Ziprasidone Plus a Mood Stabilizer in Subjects With Bipolar I Disorder: A 6-Month, Randomized, Placebo-Controlled, Double-Blind Trial

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Objective: To evaluate the efficacy and safety of ziprasidone adjunctive to a mood stabilizer for the maintenance treatment of bipolar mania.

Method: Subjects with *DSM-IV* bipolar I disorder with a Mania Rating Scale score ≥ 14 were enrolled. Subjects achieving ≥ 8 consecutive weeks of stability with open-label ziprasidone (80–160 mg/d) and lithium or valproate (period 1) were randomly assigned in the 6-month, double-blind maintenance period (period 2) to ziprasidone plus mood stabilizer or placebo plus mood stabilizer. The primary and key secondary end points were the time to intervention for a mood episode and time to discontinuation for any reason, respectively. Inferential analysis was performed using a Kaplan-Meier product-limit estimator (log-rank test). The study was conducted from December 2005 to May 2008.

Results: A total of 127 and 113 subjects were randomly assigned to ziprasidone and placebo, respectively. Intervention for a mood episode was required in 19.7% and 32.4% of ziprasidone and placebo subjects, respectively. The time to intervention for a mood episode was significantly longer for ziprasidone than placebo ($P = .0104$). The median time to intervention for a mood episode among those requiring such an intervention (n = 61) was 43.0 days for ziprasidone versus 26.5 days for placebo. The time to discontinuation for any reason was significantly longer for ziprasidone ($P = .0047$). Adjunctive ziprasidone treatment was well tolerated. Among treatment-emergent adverse events occurring in ≥ 5% of subjects in either treatment group during period 2, only tremor occurred more frequently in the ziprasidone versus placebo group (6.3% vs 3.6%).

Conclusions: Ziprasidone is an effective, safe, and well-tolerated adjunctive treatment with a mood stabilizer for long-term maintenance treatment of bipolar mania.

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Mood disturbances in bipolar disorders result in variable dysfunctions in sleep, mood activity, impulsivity, libido, and cognition that significantly impair functioning. The mood stabilizers lithium and valproate are acknowledged as cornerstones for acute and preventive treatment of mania and are often administered as monotherapy for the first-line treatment of patients with bipolar disorder.[1] However, in only 30% of patients is long-term symptom control achievable with a single mood stabilizer alone.[2] Atypical antipsychotics have been tested and shown to be effective as add-on therapy to mood stabilizers for the treatment of patients with mania.[3] Quetiapine has been shown to provide effective adjunctive maintenance therapy to lithium or divalproex[4] and has received US Food and Drug Administration (FDA) approval for this indication.[5] Both the American Psychiatric Association[6] and the Texas Medication Algorithm Project[7] guidelines specify concomitant administration of antipsychotics with lithium or valproate for mania partially responsive to monotherapy.

Previous studies of atypical antipsychotics adjunctive to mood stabilizers have demonstrated long-term efficacy for bipolar mania. A recent study[4] of the efficacy and safety of quetiapine in combination with lithium or divalproex compared with placebo with lithium or divalproex demonstrated that treatment with quetiapine plus lithium/divalproex significantly increased the time to recurrence of any mood event compared with placebo plus lithium/divalproex. In an 18-month clinical trial,[8] olanzapine was shown to provide sustained symptomatic remission (Young Mania Rating Scale total score ≤ 12 and Hamilton Depression Rating Scale score ≤ 8), but not syndromic remission (mania: *DSM-IV* "A" criteria for current manic episode no worse than mild, "B" criteria no worse than mild, and no more than 2 "B" criteria that were mild; depression: all *DSM-IV* "A" criteria for current major depressive episode no worse than mild and no more than 3 "A" criteria given mild rating), for longer than lithium or valproate monotherapy in patients with

bipolar I disorder. In a recent 6-week study[9] of aripiprazole adjunctive to lithium or valproate, subjects demonstrated significant improvements in mania symptoms as early as week 1; however, long-term data for adjunctive aripiprazole in maintenance treatment of patients with bipolar mania are not available.

Ziprasidone is a second-generation benzisothiazolyl piperazine-type atypical antipsychotic agent whose efficacy is thought to be mediated through its combined antagonism of dopamine D_2- and serotonin 5-HT_{2A}–receptors.[10] The efficacy of ziprasidone in acute mania or mixed episodes has been demonstrated in two 3-week, double-blind, placebo-controlled trials[11,12]; statistically significant improvement of manic symptoms was observed as early as day 2 of treatment. A 12-week, placebo-controlled trial[13] of subjects with acute mania confirmed the superiority of ziprasidone over placebo and demonstrated the advantageous tolerability profile of ziprasidone versus haloperidol, particularly with fewer movement-related adverse events. In longer-term open trials, ziprasidone exhibited a tolerability profile that was not associated with weight gain or dyslipidemia,[14] and switching from risperidone or olanzapine to ziprasidone resulted in sustained, clinically significant improvements in weight and plasma lipids in subjects with schizophrenia.[15]

The aim of this trial was to evaluate the efficacy and safety of ziprasidone as adjunctive treatment to a mood stabilizer in the long-term maintenance treatment of mania associated with bipolar disorder in a placebo-controlled, double-blind clinical trial. This is the first trial assessing long-term treatment of bipolar disorder with ziprasidone.

METHOD

Subjects

Subjects of either sex aged ≥ 18 years were eligible for inclusion. Women were excluded if pregnant or breastfeeding and, if of childbearing potential, were required to use effective contraception. All subjects were required to be outpatients with a recent or current manic (*DSM-IV* 296.4x) or mixed (*DSM-IV* 296.6x) episode of bipolar I disorder,[16] have a Mania Rating Scale (MRS)[17] score of ≥ 14 (scores of ≥ 2 on ≥ 4 items), and be medically compliant in the management of their bipolar disorder. Subjects who were hospitalized at the screening visit due to bipolar disorder could be enrolled if sufficiently stable for outpatient management within approximately 5 days. Receipt of lorazepam ≤ 2 mg/d for anxiety or insomnia for ≤ 4 days a week (or a benzodiazepine similar to lorazepam) or zolpidem tartrate was permitted. Subjects provided written informed consent before entering the trial. Subjects were excluded who had ≥ 8 mood episodes over the previous 12 months, had a diagnosis of mental retardation or organic brain syndrome, had a substance-induced psychotic disorder or behavioral disturbance, had a current (≤ 2 months prior to screening) substance abuse/dependence, had a history of treatment resistance to ≥ 2 other antipsychotic medications or treatment resistance or intolerance to ziprasidone, or were at risk of harm to themselves or others. Subjects receiving clozapine within 12 weeks, a depot antipsychotic within 4 weeks, or a monoamine oxidase inhibitor within 2 weeks of period 1 were also excluded. Medical reasons for exclusion included renal, hepatic, endocrine, respiratory, cardiovascular, hematologic, immunologic, or cerebrovascular disease or malignancy; body mass index (BMI) > 35 or < 18.5 kg/m^2; clinically relevant laboratory findings; an eating disorder or receipt of medication that could affect absorption of ziprasidone; and a positive urine drug screen for morphine, cocaine, or amphetamines.

Study Design

The study was approved by the institutional review board and/or independent ethics committee at each center and was conducted in compliance with the ethical principles of the Declaration of Helsinki and with all guidelines of the International Conference on Harmonization Good Clinical Practice. The study was conducted from December 2005 to May 2008.

Prior to entering period 1, subjects received either lithium or valproate at a therapeutic serum concentration (lithium 0.6–1.2 mEq/L or valproate 50–125 μg/mL) for ≥ 2 weeks. Subjects who remained symptomatic and met inclusion/exclusion criteria could enter period 1, during which open-label ziprasidone 80 to 160 mg/d (taken with food, twice daily) was added to the treatment regimen for up to 16 weeks. To be randomized into period 2, subjects were required to be stabilized for 8 consecutive weeks on the open-label adjunctive regimen. Stabilization started when symptoms improved compared to baseline as measured by a Clinical Global Impressions-Improvement scale (CGI-I)[18] score ≤ 3. While this may have occurred during week 1, the stabilization clock was not started until at least week 2. Continued stabilization required that subsequent CGI-I scores remain ≤ 3. A CGI-I score ≥ 4 was allowed at 1 visit over the 8 weeks of stabilization, but a score ≥ 4 for 2 consecutive weeks restarted the stabilization clock. Subjects who had been stabilized were randomized into period 2 in a 1:1 ratio to double-blind treatment for 6 months with either ziprasidone plus the mood stabilizer (lithium or valproic acid) or placebo plus the mood stabilizer. The clinical medical supply was blinded, and clinicians were blinded to the randomized treatment assignment. The ziprasidone dose was to remain the same as that received during the final 4 weeks of period 1. For subjects randomly assigned to placebo, ziprasidone was tapered off during week 1 of period 2 until the subjects were receiving placebo only (blind was maintained). The level of ziprasidone was decreased 20 mg bid every 2 days; subjects who received 80 mg bid, 60 mg bid, and 40 mg bid in period 1 were tapered to placebo over 6, 4, and 2 days, respectively.

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Efficacy Assessments

The primary end point was the time to intervention for a mood episode. The key secondary end point was the time to discontinuation for any reason. Subjects meeting any of the following criteria were considered to have an event (intervention for a mood episode) and were discontinued from the trial: investigator decided discontinuation was in the best interest of the subject, a loss of effect and/or requirement for an alteration to the treatment regimen (in the investigator's judgment), any time a subject was hospitalized for disease under study, an MRS rating of ≥ 18 for 2 consecutive visits scheduled no more than 10 days apart, a Montgomery-Asberg Depression Rating Scale (MADRS)[19] rating of ≥ 18 for 2 consecutive visits scheduled no more than 10 days apart. Last-observation-carried-forward (LOCF) analyses of change from baseline to the end point in MRS and MADRS scores were also performed.

Each participating site conducted rating instrument standardization training on the efficacy scales prior to the start of the study. In addition, prior to the start of the study, rater certification was conducted by the central vendor for the Schedule for Affective Disorders and Schizophrenia-Change Behavior Scale (which contains the MRS) and the MADRS for each rater. The rater had to be certified before participating in the conduct of the trial.

Safety Assessments

Treatment-emergent events (occurring during the trial and ≤ 6 days after the last dose of study drug), clinical laboratory results, physical examination findings, blood pressure and pulse rate, body weight, BMI, and waist circumference, and electrocardiography (with emphasis on QT and heart rate–corrected QT [QTc] intervals) were monitored throughout the trial.

Statistical Analyses

Study population. For purposes of sample-size estimation, a relapse rate of 60% in the group randomly assigned to placebo plus mood stabilizer and of 40% in the group randomly assigned to ziprasidone plus mood stabilizer was assumed. Hence, the number of relapse events required to yield 80% power with a 5% type 1 error rate was 100. Allowing for 15% of subjects discontinuing other than due to the primary variable, a minimum of 115 subjects would need to be randomly assigned to each double-blind treatment group.

Efficacy. The full analysis set comprised the intent-to-treat (ITT) population, which was used for all efficacy analyses and was defined as those subjects randomly assigned to treatment in the double-blind period (period 2) who took ≥ 1 dose of double-blind medication and had ≥ 1 postrandomization observation. The per-protocol (PP) analysis set, which included all subjects in the full analysis set who did not have major protocol violations, was also used in the analyses of time to intervention for a mood episode and time to discontinuation for any reason. Time to intervention for a mood episode was calculated as the number of days after double-blind randomization to intervention, defined as an investigator decision to discontinue in the best interest of the subject, loss of effect, and/or need for a change in treatment regimen based on the investigator's judgment, hospitalization for bipolar disease (derived from the Schedule for Affective Disorders and Schizophrenia-Change Version[20] with items grouped as the manic syndrome subscale [elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity], the behavior and ideation subscale [irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment], and impaired insight), or MADRS[20] score ≥ 18 on 2 consecutive visits ≤ 10 days apart. In the case of MRS or MADRS, time to intervention for a mood episode was calculated as the number of days from the day of double-blind randomization to the first observation of a score of ≥ 18.

The primary analysis was based on the Kaplan-Meier product-limit estimator, and *P* values were obtained from the log-rank test for equality of the survival curves for the 2 treatment groups. The secondary end point, time to discontinuation for any reason during period 2, was also analyzed using the Kaplan-Meier product-limit estimator and log-rank test. If the date of the intervention was missing, then the time of intervention for a mood episode was assumed to be the date of the last subject visit.

Analyses of change from baseline to end point MRS and MADRS scores were conducted using the LOCF method. In these analyses, "end point" was defined as the day of mood episode or the day of censoring (completion or discontinuation).

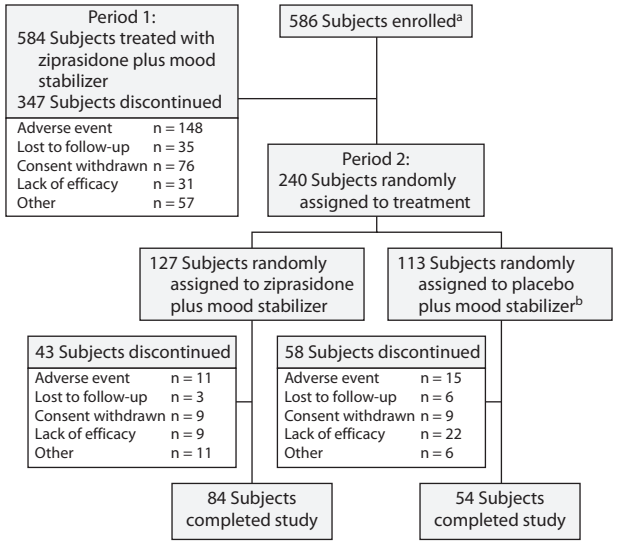
Safety. The safety populations comprised all subjects who received ≥ 1 dose of antipsychotic treatment during period 1 or period 2. Descriptive analyses of safety data were performed.

RESULTS

Subject Characteristics

Of 1,088 subjects who were screened at 98 centers (Asia: Taiwan, Hong Kong, India; Europe: France, Germany, Italy, Spain; Russian Federation; Central America: Guatemala; North American: Mexico, United States; South America: Chile, Venezuela; the range of subjects screened per center was 1–45), 586 entered period 1 (duration range, 2.5–4 months), and 584 were treated (Figure 1). For period 2, 240 patients were randomly assigned to ziprasidone (n = 127) and placebo (n = 113). Patients randomly assigned to ziprasidone during period 2 received the same dose they received during the final 4 weeks of period 1; the mean modal doses were 80 mg/d, 119 mg/d, and 160 mg/d for subjects assigned to doses of 80 mg/d (n = 60, 47.2%), 120 mg/d (n = 40, 31.5%), and 160 mg/d (n = 27, 21.3%), respectively. During period 2, mean ± SD valproate levels in

Figure 1. Subject Disposition



[a]One subject was randomized into period 2 at 2 sites; therefore, the data associated with that subject are excluded from this summary and the intent-to-treat, per-protocol, and safety analysis sets.
[b]113 subjects were randomly assigned to placebo plus mood stabilizer in period 2, but 112 were treated.

Table 1. Demographics of Subjects Receiving Double-Blind Treatment With Ziprasidone Plus a Mood Stabilizer (Lithium or Valproic Acid) or Placebo Plus a Mood Stabilizer

Parameter	Ziprasidone (n = 127)	Placebo (n = 113)
Male, n (%)	51 (40.2)	60 (53.1)
Age, y		
Mean (SD)	39.6 (12.3)	38.0 (11.6)
Range	18–64	18–71
Race, n (%)		
White	82 (64.6)	67 (59.3)
Black	5 (3.9)	6 (5.3)
Asian	31 (24.4)	29 (25.7)
Other	9 (7.1)	11 (9.7)
Weight, kg		
Mean (SD)	78.4 (19.1)	79.4 (23.9)
Range	40–133.6	35.0–150.0
Current episode type, n (%)		
Manic	73 (57.9)[a]	60 (53.1)
Mixed	53 (42.1)[a]	53 (46.9)
Concomitant medication, n (%)[b]	75 (59.1)	69 (61.1)

[a]Not recorded in 1 subject.
[b]Other than psychotropic drugs.

subjects receiving valproate were 67.4 ± 33.8 to 72.8 ± 31.3 μg/mL, and mean ± SD lithium levels in subjects receiving lithium were 0.7 ± 0.3 to 0.9 ± 0.3 mEq/L.

The demographics of the subjects randomized to period 2 are summarized in Table 1. The most frequent nonpsychiatric comorbidities were gastroesophageal reflux disease, hyperlipidemia, and hypercholesterolemia.

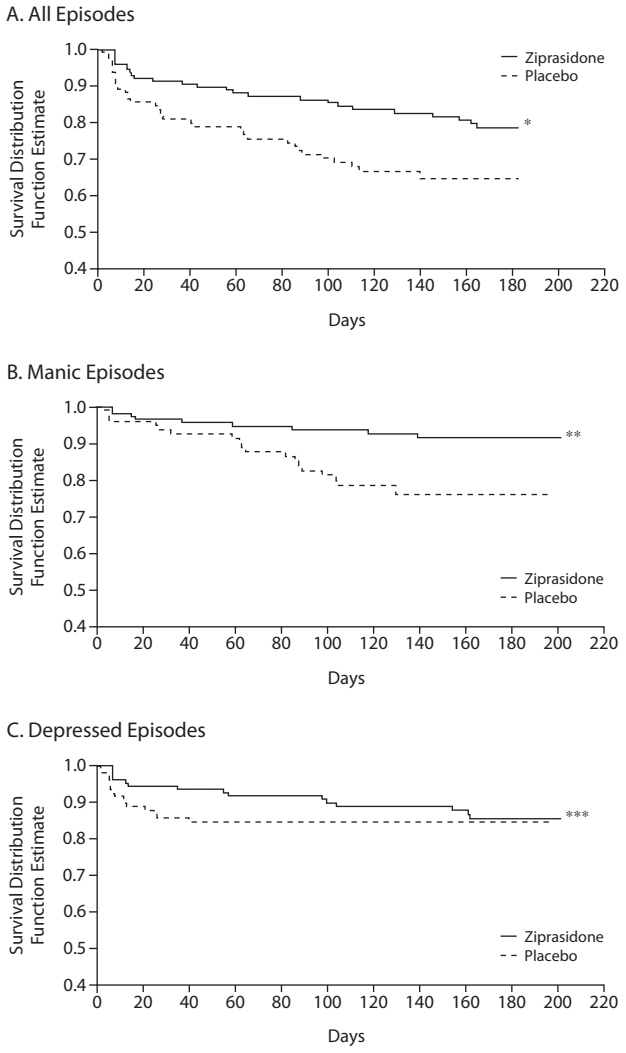
Efficacy

Time in study. The median number of treatment days during period 1 was 59.5 days, and the median number of treatment days for subjects who were ultimately randomized into period 2 was 77.0 days. During period 2, the median number of treatment days for subjects treated with ziprasidone plus mood stabilizer was 167 days, and the median number of treatment days for subjects treated with placebo plus mood stabilizer was 141 days. Overall, the median number of treatment days for subjects randomly assigned to ziprasidone plus mood stabilizer during both period 1 and period 2 was 239.0 days, and the median number of treatment days during both study periods for subjects randomly assigned to placebo plus mood stabilizer was 211.0 days.

Primary efficacy end point. In the ITT population, during the 6-month double-blind treatment, the log-rank test showed that time to intervention for a mood episode was statistically significantly longer for ziprasidone than placebo ($P = .0104$; Figure 2A). Intervention for a mood episode was required by 19.7% (25/127) of subjects receiving ziprasidone, compared with 32.4% (36/111) of subjects receiving placebo. For the PP population, time to intervention for a mood episode was also longer for ziprasidone ($P = .0123$); 21.2% and 35.6% of ziprasidone-treated subjects and placebo-treated subjects required intervention, respectively. For the ITT sample, the median time to intervention for a mood episode for ziprasidone and placebo, respectively, was 43.0 days (range, 7–165) and 26.5 days (range, 2–140) among subjects who required an intervention for a mood episode (n = 61). In the PP sample, the median time to intervention for a mood episode for ziprasidone and placebo was 43.0 days (range, 7–162) and 20.0 days (range, 2–140), respectively. Among lithium-treated subjects, 21.1% of ziprasidone subjects versus 44.9% of placebo subjects required an intervention for a mood episode (Table 2); within the subset of lithium-treated subjects requiring an intervention, the median time to intervention for a mood episode was 20.0 days (range, 7–162) (mean ± SD = 58.2 ± 62.4) and 27.5 days (range, 5–120) (mean ± SD = 51.6 ± 44.9) for ziprasidone (n = 12) and placebo (n = 22), respectively. Among valproate-treated subjects, 18.6% of ziprasidone subjects versus 22.6% of placebo subjects required an intervention (Table 2); of subjects requiring an intervention, the median time to intervention for a mood episode for ziprasidone subjects (n = 13) versus placebo subjects (n = 14) was 59.0 days (range, 7–165; mean ± SD = 65.7 ± 52.7) and 9.5 days (range, 2–105; mean ± SD = 31.2 ± 37.8), respectively.

Post hoc analyses for time to intervention for episodes of mania (including both manic and mixed episode) and depression are presented in Figure 2B and 2C. The relative risk of relapse for the ziprasidone group versus the placebo group was 0.61. The unadjusted relative risk of relapse was 0.39 and 0.87 for manic episodes and depressed episodes, respectively. Discontinuation due to a mood episode

Figure 2. Kaplan-Meier Plots of Time to Intervention for Mood Episode During Period 2 With Ziprasidone or Placebo (intent-to-treat population)



*Log-rank $P = .0104$.
**Log-rank $P = .0035$.
***Log-rank $P = .4538$.

occurred in 25 ziprasidone subjects (7 manic, 16 depressed, and 2 mixed) and 36 placebo subjects (14 manic, 16 depressed, and 6 mixed).

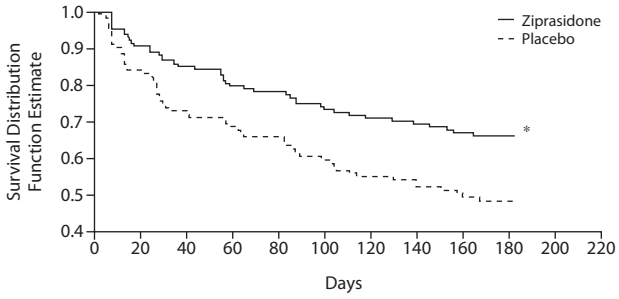
Secondary end point. Discontinuations for any reason occurred in 33.9% (43/127) of subjects receiving ziprasidone and in 51.4% (57/111) of subjects receiving placebo. Time to discontinuation for any reason during period 2 was significantly longer for the ziprasidone group than the placebo group ($P = .0047$; Figure 3).

The least squares mean difference values for change from baseline to LOCF end point in MRS and MADRS scores are presented in Table 3; while there was a significant difference between ziprasidone and placebo for the change in MRS scores ($P < .001$), the difference between ziprasidone and placebo was insignificant for the change in MADRS scores.

Table 2. Proportion of Subjects Requiring a Mood Intervention in the Intent-to-Treat Population by Mood Stabilizer

	Ziprasidone		Placebo	
Mood Stabilizer	n	Subjects Requiring Intervention, n (%)	n	Subjects Requiring Intervention, n (%)
Lithium	57	12 (21.1)	49	22 (44.9)
Valproate	70	13 (18.6)	62	14 (22.6)

Figure 3. Time to Discontinuation for Any Reason During Period 2 With Ziprasidone or Placebo (intent-to-treat population)



*Log-rank $P = .0047$.

Table 3. LS Mean Difference Between Ziprasidone and Placebo for Change From Baseline to End Point in MRS and MADRS Scores (LOCF, ITT subjects)

Rating Scale	LS Mean Difference From Placebo (SE)	95% CI for Difference From Placebo	*P* Value
MRS total score	−3.27 (0.83)	−4.91 to −1.62	< .001
MADRS total score	−0.37 (0.88)	−2.11 to 1.37	.674

Abbreviations: CI = confidence interval, ITT = intent-to-treat, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, MRS = Mania Rating Scale.

Safety

Treatment-emergent adverse events. During period 1, of the 584 evaluable subjects, 79.3% (463) experienced a total of 1,423 treatment-emergent adverse events (AEs) (all causalities). The AEs were generally mild or moderate in severity. Severe AEs, the most common being sedation and somnolence, occurred in 14.4% (84/584) of subjects. A total of 37 and 25 subjects discontinued due to sedation and somnolence, respectively, during the open-label period. Adverse events were considered serious in 2.6% (15) of subjects. Treatment was discontinued due to an AE in 24.8% (145) of subjects, mainly due to nervous system or psychiatric disorders; in 124 subjects, the AE was considered related to

Table 4. Treatment-Emergent Adverse Events (all causalities) Experienced by ≥ 5% of Subjects During Period 1 and Period 2[a]

Adverse Event	Period 1 (n = 584)	
Sedation	134 (22.9)	
Somnolence	99 (17.0)	
Tremor	73 (12.5)	
Insomnia	59 (10.1)	
Dizziness	49 (8.4)	
Akathisia	47 (8.0)	
Fatigue	44 (7.5)	
Nausea	42 (7.2)	
Headache	32 (5.5)	
	Period 2	
	Ziprasidone (n = 127)	Placebo (n = 112)
Tremor	8 (6.3)	4 (3.6)
Insomnia	7 (5.5)	12 (10.7)
Mania	3 (2.4)	8 (7.1)
Upper respiratory tract infection	5 (3.9)	6 (5.4)

[a]Values expressed as n (%).

the study drug. In 30.7% (179) of subjects, the dose of open-label treatment was reduced or temporarily discontinued. The most frequently occurring AEs (incidence ≥ 5%) were predominantly nervous system or psychiatric disorders (Table 4).

During period 2, 62.2% (79/127) of subjects receiving ziprasidone experienced a total of 177 treatment-emergent AEs (all causalities) compared with 142 AEs in 57.1% (64/112) of subjects in the placebo group. In 8.7% (11/127) of ziprasidone subjects, compared with 5.4% (6/112) of placebo subjects, the AEs were classed as severe. Among the treatment-emergent AEs occurring at a frequency ≥ 5% in either treatment group during period 2, tremor was the only one to occur more frequently in the ziprasidone group (Table 4). A serious AE occurred in 2.4% (3) of ziprasidone subjects compared with 1.8% (2) of placebo subjects. No deaths occurred.

Laboratory tests. Abnormalities were recorded in 81% of subjects during period 1 and in 81% of subjects in both the ziprasidone and the placebo groups during period 2. The majority of all abnormal test results were minor deviations, which were not considered clinically significant, were transient in nature, and resolved with continued treatment. The most common of these abnormalities were changes in liver enzymes, creatinine, and thyroid function that occurred in both subjects receiving ziprasidone and placebo. In period 1, random testing revealed 1 subject with low blood glucose and 4 with elevated levels; 1 subject had elevated fasting glucose. During period 1, prolactin levels were elevated in 19.3% (70/362) of subjects with normal baseline values. During period 2, among the ziprasidone subjects, 1 subject had low fasting glucose, 1 subject had elevated fasting glucose, and 1 subject had elevated random glucose. During period 2, prolactin levels were elevated in 12.3% (10/81) of subjects (with normal baseline values) receiving ziprasidone and 6.0% (5/83) receiving placebo.

Vital signs. Median baseline sitting blood pressure (systolic and diastolic) and pulse rate were similar throughout period 1 for all subjects who entered the trial and for subjects who were ultimately randomized into period 2. Blood pressure and pulse rate remained comparable during period 2 compared with period 1 and were also similar across treatment groups.

Body weight, serum lipids, and fasting glucose. During period 1, 5.5% of subjects experienced a ≥ 7% increase in body weight and 3.2% a ≥ 7% decrease. During period 2, 5.6% of both ziprasidone and placebo subjects experienced a ≥ 7% increase in body weight. However, 12.8% of ziprasidone subjects lost ≥ 7% in body weight, while 5.6% of placebo subjects lost ≥ 7% in body weight. Over the 24 weeks of double-blind treatment, mean weight changes were –0.8 kg (SD = 4.8) and +0.5 kg (SD = 4.9) for subjects receiving ziprasidone and placebo, respectively. Median changes in BMI and waist circumference mirrored the median changes in median body weight. Changes in serum lipids and fasting glucose were not clinically significant and were similar between ziprasidone and placebo (Table 5).

QTc interval.

Period 1. Mean QT interval values at baseline and week 16 of period 1 were 383.2 ms (range, 295.3–476.3) and 390.3 ms (range, 308.0–473.0). In no subject was the QTc (Fridericia formula; QTcF) interval ≥ 500 ms; 5 subjects experienced a QTcF interval ≥ 480 ms. During period 1, 5 subjects had an increase from the baseline QTcF interval ≥ 60 ms.

Period 2. Respective mean QT interval values in the ziprasidone and placebo group were 393.2 ms (range, 308–473) and 389.4 ms (range, 321–468) immediately before the start of period 2. At week 24, the respective mean QT interval values in the ziprasidone and placebo group were 386.2 ms (range, 303–470) and 378.8 ms (range, 322–456).

DISCUSSION

In this study, ziprasidone demonstrated a maintenance effect among subjects with bipolar I disorder who experienced continued manic or mixed episodes while taking lithium or valproate and who were subsequently stabilized by the addition of ziprasidone. This is the first adjunctive antipsychotic study that has required clinically relevant evidence that the added medication be effective for at least 8 weeks and that ziprasidone be the only medication combined with lithium or valproate for the last 4 of the 8 weeks. Both time to intervention for a mood episode and time to discontinuation for any reason were significantly longer for ziprasidone added to a mood stabilizer versus placebo plus a mood stabilizer, which addresses overall effectiveness, incorporating both efficacy and tolerability.

Post hoc analyses for relapse to mania and depression separately indicated that the time to relapse to mania was

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Table 5. Lipids and Fasting Glucose: Mean Change From Baseline[a] at Week 24, by Mood Stabilizer

	Valproate				Lithium			
	Ziprasidone		Placebo		Ziprasidone		Placebo	
Parameter	Change, Mean (SD)	n	Change, Mean (SD)	n	Change, Mean (SD)	n	Change, Mean (SD)	n
Fasting glucose, mg/dL	6 (20.8)	34	2.1 (25.7)	25	−6 (23.9)	31	3.8 (16.3)	12
LDL-C, mg/dL	3.4 (19.2)	37	11.7 (22.5)	33	−2.8 (20.8)	34	−4.7 (26.5)	12
HDL-C, mg/dL	0 (8.6)	38	−0.7 (8.1)	33	−1.4 (6.2)	35	−2.5 (11.1)	13
Cholesterol, mg/dL	3.6 (21.2)	38	17.3 (26.9)	33	−2.9 (24.7)	34	−4.8 (27.3)	13
Triglycerides, mg/dL	0.2 (54.9)	38	22.4 (73.0)	33	11.5 (72.8)	35	13.2 (137.7)	13

[a]Baseline refers to the last available observation from the open-label period.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

significantly longer for ziprasidone versus placebo; there was no significant difference in time to relapse for depression. Consistent with that result, we found that there was a significant difference in favor of ziprasidone versus placebo in the change in MRS scores, but not in the change in MADRS scores.

Ziprasidone plus a mood stabilizer was well tolerated in this 6-month maintenance study. Tremor was the only reported adverse effect significantly more common (among AEs ≥ 5%) for the ziprasidone plus mood stabilizer group compared with the mood stabilizer–alone group during period 2. Laboratory indices were similar between the 2 groups.

Importantly, neither metabolic disturbances nor clinically significant weight gain occurred when ziprasidone was added to a mood stabilizer. Concurrent administration of ziprasidone resulted in a slight decrease in mean weight, while the administration of a mood stabilizer alone resulted in a slight increase in weight. These results are in contrast to consistent evidence of metabolic disturbances and weight gain in acute and maintenance results in adjunctive studies of olanzapine and quetiapine.[21]

The study also indicates that ziprasidone used in doses ranging from 80 to 160 mg/d adjunctively with lithium or valproate for up to 6 months is not associated with clinically significant QTc prolongation. While an increase in the incidence of QTc prolongation was observed in controlled clinical trials designed to look at QTc effects,[22,23] ziprasidone is not associated with an increased risk of arrhythmia or sudden death.[24]

This study has several strengths and limitations. Only 2 other monotherapy or adjunctive treatment studies of maintenance-phase treatment for bipolar I disorder have required a duration of stabilization as long as 8 weeks,[4,25] with adjunctive treatment limited to the atypical antipsychotic during the final 4 weeks. The use of the CGI-I score for randomization separated the primary criterion for randomization from the defined maintenance outcomes and addressed all bipolar symptomatology. The design resulted in a higher proportion of patients completing the maintenance phase than prior placebo-controlled maintenance studies that did not require long stabilization periods. The performance of ziprasidone plus a mood stabilizer regarding adverse effects (tremor was the only adverse effect more common in the ziprasidone plus a mood stabilizer group; there were no clinically significant metabolic, weight, or other laboratory abnormalities) was very good, indicating that ziprasidone was well tolerated throughout the study and that the drug is not associated with increased risk of metabolic syndrome.[26]

One limitation of the study is that only patients in manic, mixed episodes were enrolled; therefore, it is not possible to infer the benefits of adjunctive ziprasidone in depressed bipolar patients in the acute phase. Additionally, the maintenance phase is relatively short. Discussions with the US FDA in recent years have resulted in a preference in registration trials for maintenance indications in bipolar disorder that emphasize longer open stabilization, followed by blinded maintenance phases of no specified duration. This is consequent to the observation that discontinuations for all reasons are strongly weighted toward the first few months of blinded, randomized phases; therefore, studies designed with a long follow-up phase have only a small proportion of subjects completing the trial. Further limitations include the fact that the enriched design of the study limits the generalization of the findings to patients who responded to adjunctive ziprasidone during period 1. However, enriched study designs have greater internal validity than nonenriched ones in addressing the question of how long a patient treated with compound "A" should stay on that treatment following remission of the acute episode.

While our post hoc analyses indicated that there was a significant difference between ziprasidone and placebo for relapse to mania but not for depression, the trial was not powered to separate ziprasidone from placebo with regard to time to intervention for mania and depression separately. Given that all the patients were enrolled while in a manic or mixed episode, and the fact that the index episode type provides better power for separation from placebo on that specific episode, this study is not conclusive with regard to the ability of adjunctive ziprasidone to prevent depressive episodes.[27] Further studies are warranted to determine whether ziprasidone prevents relapse to mania and depression separately.

In summary, ziprasidone plus lithium or valproate was superior to placebo plus lithium or valproate in the maintenance treatment of subjects continuing to present with manic or mixed symptoms of bipolar I disorder following at least 2 weeks of treatment with either lithium or valproate. Adjunctive ziprasidone yielded both significantly longer time to intervention for any mood episode and greater overall effectiveness, based on the significantly longer to time to discontinuation for any reason. Adjunctive ziprasidone, given at doses between 80 and 160 mg/d for maintenance therapy of bipolar mania for up to 10 months, was also well tolerated, with no indication of metabolic disturbances nor clinically meaningful weight gain.

Drug names: divalproex (Depakote and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon), zolpidem (Ambien, Zolpimist, Edluar, and others).

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