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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Geodon®/Ziprasidone Hydrochloride

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NATIONAL CLINICAL TRIAL NO.: NCT00280566

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: Chile (3), France (3), Germany (4), Guatemala (1), Hong Kong (1), India (6), Italy (4), Mexico (2), Russian Federation (2), Spain (3), Taiwan (1), United States (57), Venezuela (2)

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

Phase of Development: Phase 3

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 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.

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 238 subjects were analyzed for efficacy in the double-blind period only. In the open-label period, 584 subjects were analyzed for adverse events (AEs) and laboratory data were analyzed in 482 subjects. In the double-blind period, a total of 239 subjects were analyzed for AEs, and laboratory data were analyzed in 230 subjects (Table S1).

Diagnosis and Main Criteria for Inclusion: Subjects that were screened had a primary diagnosis of Bipolar I Disorder, with a recent or current manic or mixed episode, with symptoms that began no more than 90 days prior to the screening visit. The subjects were to have an MRS score ≥14 if currently receiving lithium or valproic acid or an MRS score of ≥18, if not currently on lithium or valproic acid. All subjects were to have an MRS score ≥14 at the baseline visit prior to entry into the open-label period.

Study Treatment: 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 twice daily (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 Evaluations: Primary Endpoint: The time to intervention for a mood episode (TIME) during the double-blind maintenance period.

Secondary Endpoints: Time to discontinuation for any reason during the double-blind period (key-secondary); CGI-I; Change from final visit in the open-label period during the double-blind period in MRS, MADRS, PANSS, and CGI-S, and Modified TIME during the double-blind period. 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.

Cognition and Outcome Evaluations: Cognitive test battery (central nervous system [CNS] Vital Signs [VS]), Changes in Sexual Functioning Questionnaire (CSFQ), Sheehan Disability Scale (SDS) and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scales were performed.

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

Statistical Methods: 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 intent-to-treat (ITT) and Per-Protocol (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 [defined under “Efficacy Evaluations”] 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 2 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 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 (final open-label visit) as a

covariate. Analysis during the double-blind Period 2 of CGI-I scores was 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.

RESULTS

Subject Disposition and Demography: Table S1 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. Age ranged from 18 to 71 years, with a mean age of 38.8 years. The majority of subjects were white, female, and of non-Hispanic/Latino ethnicity.

Table S1. Subject Disposition

	Open-Label Period	Double-Blind Period	
Number (%) of Subjects	**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)

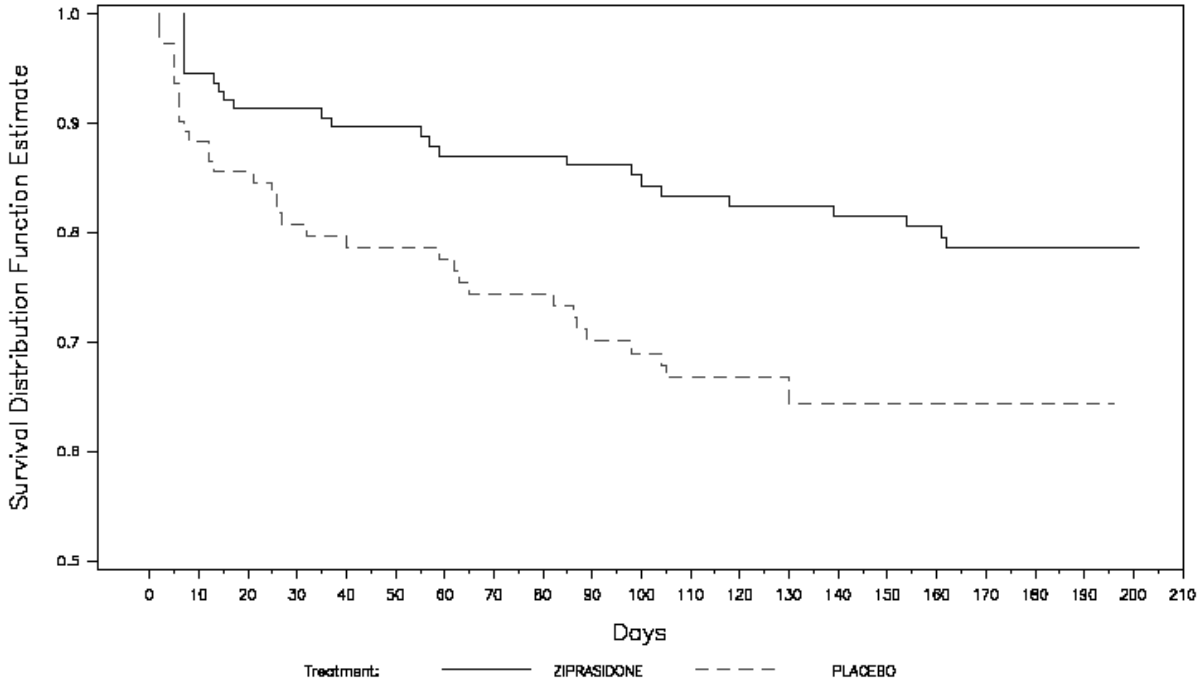
Abbreviation: NA = not applicable, ITT = intent-to-treat, PP = per protocol
[a]One subject was randomized into the double-blind phase at both sites 1024 and 1064; therefore, the data associated with the corresponding subject numbers are excluded from this summary, the ITT, PP, and safety analysis sets.

Efficacy Results: This study demonstrates the efficacy of ziprasidone in the maintenance treatment of Bipolar 1 Disorder in subjects who met Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) criteria for Bipolar Disorder, whose most recent episode was manic or mixed, and who were receiving adjunctive treatment with either lithium or valproic acid.

Primary: 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 Period 2 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.

The survival probability of the ziprasidone group was consistently higher than the placebo group during the 6 month double-blind period (Figure S1, below).

Figure S1. Kaplan-Meier Plot of Time to Intervention for Mood Episode (ITT Analysis Set)



Abbreviation: ITT = intent-to-treat

Secondary: 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, Table S2) 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 S2. Key Secondary Analysis – Log-Rank Test for Time to Discontinuation for Any Reason During Double-Blind Period (ITT Analysis Set)

	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)
P-value (vs Placebo)	0.0047	-

Abbreviation: ITT = intent-to-treat
P-value was calculated from a log-rank test at a 0.05 level of significance.

The survival probability of the ziprasidone group was consistently higher than the placebo group during the 6 month double-blind period.

Clinical Rating Scales During the Double-Blind Period: For other secondary endpoints overall, the baseline clinical severity of the subjects randomized to ziprasidone or placebo in Period 2 was similar across all secondary clinical ratings, including the MRS, the CGI-S, the MADRS, and the PANSS, further reflecting the fact that subjects randomized into Period 2 had achieved the 8-week required clinical stability criteria specified by the protocol prior to randomization.

At the end of the open-label treatment period, the mean ± standard deviation (SD) MRS scores in subjects randomized to ziprasidone was 4.1± 4.6 and 4.1± 4.8 in the placebo subjects, indicating a comparable baseline level of severity of manic symptoms upon their randomization into double-blind Period 2. For all visits beginning at Week 12 of randomization, 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 with ziprasidone.

There were no significant differences in the change from baseline in CGI-S scores between the ziprasidone and placebo groups (except for Week 1) during the double-blind period. The CGI-I score for ziprasidone group was significantly lower (ie, indicating greater improvement) than the placebo group during Weeks 1, 4, and 16.

There were no significant differences in the change from baseline in MADRS total score between ziprasidone and placebo groups (except for Week 1) during the double-blind period, and there were no significant differences in the change from baseline in PANSS total score between ziprasidone and placebo groups during any double-blind study visits.

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). 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.

The results from the PP Analysis Set were consistent with those from the ITT analysis. The Modified TIME was statistically significant in favor of the ziprasidone treated subjects ($p = 0.0255$, log-rank test) (Table 13.4.6.2). Only 24.2% of 99 ziprasidone subjects required intervention compared with 36.7% of 90 placebo subjects (Table 13.4.6.2).

Safety Results: There were no deaths reported during this study. Ziprasidone was well tolerated during the trial, with a safety profile that is similar to that in previous schizophrenia clinical trials and in acute bipolar mania trials. The most common AEs were sedation and somnolence. Ziprasidone had no remarkable effect on weight or blood glucose. The most frequently reported movement disorders were akathisia and tremor. For the most part, the effect of ziprasidone on the QTc value and the change in QTc was similar to other trials in which ziprasidone was administered as a monotherapy. It was noted that 1 subject who received ziprasidone plus lithium experienced a QTc value > 500 msec during the trial. The only QTcF value >500 msec for this subject occurred at Week 8 (556 msec), and subsequent values were ≤ 450 msec. Table S3 summarizes all causality, treatment-emergent AEs in this study.

Table S3. Summary of Treatment-Emergent Adverse Events (All Causalities) for Open-Label and Double-Blind Periods

	Open-Label Period	Double-Blind Period	
	Total	Ziprasidone	Placebo
Number (%) of subjects:			
Subjects evaluable for adverse events	584	127	112
Number of adverse events	1423	177	142
Subjects with adverse events	463 (79.3)	79 (62.2)	64 (57.1)
Subjects with serious adverse events	15 (2.6)	3 (2.4)	2 (1.8)
Subjects with severe adverse events	84 (14.4)	11 (8.7)	6 (5.4)
Subjects discontinued due to adverse events	145 (24.8)	16 (12.6)	16 (14.3)
Subjects with dose reduced or temporary discontinuation due to adverse events	179 (30.7)	2 (1.6)	1 (0.9)

Includes data up to 6 days after last dose of study drug.
Except for the Number of Adverse Events, subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.

AEs, discontinuations due to AEs, serious AEs (SAEs), and ECG results are summarized below by open-label and double-blind periods.

Open-label: The majority of AEs in Period 1 were mild or moderate in severity and the treatment-related AEs were generally similar to the all causality events. Organ systems with the highest frequency of all causality events included nervous system disorders (61.3%), psychiatric disorders (26.4%), gastrointestinal disorders (18.8%), general disorders and administrative site conditions (13.9%), and musculoskeletal and connective tissue disorders (12.0%). The incidence of all causality, treatment-emergent AEs that occurred at a rate of ≥5% in the open-label period are presented in Table S4, below.

During the open-label Period 1, a total of 145 subjects (24.8%) discontinued the study due to all causality AEs. Of these, 124 subjects (21.2%) permanently discontinued due to AEs related to study drug. Three subjects discontinued in the open-label Period 1 due to laboratory abnormalities. The investigator considered the AEs of increased alanine aminotransferase (ALT) and creatinine in 1 subject to be related to study drug. The most

common reasons for discontinuation from study by system organ class were nervous system disorders and psychiatric disorders.

A total of 21 subjects were reported to have an SAE while on ziprasidone and all SAEs resolved. Most SAEs were related to psychiatric symptoms, including 4 subjects with suicidal ideation, 1 subject with suicidal depression and 1 subject with a suicide attempt. Two subjects became pregnant during open-label treatment and ultimately experienced a spontaneous abortion. One subject experienced a serious dystonic reaction. Twelve subjects permanently discontinued study drug due to SAEs. Table S4 presents SAEs by mood stabilizer in the open-label period.

Table S4. Serious Adverse Events by Mood Stabilizer (Open-Label Period 1)

MedDRA (v11.0) Preferred Term	Action Taken	Outcome	Causality
Ziprasidone + Valproic Acid			
Psychiatric decompensation	Discontinued	Resolved	DUS
Suicidal ideation	Discontinued	Resolved	DUS
Bipolar disorder	Discontinued	Resolved	DUS
Bipolar disorder	Discontinued	Resolved	DUS
Thrombophlebitis	Discontinued	Resolved	Other illness
Chronic obstructive pulmonary disease	None	Resolved	Other
Suicidal ideation	None	Resolved	DUS
Influenza	Treatment given	Resolved	Other
Dystonia	None	Resolved	Study drug
Depression	Discontinued	Resolved	DUS
Bipolar 1 disorder	None	Resolved	DUS
Bipolar 1 disorder	None	Resolved	DUS
Affect lability	None	Resolved	DUS
Pregnancy[a]	Discontinued	Resolved	Other
Mania	Discontinued	Resolved	DUS
Ziprasidone + Lithium			
Suicidal ideation	Discontinued	Resolved	DUS
Suicide attempt	Ziprasidone dose increased	Resolved	DUS
Pregnancy[a]	Discontinued	Resolved	Other
Bipolar 1 disorder	Discontinued	Resolved	DUS
Psychotic disorder	None	Resolved	Other
Anxiety	Discontinued	Resolved	DUS
Depression, suicidal	Discontinued	Resolved	DUS
Mania	Discontinued	Resolved	DUS
Psychotic disorder	Discontinued	Resolved	Study drug
Suicidal ideation	Treatment given	Resolved	DUS

[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.
Abbreviations: DUS= disease under study; MedDRA=Medical Dictionary of Regulatory Activities

The magnitude of the increase in the QTc interval observed in the open-label period when all subjects received adjunctive ziprasidone was generally comparable to that reported previously for oral ziprasidone in subjects with schizophrenia or acute bipolar mania. Table S5 summarizes mean QT and QTc intervals and ranges, and Table S6 summarizes the incidence of categorical increases in QTc intervals in the open-label period.

Table S5. QT and QTc Intervals: Mean Baseline and Week 16 Values (msec) and Mean Change From Baseline to Week 16 (msec) During the Open-Label Treatment Period 1

	Baseline (N=574)		Week 16 (N =294)		Week 16 (N = 287)	
	Mean	Range	Mean	Range	Mean Change	Range
QT interval (msec)	383.2	295.3-476.3	390.3	308.0-473.0	9.3	-79.0-97.7
QTcB	414.3	348.0-484.0	418.4	343.0-490.0	4.2	-81.3-86.7
QTcF	403.3	344.0-463.3	408.4	345.0-482.0	5.9	-46.0-90.7

Abbreviations: N = number of subjects; QT = time corresponding to the beginning of depolarization to repolarization of the ventricles; QTcB = the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate using Bazett's formula; QTcF = the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate using Fridericia's formula

Table S6. Incidence of Categorical Increases in QTc Intervals During the Open-Label Treatment Period 1: Number (%) of Subjects

	Fridericia	Bazett
Incidence[a]		
QTc ≥450 msec	51 (8.7)	169 (28.9)
QTc ≥480 msec	5 (0.9)	19 (3.3)
QTc ≥500 msec	0	5 (0.9)
Increase from Baseline[a]		
≥30 msec	97 (18.2)	139 (26.0)
≥60 msec	5 (0.9)	10 (1.9)
≥75 msec	2 (0.4)	3 (0.6)
Percent change ≥20%	2 (0.4)	3 (0.6)

[a]N = 584 for Incidence and N = 534 for increase from baseline
Abbreviations: N = number of subjects; QTc = the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate

Double-blind: The majority of AEs in Period 2 were mild or moderate in severity and the treatment-related AEs were generally similar to the all causality events. Body systems with the highest frequency of all causality events in ziprasidone vs placebo subjects were similar to the open-label period and included gastrointestinal disorders (11.0% vs 7.1%), infections and infestations (16.5% vs 9.8%), investigations (13.4% vs 3.6%), nervous system disorders (20.5% vs 15.2%) and psychiatric disorders (18.1% vs 27.7%). The incidence of all causality, treatment-emergent AEs that occurred at a rate of ≥5% in the double-blind period are presented in Table S7 below.

During the double-blind period, 3.9% (5/127) of the subjects randomized to ziprasidone and 5.4% (6/112) of the subjects randomized to placebo discontinued the study due to AEs related to 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 system organ class was psychiatric disorders in both the ziprasidone and placebo groups.

A total of 7 subjects reported SAEs: 3 subjects (ziprasidone) and 4 (placebo). All the SAEs resolved. Two of the ziprasidone subjects experienced suicidal ideation and 1 reported an arrhythmia. All SAEs in the placebo-randomized subjects were related to mania or hypomania. Six subjects permanently discontinued study drug due to SAEs. Table S7 presents SAEs in each treatment group and by mood stabilizer in the double-blind period.

Table S7. Serious Adverse Events by Study Drug Assignment and Mood Stabilizer (Double-Blind Period 2)

MedDRA (v11.0) Preferred Term	Action Taken	Outcome	Causality
Ziprasidone + Valproic Acid			
Suicidal ideation	Discontinued	Resolved	DUS
Suicidal ideation	Discontinued	Resolved	Other
Arrythmia[a]	Discontinued	Resolved	Study drug
Placebo + Lithium			
Mania	Discontinued	Resolved	Other
Mania	Discontinued	Resolved	Other
Mania	Discontinued	Resolved	DUS
Placebo + Valproic Acid			
Hypomania	None	Resolved	DUS

[a] Ventricular extrasystole
Abbreviations: DUS= disease under study; MedDRA=Medical Dictionary of Regulatory Activities

The mean changes in QT, QTcB, and QTcF were greater in the ziprasidone group than in the placebo group, although smaller in magnitude than previously reported for oral ziprasidone in subjects with schizophrenia. Table S8 summarizes mean QT and QTc intervals and ranges, and Table S9 summarizes the incidence of categorical increases in QTc intervals in the double-blind period.

Table S8. QT and QTc Intervals: Mean Baseline and Week 24 Values (msec) and Mean Change From Baseline to Week 24 (msec) During the Double-Blind Treatment Period 2

	Baseline		Week 24			
	Mean	Range	Mean	Range	Mean Change	Range
QT interval (msec)						
Ziprasidone[a]	393.2	308.0 – 473.0	386.2	303.0 – 470.0	-3.3	-61.0 – 60.0
Placebo[b]	389.4	321.0 – 468.0	378.8	322.0 – 456.0	-8.7	-73.0 – 72.0
QTcB						
Ziprasidone[a]	420.2	348.0 – 469.0	422.1	366.0 – 482.0	2.1	-85.0 – 64.0
Placebo[b]	415.9	343.0 – 490.0	410.8	364.0 – 466.0	-2.0	-42.0 – 70.0
QTcF						
Ziprasidone[a]	410.6	345.0 – 464.0	409.4	350.0 – 460.0	0.2	-69.0 – 60.0
Placebo[b]	406.5	349.0 – 482.0	399.5	355.0 – 463.0	-4.3	-38.0 – 47.0

[a]Ziprasidone, N=126 at baseline, N=84 at Week 24, N=82 Mean change
[b]Placebo, N=109 at baseline, N=50 at Week 24, N=49 Mean change
Abbreviations: N = number of subjects; QT = time corresponding to the beginning of depolarization to repolarization of the ventricles; QTcB = the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate using Bazett's formula; QTcF = the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate using Fridericia's formula

Table S9. Incidence of Categorical Increases in QTc Intervals During the Double-Blind Treatment Period 2: Number (%) of Subjects

	Ziprasidone (N= 127)		Placebo (N =112)	
	Fridericia	Bazett	Fridericia	Bazett
Incidence				
QTc ≥450 msec	17 (13.4)	40 (31.5)	4 (3.6)	21 (18.8)
QTc ≥480 msec	2 (1.6)	7 (5.5)	1 (0.9)	1 (0.9)
QTc ≥500 msec	1 (0.8)	1 (0.8)	0	0
Increase from Baseline[a]	N = 125	N = 125	N = 105	N = 105
≥30 msec	17 (13.6)	34 (27.2)	7 (6.7)	13 (12.4)
≥60 msec	3 (2.4)	7 (5.6)	0	1 (1.0)
≥75 msec	2 (1.6)	2 (1.6)	0	0
Percent change ≥20%	2 (1.6)	1 (0.8)	0	1 (1.0)

Abbreviations: N = number of subjects; QTc = the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate
[a]N = 125 for increase from baseline (ziprasidone), N = 105 for increase from baseline (placebo).

The incidence of all causality, treatment-emergent AEs that occurred at a rate of ≥5% in the open-label and double-blind periods are presented in Table S10 and Table S11, respectively, below.

Table S10. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects by System Organ Class (All Causalities) During the Open-Label Period

System Organ Class MedDRA (v11.0) Preferred Term	Total
Number (%) of subjects	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)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities

Table S11. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects in Either Treatment Group by System Organ Class (All Causalities) During the Double-Blind Period

System Organ Class MedDRA (v11.0) Preferred Term	Ziprasidone	Placebo
Number (%) of subjects	127	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)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities

Clinical Laboratory Tests: The majority of abnormal laboratory test results in both the open-label and double-blind periods of the study were regarded as minor deviations which were not considered clinically significant, were transient in nature, and resolved with continued treatment. During the open-label period, 3 subjects discontinued due to laboratory test abnormalities and during the double-blind period, 1 subject discontinued.

In this study, the week 24 mean change from baseline for fasting glucose was +0.3 ± 22.9 mg/dL in the ziprasidone-treated patients (N=65) and +2.6 ± 22.9 mg/dL in the

placebo-treated patients (N=37). The mean changes from baseline in fasting levels of total cholesterol (+0.7± 22.1 vs +5.0 ± 30.0 mg/dL; N = 64 vs N = 37), low density lipoproteins (-0.1 ± 19.0 vs +3.7 ± 23.2 mg/dL; N = 63 vs N = 36), high density lipoproteins (-0.7 ± 7.6 vs -0.8 ± 9.5 mg/dL; N=65 vs N=37) and triglycerides (+5.2 ± 61.0 vs -0.8 ± 82.8 mg/dL; N = 64 vs N = 37) were similar in the ziprasidone and placebo patients.

Body Weight, BMI and Waist Circumference: Body weight changes (increase or decrease) of ≥7% were assessed. For all subjects in the open-label period, 5.5% experienced ≥7% increase in body weight and 3.2% experienced ≥7% decrease. For subjects who were ultimately randomized into the double-blind period, 8.8% had ≥7% increase in body weight and 2.9% experienced ≥7% decrease.

Seven percent body weight changes were not assessed by mood stabilizer status. These observations were consistent with the low incidence of AEs reported for changes in body weight for subjects during the open-label Period 1.

The ≥7% changes in body weight during the double-blind period were similar across both treatment groups for weight increases (5.6% in both ziprasidone- and placebo-randomized subjects); however, 12.8% of ziprasidone-randomized subjects lost ≥7% in body weight, while 5.6% of placebo-randomized subject lost ≥7% in body weight. These observations were also consistent with the low incidence of weight change AEs during double-blind treatment.

The mean weight at baseline for subjects in the double-blind Period 2 (ziprasidone only) was 79.6 kg, and the change from baseline to Week 24 was similar for placebo and ziprasidone groups; however, the ziprasidone-randomized subjects lost a mean of 0.8 kg and the placebo-randomized subjects gained a mean of 0.5 kg. There was no remarkable change in median changes in body weight, body mass, and waist circumference in the open-label or double-blind periods, and no apparent effect of mood stabilizer was noted.

Cognition and Outcome Measures: There were no significant differences between placebo and ziprasidone treatment groups in the CNS VS, CSFQ, SDS, and Q-LES-Q endpoints with the exception of Weeks 8 and 16 in the SDS for days unproductive at work/school. A significant difference ($p<0.05$) was demonstrated with the placebo treatment group showing greater decreases at both these time points.

Conclusions: This study demonstrated 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 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.