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# Adjunctive Oral Ziprasidone in Patients With Acute Mania Treated With Lithium or Divalproex, Part 1: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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**ABSTRACT**

***Objective:*** To assess the efficacy and safety of adjunctive ziprasidone in subjects with acute mania treated with lithium or divalproex, with an inadequate response to the mood stabilizer.

***Method:*** The study enrolled subjects aged 18–65 years who had a primary *DSM-IV* diagnosis of bipolar I disorder, with the most recent episode manic or mixed, with or without rapid cycling, and a Young Mania Rating Scale (YMRS) score ≥ 18. Subjects were randomized under double-blind conditions to receive ziprasidone, 20 to 40 mg (n = 226) or 60 to 80 mg (n = 232), or placebo (n = 222) twice a day for 3 weeks in addition to their mood stabilizer. The primary efficacy variable was change in YMRS scores from baseline to 3 weeks. Secondary efficacy measures included the Montgomery-Asberg Depression Rating Scale, Positive and Negative Syndrome Scale, Clinical Global Impressions-Severity of Illness and -Improvement scales, and Global Assessment of Functioning. Computer-administered YMRS was included for quality control and to evaluate study performance. The study was conducted between April 2006 and December 2008.

***Results:*** Least-squares mean ± standard error changes in YMRS scores from baseline to week 3 were –10.2 ± 0.80 in the mood stabilizer + ziprasidone 60- to 80-mg group, –11.0 ± 0.80 in the mood stabilizer + ziprasidone 20- to 40-mg group, and –9.5 ± 0.80 in the mood stabilizer + placebo group. Mean treatment differences between adjunctive ziprasidone groups and placebo were not statistically significant on primary or secondary efficacy measures. Ziprasidone was well tolerated.

***Conclusions:*** Adjunctive ziprasidone treatment failed to separate from mood stabilizer (lithium or divalproex) treatment on primary and secondary end points.

***Trial Registration:*** ClinicalTrials.gov identifier: NCT00312494

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The American Psychiatric Association guidelines for the management of bipolar disorder recommend that patients with acute episodes of severe mania should receive a combination of lithium or divalproex with an atypical antipsychotic as first-line therapy.[1]

Several atypical antipsychotics, including olanzapine, risperidone, and quetiapine, have been shown to be more efficacious than placebo as adjuncts to mood stabilizers for the treatment of bipolar mania. Conversely, other agents with proven antimanic activity as monotherapy may not confer additional efficacy in combination with mood stabilizers.[2] The effectiveness of some efficacious second-generation antipsychotics is reduced by adverse events, such as weight gain, extrapyramidal symptoms, and dysregulation of glucose or lipid metabolism.[3]

In placebo-controlled monotherapy trials,[4,5] ziprasidone has demonstrated efficacy for the treatment of acute bipolar manic and mixed episodes and does not appear to be associated with metabolic adverse events. A prior adjunctive ziprasidone study[6] failed to detect greater efficacy of adjunctive ziprasidone in acutely manic patients but found improvements in blood lipid profiles. The present study was designed to investigate the efficacy and safety of adjunctive ziprasidone in patients with acute mania with inadequate response to treatment with lithium or divalproex. The primary hypothesis was that both high- and low-dose adjunctive ziprasidone would be associated with a significantly greater change in the Young Mania Rating Scale (YMRS) total score from baseline to day 21 than the mood stabilizer alone.

## METHOD

This randomized, double-blind, placebo-controlled study (ClinicalTrials.gov identifier: NCT00312494) was conducted at 47 centers in the United States, after institutional review board approval at each center and in accordance with the International Conference on Harmonization guidelines on Good Clinical Practice and appropriate local regulatory requirements. Written informed consent was obtained from all patients or their authorized representatives.

### Participants

Men and women aged 18 to 65 years were included in the study if they had a primary diagnosis of bipolar I disorder, with the most recent episode manic (296.4x) or mixed (296.6x), with or without rapid cycling, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*).[7] The diagnosis was confirmed by the Mini-International Neuropsychiatric Interview (MINI).[8] Subjects were required to have experienced at least 1 prior mood episode according to the *DSM-IV* criteria, with or without hospitalization, during the previous 5 years, and to have a YMRS[9] score ≥ 18 at both screening and baseline (obtained at least 3 days apart), with < 25% improvement in YMRS scores between the 2 visits. The duration of the current episode

**Clinical Points**

- Combination therapy with a mood stabilizer and an atypical antipsychotic is recommended by most guidelines for the management of acute episodes of severe mania associated with bipolar disorder unresponsive to monotherapy.
- Adjunctive ziprasidone failed to separate from lithium or divalproex plus placebo treatment in key efficacy measures.
- No new clinically relevant safety data related to adjunctive ziprasidone use emerged from this study.

was required to be ≤ 3 months, and the duration of hospitalization for the index episode to be ≤ 4 weeks. Subjects were required to have documented therapeutic blood lithium concentration of 0.6 to 1.2 mEq/L or blood divalproex concentration of 50 to 125 μg/mL within 7 days prior to randomization.

Subjects who met the *DSM-IV* criteria for diagnosis of schizophrenia, schizoaffective, schizophreniform, delusional, or psychotic disorder; or had concomitant *DSM-IV* Axis I or Axis II disorders that were clinically unstable or required treatment were excluded. Other exclusion criteria were ultrafast rapid cycling (≥ 8 mood episodes in preceding 12 months), recent history of alcohol abuse or psychoactive substance abuse and suicide attempt (all within 3 months of screening), and a score ≥ 4 on the Montgomery-Asberg Depression Rating Scale (MADRS) suicide item.[10] Subjects were excluded if they had received monoamine oxidase inhibitors, fluoxetine, or the olanzapine and fluoxetine combination during the previous 4 weeks. In addition, subjects who had failed ≥ 2 adequate trials of an antipsychotic agent, as monotherapy or in combination therapy with lithium or an anticonvulsant, in a previous manic or mixed episode, were excluded. Subjects were also excluded if they had a corrected QT (QTc) interval ≥ 500 ms, a history of QTc prolongation, or any condition or drug treatment that could contribute to QTc prolongation.

### Study Design

Detailed study design, primary and secondary efficacy measures, safety and tolerability assessments, and subject flow during the study are shown in Figure 1. Within 30 days prior to screening, all subjects were required to have documented therapeutic blood lithium concentration (0.6–1.2 mEq/L) or blood divalproex concentration (50–125 μg/mL). Following a screening period of 3 to 7 days, 680 subjects (of 1,203 screened) who remained symptomatic despite having therapeutic levels of lithium or divalproex were randomized in a 1:1:1 ratio to receive flexible dosing with their mood stabilizer and a low dose (20–40 mg twice a day (bid) of ziprasidone (mood stabilizer + low-dose ziprasidone), a high dose (60–80 mg bid of ziprasidone (mood stabilizer + high-dose ziprasidone), or placebo (mood stabilizer + placebo) for 3 weeks (Figure 1).

Randomization was stratified by length of previous mood stabilizer treatment (7–14 days vs > 14 days), type of mood stabilizer therapy (lithium vs divalproex), rapid cycling (< 4 episodes vs 4–7 episodes in the previous 12 months), and hospitalization status (inpatient vs outpatient).

Mood stabilizer + low-dose ziprasidone subjects received an initial dose of 20 mg bid ziprasidone for 6 days, followed by flexible dosing for the remainder of the study. Mood stabilizer + high-dose ziprasidone subjects received an initial dose of 40 mg bid on day 1, followed by 60 mg bid on days 2 to 6 and flexible dosing for the remainder of the study. Doses could be increased in 20-mg increments at days 7 or 14, depending on efficacy and tolerability, while further dose adjustments were permitted for tolerability reasons only. Subjects were to be maintained on stable doses of mood stabilizer throughout the study (determined via blood sample evaluations at baseline, week 1, and week 3); dose adjustments were permitted only to reestablish therapeutic blood concentrations or if tolerability issues developed that, in the opinion of the investigator, might lead to withdrawal from the study.

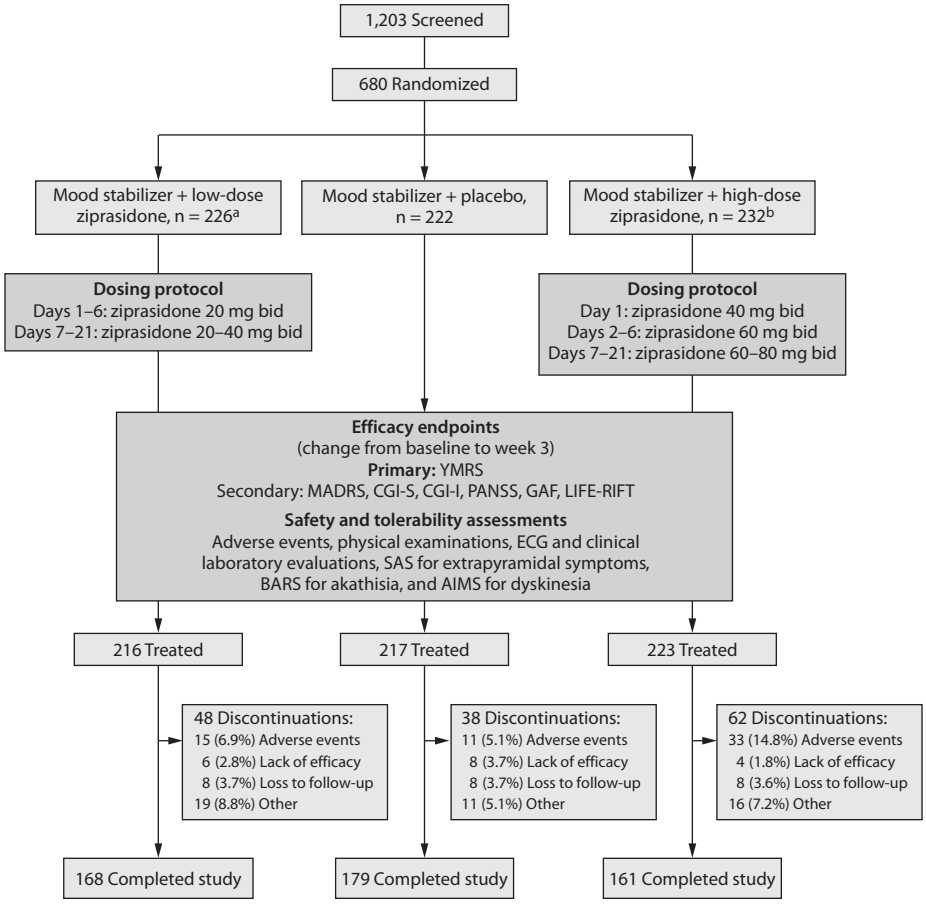
Adherence to study medication and mood stabilizer (beyond blood level assessments mentioned above) was assessed by pill counts; subjects who took < 80% or > 120% of their prescribed medication were withdrawn from the study. All other psychotropic medications, except for lithium, divalproex, benzodiazepines, and US Food and Drug Administration–approved nonbenzodiazepine sleep medications were withdrawn at least 2 days before randomization. Lorazepam was permitted at doses of up to 6 mg/d during screening and 4 mg/d during the first week of study treatment; use after day 9 was not permitted. US Food and Drug Administration–approved sleep medication (eg, zolpidem ≤ 10 mg/d, extended-release zolpidem ≤ 12.5 mg/d, or ramelteon ≤ 8 mg/d) was permitted only during the first 2 weeks of study treatment. Benztropine (≤ 6 mg/d) and propranolol (≤ 120 mg/d) could be used on an as-needed basis to control extrapyramidal symptoms and akathisia, respectively.

Efficacy measures were assessed at baseline and weeks 1, 2, and 3. The primary efficacy variable was change in YMRS score from baseline to 3 weeks. Secondary efficacy variables included MADRS,[10] Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales,[11] Positive and Negative Syndrome Scale (PANSS),[12] Global Assessment of Functioning (GAF),[13] and the Range of Impaired Functioning Tool (LIFE-RIFT).[14]

Safety and tolerability were assessed by recording of adverse events, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluation. Extrapyramidal symptoms were assessed by using the Simpson Angus Scale (SAS),[15] akathisia by using the Barnes Akathisia Rating Scale (BARS),[16] and dyskinesia by using the Abnormal Involuntary Movement Scale (AIMS).[11]

At each visit, the YMRS was administered by site-based trained and certified raters who had ≥ 2 years' clinical experience. Both raters and subjects were blinded to study

**Figure 1. Study Design and Subject Flow**




[a]Low-dose ziprasidone equals 20–40 mg twice a day.
[b]High-dose ziprasidone equals 60–80 mg twice a day.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, bid = twice a day, CGI-I = Clinical Global Impressions Improvement scale, CGI-S = Clinical Global Impressions Severity of Illness scale, ECG = electrocardiogram, GAF = Global Assessment of Functioning, LIFE-RIFT = Range of Impaired Functioning Tool, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson Angus Scale, YMRS = Young Mania Rating Scale.

treatment. In addition, a computerized interactive Remote-Site Monitoring system (Concordant Rater Systems, Boston, Massachusetts) was used to collect data on the primary efficacy variable YMRS from subjects and to provide feedback to the YMRS raters. The results from the Remote-Site Monitoring system are reported separately in a companion article.[17]

### Statistical Analyses

***Sample-size estimation.*** The sample size was 135 subjects per arm (total N = 405) to have 85% power for a 2-sample *t* test (2-sided $\alpha = .05$), assuming a true mean treatment difference from placebo of 3.5 and a standard deviation of 10 for the primary efficacy variable. A protocol-specified interim analysis, with the objective of validating the sample size assumptions and potentially adjusting the sample size, was performed after the first 207 subjects completed the study (or discontinued prematurely). On the basis of the recommendations from the independent interim analysis statistician, the study size was increased to 669 subjects (223 per arm) to ensure that the study had the desired power.

The primary efficacy analysis used the intent-to-treat (ITT) analysis set, excluding data from 2 sites that were closed because of Good Clinical Practice violations. The safety analysis set included all subjects who took at least 1 dose of double-blind study medication (including the 2 closed sites).

The primary efficacy analysis used mixed-model repeated measures analysis. The main effect in this model was treatment group; covariates were baseline YMRS score, length of previous mood stabilizer therapy (7–14 days vs > 14 days), type of mood stabilizer (lithium vs divalproex), rapid cycling (< 4 vs 4–7 episodes in the previous 12 months), and hospitalization status (inpatient vs outpatient). The model also included visit and treatment-by-visit interaction. The appropriate contrasts were constructed to compare the mean change from baseline to day 21 in YMRS total score between the ziprasidone dose groups and placebo (ie, mood stabilizer + high-dose ziprasidone vs mood stabilizer + placebo; and mood stabilizer + low-dose ziprasidone vs mood stabilizer + placebo). The Dunnett procedure was used to adjust for multiple active-treatment–group comparisons with placebo in the primary analysis. No other adjustments for multiple comparisons were made in any of the other analyses in this study. As a sensitivity check for the primary analysis, an analysis of covariance (ANCOVA) approach was used to compare adjunctive ziprasidone and placebo with respect to the primary efficacy variable. Mixed-model repeated measures analyses similar to the primary analysis were used for change from baseline in MADRS total score, CGI-S, and CGI-I scores (baseline value was not included in the model for the CGI-I).

## RESULTS

A total of 1,203 subjects were screened between April 2006 and December 2008, of whom 680 were randomized and 656 treated (modified ITT population; Figure 1); 220 subjects received lithium, and 436 subjects received divalproex as

**Table 1. Baseline Demographics and Clinical Characteristics**

| Variable | Mood Stabilizer + Placebo (n = 217) | Mood Stabilizer + Low-Dose Ziprasidone (n = 216)[a] | Mood Stabilizer + High-Dose Ziprasidone (n = 223)[b] |
|---|---|---|---|
| Age, arithmetic mean ± SD (range), y | 41.5 ± 10.3 (18–65) | 41.3 ± 11.1 (18–64) | 41.5 ± 11.1 (18–65) |
| Men, n (%) | 107 (49.3) | 108 (50.0) | 123 (55.2) |
| Women, n (%) | 110 (50.7) | 108 (50.0) | 110 (44.8) |
| Race, n (%) | | | |
| White | 137 (63.1) | 143 (66.2) | 146 (65.5) |
| Black | 66 (40.4) | 68 (31.5) | 63 (28.3) |
| Asian | 5 (2.3) | 0 (0) | 3 (1.3) |
| Other | 9 (4.1) | 5 (2.3) | 11 (4.9) |
| Weight, arithmetic mean ± SD (range), kg | 85.8 ± 23.7 (40.4–199.1) | 87.3 ± 20.6 (34.9–186.0) | 92.2 ± 20.1 (40.8–170.6) |
| Primary diagnosis, n (%) | | | |
| Manic | 128 (59) | 134 (62) | 142 (64) |
| Mixed | 89 (41) | 82 (38) | 81 (36) |
| Time since diagnosis, mean (range), y | | | |
| Manic | 17.3 (0.1–42.7) | 18.1 (1.5–45.4) | 16.4 (0.1–46.8) |
| Mixed | 17.4 (0.1–41.3) | 15.9 (0.0–43.7) | 17.6 (0.0–38.7) |
| Age at first manic episode, arithmetic mean ± SD (range), y | 23 ± 10 (7–55) | 23 ± 9 (6–53) | 23 ± 10 (8–56) |
| Age at first depressive episode, arithmetic mean ± SD (range), y | 21 ± 8 (5–48) | 21 ± 8 (6–45) | 21 ± 9 (6–56) |
| Time since last manic/mixed episode, arithmetic mean ± SD (range), mo | 11 ± 11 (0–72) | 11 ± 14 (0–96) | 10 ± 12 (0–116) |
| Previous suicidal thoughts, n (%) | 115 (53.5) | 113 (52.3) | 127 (57.0) |
| Previously attempted suicide, n (%) | 87 (40.1) | 85 (39.4) | 105 (47.1) |
| Previous hospitalization, n (%) | 188 (86.6) | 179 (82.9) | 186 (83.4) |
| | n = 201[c] | n = 210[c] | n = 211[c] |
| YMRS total score, arithmetic mean ± SD (range) | 26.0 ± 5.3 (18.0–45.0) | 26.7 ± 5.3 (18.0–42.0) | 27.7 ± 5.9 (18.0–45.0) |
| CGI-S score, arithmetic mean ± SD (range) | 4.4 ± 0.7 (3.0–6.0) | 4.4 ± 0.7 (3.0–6.0) | 4.5 ± 0.7 (3.0–7.0) |

[a]Low-dose ziprasidone equals 20–40 mg twice a day.
[b]High-dose ziprasidone equals 60–80 mg twice a day.
[c]Intent-to-treat population excluding the 2 sites closed for Good Clinical Practice violations.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, YMRS = Young Mania Rating Scale.

their mood stabilizer. Reasons for not receiving treatment included patients being lost to follow-up or no longer willing to participate in study, protocol violation, laboratory or electrocardiogram abnormality, or investigator decision. The majority of patients (92%) had experienced < 4 episodes, and 202 patients (31%) were hospitalized.

While 508 subjects completed the study, 148 subjects were withdrawn during the course of the study, including 59 who withdrew because of adverse events (Figure 1). The most common adverse events leading to discontinuation were sedation (mood stabilizer + placebo, 2 subjects; mood stabilizer + high-dose ziprasidone, 5 subjects), somnolence (mood stabilizer + high-dose ziprasidone, 3 subjects; mood stabilizer + low-dose ziprasidone, 1 subject), nausea (mood stabilizer + high-dose ziprasidone, 2 subjects; mood stabilizer + placebo, 1 subject), akathisia (mood stabilizer + high-dose ziprasidone, 3 subjects; mood stabilizer + low-dose ziprasidone, 1 subject), and psychiatric disorders/worsening of mania (mood stabilizer + high-dose ziprasidone, 2 subjects; mood stabilizer + low-dose ziprasidone, 1 subject; mood stabilizer + placebo, 1 subject).

The treatment groups were well matched by clinical characteristics (Table 1).

For both mood stabilizers, the mean blood levels across treatment groups were within the specified therapeutic range at baseline through day 24. The mean ± SD serum divalproex levels on the visit that occurred between days 18 and 24 were 74.8 ± 28.3 μg/mL for mood stabilizer + high-dose ziprasidone (n = 109), 73.8 ± 28.2 μg/mL for mood stabilizer + low-dose ziprasidone (n = 106), and 72.8 ± 32.6 μg/mL for mood stabilizer + placebo (n = 113). At the same time point, the mean ± SD serum lithium levels were 0.8 ± 0.4 mEq/L for mood stabilizer + high-dose ziprasidone (n = 45), 0.8 ± 0.3 mEq/L for mood stabilizer + low-dose ziprasidone (n = 50), and 0.8 ± 0.3 mEq/L for mood stabilizer + placebo (n = 55). More subjects reported using antimuscarinic agents in the mood stabilizer + high-dose ziprasidone group (9.4%) than in the mood stabilizer + low-dose ziprasidone (6.5%) or mood stabilizer + placebo (1.8%) groups, while the proportion of subjects using lorazepam was consistent in the 3 groups (27.4%, 27.7%, and 26.3%, respectively). The most common comorbid psychiatric symptoms at screening were insomnia (29.3%), anxiety (20.4%), depression (14.5%), and agitation (11.7%). Overall, 58 subjects (8.8%) had a family history of schizophrenia, and 32 subjects (4.9%) had family history of suicide.

## Efficacy

The mean ± SD daily doses of ziprasidone were 54.3 ± 13.4 mg in the mood stabilizer + low-dose ziprasidone group (n = 216) and 124.6 ± 18.7 mg in the mood stabilizer + high-dose ziprasidone group (n = 223). Mean modal ziprasidone doses were 60.09 and 133.81 mg/d, respectively, for the 2 groups. Mean ± SD doses of divalproex at baseline were 1,243 ± 376 mg/d (mood stabilizer + placebo), 1,270 ± 387 mg/d (mood stabilizer + low-dose ziprasidone), and 1,321 ± 474 mg/d (mood stabilizer + high-dose ziprasidone). Mean ± SD lithium doses at baseline were 1,021 ± 231 mg/d (mood stabilizer + placebo), 1,010 ± 252 mg/d (mood stabilizer + low-dose ziprasidone), and 1,013 ± 283 mg/d (mood

**Table 2. Summary of Primary and Secondary Efficacy Analyses: Mixed-Model Repeated Measures Analysis, Intent-to-Treat Population[a]**

| Analysis | Mood Stabilizer + Placebo | Mood Stabilizer + Low-Dose Ziprasidone[b] | Mood Stabilizer + High-Dose Ziprasidone[c] | Pairwise Comparisons[d] Mood Stabilizer + High-Dose Ziprasidone vs Mood Stabilizer + Placebo[e,f] | | Mood Stabilizer + Low-Dose Ziprasidone vs Mood Stabilizer + Placebo[f] | |
|---|---|---|---|---|---|---|---|
| | | | | *P* Value | 95% CI | *P* Value | 95% CI |
| Primary efficacy analysis: YMRS total score | | | | | | | |
| Change from baseline to wk 1 | | | | | | | |
| n | 200 | 205 | 202 | | | | |
| Mean ± SD | −5.5 ± 7.0 | −5.2 ± 6.7 | −5.5 ± 6.9 | | | | |
| LS mean ± SE | −5.1 ± 0.7 | −4.6 ± 0.7 | −4.4 ± 0.7 | .283 | −0.60 to 2.06 | .403 | −0.74 to 1.83 |
| Change from baseline to wk 2 | | | | | | | |
| n | 186 | 188 | 178 | | | | |
| Mean ± SD | −8.6 ± 8.1 | −8.3 ± 8.6 | −8.2 ± 8.0 | | | | |
| LS mean ± SE | −8.2 ± 0.8 | −7.6 ± 0.7 | −7.1 ± 0.7 | .153 | −0.42 to 2.71 | .413 | −0.94 to 2.3 |
| Change from baseline to wk 3[d] | | | | | | | |
| n | 170 | 172 | 163 | | | | |
| Mean ± SD | −9.8 ± 9.1 | −11.6 ± 9.1 | −11.2 ± 8.5 | | | | |
| LS mean ± SE | −9.5 ± 0.8 | −11.0 ± 0.8 | −10.2 ± 0.8 | .427 | −2.52 to 1.07 | .108 | −3.3 to 0.33 |
| Secondary efficacy analyses | | | | | | | |
| MADRS total score: change from baseline to wk 3 | | | | | | | |
| n | 170 | 172 | 163 | | | | |
| LS mean ± SE | −2.9 ± 0.7 | −3.8 ± 0.6 | −4.2 ± 0.6 | .0796 | −2.75 to 0.15 | .2302 | −2.33 to 0.56 |
| CGI-S score: change from baseline to wk 3 | | | | | | | |
| n | 171 | 172 | 163 | | | | |
| LS mean ± SE | −0.9 ± 0.1 | −1.1 ± 0.1 | −0.9 ± 0.1 | .5558 | −0.15 to 0.28 | .2385 | −0.34 to 0.08 |
| CGI-I score: change from baseline to wk 3 | | | | | | | |
| n | 171 | 172 | 163 | | | | |
| LS mean ± SE | 2.7 ± 0.2 | 2.6 ± 0.2 | 2.7 ± 0.2 | .5967 | −0.32 to 0.18 | .2378 | −0.39 to 0.1 |
| PANSS total score: change from baseline to wk 3 | | | | | | | |
| n | 189 | 199 | 198 | | | | |
| LS mean ± SE | −3.4 ± 1.8 | −5.3 ± 1.7 | −4.9 ± 1.9 | .2499 | −3.85 to 1.00 | .1063 | −4.19 to 0.41 |
| GAF score: change from baseline to wk 3 | | | | | | | |
| n | 190 | 199 | 199 | | | | |
| LS mean ± SE | 7.8 ± 1.2 | 9.6 ± 1.3 | 8.8 ± 1.2 | .3174 | −0.96 to 2.95 | .0728 | −0.17 to 3.83 |
| LIFE-RIFT score: change from baseline to wk 3 | | | | | | | |
| n | 188 | 197 | 196 | | | | |
| LS mean ± SE | −1.3 ± 0.5 | −1.6 ± 0.5 | −1.7 ± 0.5 | .3253 | −1.23 to 0.41 | .4460 | −1.08 to 0.48 |

[a]Excluding the 2 sites closed for Good Clinical Practice violations.
[b]Low-dose ziprasidone equals 20–40 mg twice a day.
[c]High-dose ziprasidone equals 60–80 mg twice a day.
[d]95% CIs and *P* values presented are not adjusted for multiple-dose comparisons to placebo.
[e]Primary efficacy analysis.
[f]95% CI reported is for the treatment difference.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, LIFE-RIFT = Range of Impaired Functioning Tool, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SE = standard error, YMRS = Young Mania Rating Scale.

stabilizer + high-dose ziprasidone). Mood stabilizer doses did not change appreciably during the study.

***Primary efficacy analysis.*** Table 2 summarizes the mixed-model repeated measures analysis results for the change from baseline YMRS total score by week. The mean treatment differences in the primary efficacy variable between each of the adjunctive ziprasidone dose groups and the mood stabilizer + placebo group were not statistically significant (ie, unadjusted *P* values were > .027 [α = .027 for Dunnett critical value 2.21] for each of the 2 comparisons in the primary analysis). Results from the sensitivity analyses (ANCOVA using both last-observation-carried-forward and observed cases data) were also consistent with those from the primary efficacy analyses.

***Secondary efficacy analyses.*** Overall, there were no statistically significant differences between either mood stabilizer + low-dose ziprasidone or mood stabilizer + high-dose ziprasidone and mood stabilizer + placebo at week 3, or at any other time point (Table 2), although a marginally significant effect on MADRS (*P* = .0796) was seen in the mood stabilizer + high-dose ziprasidone group. The per protocol analysis results for the primary and secondary variables were consistent with the results of the ITT analysis.

Additional post hoc subgroup analyses (subgroups based on stratification variables used in the randomization for this study) were conducted for exploratory purposes. These post hoc subgroup analyses showed that subjects who were hospitalized (n = 180) tended to show a larger effect on the primary efficacy measure compared with nonhospitalized subjects (n = 444). At week 3, the LS mean ± standard error (SE) difference from the mood stabilizer + placebo group (n = 52) in the hospitalized subgroup was −1.1 ± 1.1 for the

**Table 3. Summary of Adverse Events (all causalities)**

| Variable | Mood Stabilizer + Placebo (n = 217) | Mood Stabilizer + Low-Dose Ziprasidone (n = 216)[a] | Mood Stabilizer + High-Dose Ziprasidone (n = 223)[b] |
|---|---|---|---|
| No. of adverse events | 211 | 322 | 407 |
| Adverse events, n (%) | 107 (49.3) | 136 (63.0) | 166 (74.4) |
| Severe adverse events, n (%) | 6 (2.8) | 7 (3.2) | 18 (8.1) |
| Serious adverse events, n (%) | 6 (2.8) | 5 (2.3) | 6 (2.7) |
| Adverse events occurring in ≥ 5% of patients, n (%) | | | |
| Sedation | 18 (8.3) | 17 (7.9) | 33 (14.8) |
| Headache | 16 (7.4) | 19 (8.8) | 10 (4.5) |
| Dizziness | 6 (2.8) | 5 (2.3) | 16 (7.2) |
| Diarrhea | 7 (3.2) | 10 (4.6) | 12 (5.4) |
| Nausea | 13 (6.0) | 11 (5.1) | 11 (4.9) |
| Vomiting | 4 (1.8) | 6 (2.8) | 13 (5.8) |
| Akathisia | 5 (2.3) | 8 (3.7) | 15 (6.7) |
| Somnolence | 5 (2.3) | 19 (8.8) | 26 (11.7) |
| Tremor | 7 (3.2) | 6 (2.8) | 12 (5.4) |

[a]Low-dose ziprasidone equals 20–40 mg twice a day.
[b]High-dose ziprasidone equals 60–80 mg twice a day.

**Table 4. Summary of Changes in Metabolic Indices**

| Variable | Mood Stabilizer + Placebo | Mood Stabilizer + Low-Dose Ziprasidone[a] | Mood Stabilizer + High-Dose Ziprasidone[b] |
|---|---|---|---|
| Waist circumference, median, cm | | | |
| n | 199 | 203 | 209 |
| Baseline | 94.0 | 96.5 | 100.8 |
| Change from baseline to end of study | 0.0 | 0.0 | 0.0 |
| Body mass index (kg/m$^2$), median | | | |
| n | 217 | 215 | 221 |
| Baseline | 27.8 | 29.3 | 29.9 |
| n | 201 | 205 | 204 |
| Change from baseline to end of study | 0.1 | 0.2 | 0.1 |
| Total cholesterol, median, mg/dL | | | |
| n | 199 | 192 | 191 |
| Baseline | 171 | 164 | 166 |
| Change from baseline to end of study | 1 | −3 | −9 |
| LDL cholesterol, median, mg/dL | | | |
| n | 192 | 185 | 181 |
| Baseline | 106 | 100 | 104 |
| Change from baseline to end of study | 0 | −3 | −7 |
| HDL cholesterol, median, mg/dL | | | |
| n | 199 | 192 | 191 |
| Baseline | 118 | 118 | 111 |
| Change from baseline to end of study | 0 | 0 | 6 |

[a]Low-dose ziprasidone equals 20–40 mg twice a day.
[b]High-dose ziprasidone equals 60–80 mg twice a day.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

mood stabilizer + high-dose ziprasidone group (n = 62) and −3.1 ± 2.0 for the mood stabilizer + low-dose ziprasidone group (n = 66). At the same time point, the LS mean ± SE difference from the mood stabilizer + placebo group (n = 150) in the nonhospitalized subgroup was −0.4 ± 1.1 for mood stabilizer + high-dose ziprasidone group (n = 149) and −0.9 ± 1.9 for the mood stabilizer + low-dose ziprasidone group (n = 145).

### Safety and Tolerability

Adverse event data by treatment are summarized in Table 3. Most adverse events were mild or moderate in severity; severe adverse events were reported by < 10% of subjects in each group. More subjects discontinued treatment because of adverse events in the mood stabilizer + high-dose ziprasidone group (14.8%) than in the other groups (mood stabilizer + low-dose ziprasidone, 6.9%; mood stabilizer + placebo, 5.1%). Among treatment-related adverse events reported by ≥ 5% of subjects, the most frequently reported adverse events in the adjunctive ziprasidone groups were sedation and somnolence. Serious adverse events were reported by 11 adjunctive ziprasidone-treated subjects and 6 subjects in the placebo group. None were considered to be treatment-related. These included bipolar I disorder; single cases of suicidal ideation, multiple drug overdose, and chest pain; suicide attempt, mania, aggression, hypertension, overdose, anterograde amnesia, drug dependence, and alcoholism; and acute psychosis, chemical burn of the skin, mania, and cellulitis.

Ziprasidone did not show an effect on weight, body mass index, or waist circumference (Table 4). The blood lipid profile showed some improvement: total cholesterol and low-density lipoprotein decreased, while high-density lipoprotein increased in the mood stabilizer + high-dose ziprasidone group only. There was no effect of adjunctive ziprasidone on fasting blood glucose or glycosylated hemoglobin levels.

There was no evidence of increases in liver enzymes or liver function tests with adjunctive ziprasidone (compared with placebo). Increases in prolactin of 0.9 and 1.8 ng/mL were observed in the low- and high-dose ziprasidone groups, respectively; however, there were no increases in adverse events related to prolactin among the adjunctive ziprasidone groups. No QTc prolongation (defined as QT corrected for heart rate according to Fridericia or Bazett formulas) above 500 ms was observed in any treatment group.

The incidence of treatment-related extrapyramidal symptom adverse events was higher in the mood stabilizer + high-dose ziprasidone group (4.9%) than in the mood stabilizer + low-dose ziprasidone (1.9%) and mood stabilizer + placebo (0.5%) groups. Results from the SAS and BARS scales indicated a small but significant worsening of effect with mood stabilizer + high-dose ziprasidone treatment (LS mean [SE] treatment difference from placebo: 0.26 [0.11], $P = .0042$, for SAS; and 0.11 [0.17], $P = .0447$, for BARS). Results of the AIMS scale did not indicate any meaningful changes in abnormal movements (dyskinesia). One subject in

the mood stabilizer + high-dose ziprasidone group reported an adverse event of dyskinesia.

## DISCUSSION

This study did not find a significant benefit of adjunctive ziprasidone over placebo for treatment of acute mania in subjects receiving lithium or divalproex. Although this finding is in broad agreement with those in a previous trial[6] with adjunctive ziprasidone, it is surprising, considering the evidence of ziprasidone's antimanic efficacy in monotherapy trials. In the absence of an active control arm, however, assay sensitivity was not established. Therefore, our results cannot confidently distinguish between a negative finding and a failed study.

Add-on treatment with ziprasidone was generally well tolerated in this study. The adverse event profile was consistent with those of other atypical antipsychotics. However, ziprasidone may offer important tolerability advantages in terms of a lower risk of weight gain and other undesirable metabolic effects, compared with other atypical antipsychotics. Indeed, in this study, adjunctive ziprasidone was not associated with weight gain or with clinically relevant changes in glucose or lipid levels. In fact, there was slight improvement in lipid levels, as seen in a previous study.[8] Extrapyramidal symptoms were more prevalent in the mood stabilizer + high-dose ziprasidone group compared with the mood stabilizer + low-dose ziprasidone group and may reflect greater dopamine $D_2$ receptor blockade at higher doses. Overall, the adverse event profile was higher in the mood stabilizer + high-dose ziprasidone group compared with the mood stabilizer + low-dose ziprasidone and mood stabilizer + placebo groups, indicating that the low dose is better tolerated, as would be expected.

The failure to demonstrate efficacy of adjunctive ziprasidone in acute mania in this trial does not support our hypothesis that ziprasidone is an efficacious adjunctive agent in acute mania. Although possibly accurate, the lack of efficacy in this study is surprising in light of the successful monotherapy studies and is at odds with data from a study demonstrating the efficacy of ziprasidone as adjunctive maintenance treatment following acute mania.[18] These results raise the possibility that the study may have failed for reasons other than lack of efficacy.[11]

High placebo response is often cited as a reason for study failure, but it does not seem to explain our results. The results for mood stabilizer + placebo in this study are less robust than those reported for some true (monotherapy) placebo groups and all the active monotherapy groups in monotherapy trials. The placebo response in this study is modest in comparison with the placebo response in most other adjunct and monotherapy studies.[4,19–22] In contrast with this study, the ziprasidone monotherapy studies[4,5] enrolled inpatients exclusively, dosed more aggressively, and had more protocol-specified controls to assure that doses were delivered with food, thus ensuring better absorption. Other factors that may have contributed to the failure to demonstrate efficacy are noncompliance with study treatment and enrollment of inappropriate subjects.

Post hoc analyses revealed that hospitalized subjects showed a larger effect on the primary efficacy measure than did nonhospitalized subjects. This outcome is consistent with findings from prior outpatient mania studies.[22] Hospitalized subjects may have a more severe disease, may receive a study drug more reliably, and may gain some therapeutic benefit from the structured setting of the hospital.

It is worth noting also that, in the higher dose group, ziprasidone showed a near-significant improvement in MADRS scores, indicating that ziprasidone may be more beneficial in treating the depressive symptoms evaluated with MADRS than the mania spectrum.

In conclusion, adjunctive ziprasidone treatment failed to separate from lithium or divalproex treatment alone on the analysis of the primary and key secondary end points in this study. Several factors may have contributed to this outcome, but high placebo response does not appear to account for the findings. The companion article[11] uses analyses from computer-based assessments to examine the impact of eligibility criteria in more detail.

***Drug names:*** benztropine (Cogentin and others), divalproex (Depakote and others), fluoxetine (Prozac and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa and others), propranolol (Inderal, InnoPran, and others), quetiapine (Seroquel and others), ramelteon (Rozerem), risperidone (Risperdal and others), ziprasidone (Geodon and others), zolpidem (Ambien, Edluar, and others).

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