = confidence interval; ET/OW = Early Termination or Out of Window visit; ITT = intent-to-treat; N = total number of subjects; PANSS = Positive and Negative Syndrome Scales; SD = standard deviation.

Table 19. Secondary Analysis – Change in PANSS Total Score During Double-Blind Period (ITT Analysis Set)

Visit	Ziprasidone		
	Difference From Placebo LS Mean (SE)	95% CI for the Difference From Placebo	p-value
Total PANSS			
Week 4	-0.49 (0.93)	(-2.31, 1.32)	0.5954
Week 8	0.89 (0.93)	(-0.94, 2.71)	0.3414
Week 12	0.04 (1.23)	(-2.37, 2.45)	0.9745
Week 16	-0.85 (1.47)	(-3.73, 2.03)	0.5627
Week 20	0.36 (1.10)	(-1.79, 2.52)	0.7410
Week 24	-0.04 (0.88)	(-1.76, 1.68)	0.9632
PANSS positive scale			
Week 4	0.01 (0.22)	(-0.41, 0.44)	0.9538
Week 8	0.05 (0.25)	(-0.45, 0.54)	0.8541
Week 12	-0.52 (0.32)	(-1.16, 0.12)	0.1084
Week 16	-0.56 (0.27)	(-1.08, -0.03)	0.0380
Week 20	-0.39 (0.35)	(-1.08, 0.30)	0.2649
Week 24	-0.32 (0.27)	(-0.86, 0.21)	0.2394
PANSS negative scale			
Week 4	0.07 (0.29)	(-0.50, 0.64)	0.8117
Week 8	0.51 (0.26)	(0.01, 1.02)	0.0443
Week 12	0.29 (0.28)	(-0.26, 0.83)	0.3039
Week 16	0.00 (0.46)	(-0.91, 0.91)	0.9953
Week 20	0.44 (0.32)	(-0.18, 1.07)	0.1653
Week 24	0.18 (0.32)	(-0.45, 0.81)	0.5771

Results were obtained from a mixed effects repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and Baseline score (final open-label visit) as a covariate.
Windowing was applied to all visits, including early termination, based on study day of treatment.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; PANSS = Positive and Negative Syndrome Scales; SE = standard error.

Safety Results:

Treatment Emergent AE (All Causality): The incidence of all causality, treatment-emergent AEs (TEAEs) occurring in ≥5% of subjects is summarized for the open-label period in Table 20 and for the double-blind period in Table 21.

Table 20. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects by System Organ Class (All Causalities) During the Open-Label Period

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA Preferred Term	Total (N=584)
Gastrointestinal disorders	
Nausea	42 (7.2)
General disorders and administration site conditions	
Fatigue	44 (7.5)
Nervous disorders	
Akathisia	47 (8.0)
Dizziness	49 (8.4)
Headache	32 (5.5)
Sedation	134 (22.9)
Somnolence	99 (17.0)
Tremor	73 (12.5)
Psychiatric disorders	
Insomnia	59 (10.1)

SAEs and AEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAEs = serious adverse events.

Table 21. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects in Either Treatment Group by System Organ Class (All Causalities) During the Double-Blind Period

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA Preferred Term	Ziprasidone (N=127)	Placebo (N=112)
Nervous system disorders		
Tremor	8 (6.3)	4 (3.6)
Psychiatric disorders		
Insomnia	7 (5.5)	12 (10.7)
Mania	3 (2.4)	8 (7.1)
Infections and infestations		
Upper respiratory tract infection	5 (3.9)	6 (5.4)

SAEs and AEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAEs = serious adverse events.

Treatment Emergent AEs (Treatment-Related): The incidence of treatment-emergent, treatment-related AEs occurring in ≥5% of subjects are summarized for the open-label period in Table 22 and for the double-blind period in Table 23.

Table 22. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects by System Organ Class (Treatment Related) During the Open-Label Period

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA Preferred Term	Total (N=584)
Gastrointestinal disorders	85 (14.6)
Nausea	37 (6.3)
General disorders and administration site conditions	68 (11.6)
Fatigue	42 (7.2)
Nervous system disorders	340 (58.2)
Akathisia	47 (8.0)
Dizziness	45 (7.7)
Sedation	132 (22.6)
Somnolence	95 (16.3)
Tremor	66 (11.3)
Psychiatric disorders	101 (17.3)
Insomnia	39 (6.7)

Includes data up to 6 days after last dose of study drug.
MedDRA (version11.0) coding dictionary applied.
SAEs and AEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAEs = serious adverse events.

Table 23. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects in Either Treatment Group by System Organ Class (Treatment-Related) During the Double-Blind Period

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA Preferred Term	Ziprasidone (N=127)	Placebo (N=112)
Nervous system disorders	20 (15.7)	13 (11.6)
Tremor	7 (5.5)	4 (3.6)
Psychiatric disorders	9 (7.1)	19 (17.0)
Insomnia	3 (2.4)	7 (6.3)

Includes data up to 6 days after last dose of study drug.
MedDRA (version 11.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAEs = serious adverse events.

Serious Adverse Events (SAEs): During the open-label period, a total of 21 subjects were reported to have a SAE while on ziprasidone (Table 24).

Table 24. Serious Adverse Events by Mood Stabilizer (Open-Label Period)

Serial Number	MedDRA Preferred Term	Action Taken	Outcome	Causality
Ziprasidone + Valproic Acid				
1	Psychiatric decompensation	Discontinued	Resolved	DUS
2	Suicidal ideation	Discontinued	Resolved	DUS
	Bipolar disorder	Discontinued	Resolved	DUS
3	Bipolar disorder	Discontinued	Resolved	DUS
4	Thrombophlebitis	Discontinued	Resolved	Other illness
5	Chronic obstructive pulmonary disease	None	Resolved	Other
6	Suicidal ideation	None	Resolved	DUS
7	Influenza	Treatment given	Resolved	Other
8	Dystonia	None	Resolved	Study drug
9	Depression	Discontinued	Resolved	DUS
10	Bipolar 1 disorder	None	Resolved	DUS
	Bipolar 1 disorder	None	Resolved	DUS
11	Affect lability	None	Resolved	DUS
12	Pregnancy[a]	Discontinued	Resolved	Other
13	Mania	Discontinued	Resolved	DUS
Ziprasidone + Lithium				
14	Suicidal ideation	Discontinued	Resolved	DUS
15	Suicide attempt	Ziprasidone dose increased	Resolved	DUS
16	Pregnancy[a]	Discontinued	Resolved	Other
17	Bipolar 1 disorder	Discontinued	Resolved	DUS
18	Psychotic disorder	None	Resolved	Other
19	Anxiety	Discontinued	Resolved	DUS
	Depression, suicidal	Discontinued	Resolved	DUS
20	Mania	Discontinued	Resolved	DUS
	Psychotic disorder	Discontinued	Resolved	Study drug
21	Suicidal ideation	Treatment given	Resolved	DUS

MedDRA 11.0 coding dictionary applied.
DUS = disease under study; MedDRA = Medical Dictionary for Regulatory Activities.
a. Pregnancy is not normally considered a serious adverse event, although it was considered to be a serious event by the Investigators in this study.

During the double-blind period, a total of 7 subjects reported SAEs (3 subjects randomized to ziprasidone and 4 to placebo; (Table 25).

Table 25. Serious Adverse Events by Study Drug Assignment and Mood Stabilizer (Double-Blind Period)

Serial Number	MedDRA Preferred Term	Action Taken	Outcome	Causality
Ziprasidone + Valproic Acid				
1	Suicidal ideation	Discontinued	Resolved	DUS
2	Suicidal ideation	Discontinued	Resolved	Other
3	Arrythmia[a]	Discontinued	Resolved	Study drug
Placebo + Lithium				
4	Mania	Discontinued	Resolved	Other
5	Mania	Discontinued	Resolved	Other
6	Mania	Discontinued	Resolved	DUS
Placebo + Valproic Acid				
7	Hypomania	None	Resolved	DUS

MedDRA 11.0 coding dictionary applied.
DUS = disease under study; MedDRA= Medical Dictionary for Regulatory Activities.
a. Ventricular extrasystole.

Discontinuation: There were no temporary discontinuations in the double-blind period; however, 17 subjects had a reduction in the dose of study drug: 8 in the ziprasidone group, and 9 in the placebo group.

During the open-label period, a total of 145 subjects discontinued the study due to all causality AEs. Of these, 124 subjects permanently discontinued due to AEs related to study drug. Three subjects discontinued in the open-label period due to laboratory abnormalities. The Investigator considered the AEs of increased alanine aminotransferase and creatinine for 1 subject to be related to study drug. The most common reasons for discontinuation from study by System Organ Class (SOC) were nervous system disorders and psychiatric disorders.

During the double-blind period, a total of 16 subjects randomized to ziprasidone and 16 subjects randomized to placebo discontinued the study due to all-causality AEs. Of these, 7 subjects randomized to ziprasidone, and 7 subjects randomized to placebo permanently discontinued the study due to AEs judged related to the study drug. One ziprasidone subject discontinued the study due to a severe, treatment-related elevation of liver enzymes. The most common reason for discontinuation from study by SOC was psychiatric disorders in both the ziprasidone and placebo groups.

Deaths: There were no deaths among subjects who participated in this study.

CONCLUSIONS: This study demonstrates the superiority of ziprasidone plus lithium or valproic acid compared to placebo plus either mood stabilizer in the maintenance treatment of subjects initially presenting with manic or mixed symptoms of Bipolar I Disorder, based on the primary endpoint (TIME) and the key secondary endpoint (time to discontinuation for any reason). A statistically significant treatment effect on the primary (TIME) and key secondary (discontinuation for any reason) endpoints was demonstrated. Changes in CGI-S were evaluated, but robust effects were not observed.

The adjunctive ziprasidone treatment regimen was well tolerated for up to 10 months of treatment.