Two 6-Week, Randomized, Double-Blind, Placebo-Controlled Studies of Ziprasidone in Outpatients With Bipolar I Depression

Did Baseline Characteristics Impact Trial Outcome?

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Abstract: Two randomized, double-blind, placebo-controlled, 6-week studies comparing ziprasidone versus placebo for treatment of bipolar depression (BPD) failed to meet their primary study objectives, indicating that either ziprasidone is ineffective in the treatment of BPD or the study failed.

Adult outpatients with bipolar I depression with 17-item Hamilton Rating Scale for Depression total score more than 20 at screening and baseline received either ziprasidone 40 to 80 mg/d, 120 to 160 mg/d, or placebo (study 1), or ziprasidone 40 to 160 mg/d or placebo (study 2). Primary efficacy measure in both studies was change from baseline in Montgomery-Åsberg Depression Rating Scale total scores at week 6 (end of the study). Mixed-model repeated-measures methodology was used to analyze the primary efficacy measure in both studies. Secondary efficacy measures in both studies included Hamilton Rating Scale for Depression total score and Clinical Global Impression-Improvement score. Post hoc analyses were conducted for both studies to examine potential reasons for study failure. In both, ziprasidone treatment groups failed to separate statistically from placebo for change from baseline Montgomery-Åsberg Depression Rating Scale score at week 6. Response rates were 49%, 53%, and 46% for placebo, ziprasidone 40 to 80 mg/d, and ziprasidone 120 to 160 mg/d, respectively (study 1), and 51% and 53% for placebo and ziprasidone 40 to 160 mg/d, respectively (study 2).

Ziprasidone 40 to 160 mg/d did not show superiority over placebo at week 6 in the treatment of BPD. Post hoc analyses revealed serious inconsistencies in subject rating that may have limited the ability to detect a difference between drug and placebo response. Rating reliability warrants further investigation to improve clinical trial methodology in psychiatry.

Key Words: bipolar depression, atypical antipsychotic, placebo response

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Acute bipolar depression (BPD) is defined by a major depressive episode in a patient with bipolar disorder. Episodes of BPD share diagnostic criteria such as sadness, anxiety, guilt, anger, and sleep disturbances, with episodes of major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]*). Despite the cross-sectional clinical similarities, BPD responds poorly to standard antidepressants as monotherapy or as an adjunct to mood stabilizers.[1–3] Other classes of medication have, however, demonstrated efficacy for BPD.[1,4,5]

In 2003, Tohen et al[5] reported that olanzapine and the combination of olanzapine and fluoxetine (OFC) were superior to placebo for treatment of BPD, and the US Food and Drug Administration granted approval to OFC in December 2003. Interest in atypical antipsychotic medication as treatment for BPD followed this success in the hopes that, as a class, atypical antipsychotics might be effective for the treatment of BPD,[5–7] but results from clinical trials have been mixed. Whereas quetiapine[6,7] and OFC[6] have demonstrated efficacy for the treatment of BPD, bifeprunox and aripiprazole failed to demonstrate superiority to placebo in 2 recent clinical trials based on the change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to the end of the study.[8,9] Studies of lamotrigine for BPD have also produced inconsistent results.[10]

Placebo response is a common problem in clinical trials for psychiatric disorders.[11] In randomized trials for bipolar disorder, there has been a pronounced increase in placebo response during the last several years.[12] Some investigators have suggested that a component of the apparent placebo response may be attributable to a phenomenon referred to as baseline inflation, in which the baseline scores of subjects entering trial may be exaggerated so as to be above the threshold required for study entry.[13]

Ziprasidone is an atypical antipsychotic that, like most commonly prescribed antidepressants, inhibits the reuptake of serotonin and norepinephrine. Given that several small studies supported the use of ziprasidone for BPD,[14–16] the primary objective of the present studies was to compare the efficacy of ziprasidone with placebo during a 6-week course of treatment in outpatients with bipolar I disorder. In an effort to mitigate baseline inflation of the primary efficacy measure, the 17-item Hamilton Rating Scale for Depression (HAM-D-17) was used to determine eligibility, and the MADRS was the primary measure of efficacy. Here, we describe the findings of the 2 studies; in both, ziprasidone failed to separate statistically from placebo for the change from baseline MADRS score at week 6. To better understand the outcome of the 2 present studies, we further examined the relationship between the HAM-D-17 and MADRS scores at screening and at baseline. The concurrent use of 2 rating scales allowed for evaluation of the reliability of illness severity ratings and may provide insights applicable to broader clinical trial methodology.

MATERIALS AND METHODS

Study Population

Inclusion Criteria

Subjects who met the following criteria were included in both studies: (1) men and women aged 18 years or older at the time of consent, with a primary diagnosis of bipolar I disorder,

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most recent episode depressed, with or without rapid cycling, and without psychotic features, as defined in the *DSM-IV-Text Revision* (296.5X) and confirmed by the Mini International Neuropsychiatric Interview version 5.0.0.[17]; (2) lifetime history of at least 1 bipolar manic or mixed-manic episode (the initial protocol required at least 1 lifetime hospitalization for a bipolar manic or mixed-manic episode; this requirement was dropped in May 2007); (3) HAM-D-17 total score more than 20 at screening and at baseline (HAM-D-17 score was derived from the first 17 items of the HAM-D-25[18]), obtained at least 3 days apart, and screening-to-baseline improvement in HAM-D-17 total score less than 25%; (4) Young Mania Rating Scale (YMRS[19]) score less than 12 at screening and at baseline, obtained at least 3 days apart; duration of the current bipolar I disorder depressive episode of more than 2 weeks and less than 6 months.

Exclusion Criteria

The following subjects were excluded from both studies: (1) subjects diagnosed with schizophrenia or schizoaffective disorder, schizophreniform disorder, delusional disorder, or psychotic disorders not otherwise specified; (2) subjects who failed 3 or more adequate studies (more than 4 weeks at an adequate dose) of an antidepressant either as monotherapy or in combination therapy (with lithium or an anticonvulsant) in a previous depressive episode or within the current episode; (3) subjects with psychotic features associated with bipolar I depression within the index (ie, current) episode; (4) subjects with ultrafast rapid cycling (defined as 8 or more mood episodes during the 12-month period preceding the screening visit); (5) subjects with YMRS score more than 16 at screening or at baseline were discontinued from the study and provided with appropriate treatment or referral by the investigator; (6) subjects with a YMRS score greater than or equal to 16 at any postbaseline visit; (7) subjects with *DSM-IV-Text Revision*–defined alcohol or psychoactive substance abuse in the 3-month period preceding the screening visit or significant risk of self-injurious/suicidal or violent/homicidal behavior; (8) subjects with a history of inadequate response to ziprasidone (at least 6 weeks' duration) for the treatment of BPD or a history of intolerance to ziprasidone; (9) subjects who had ever been discontinued from ziprasidone treatment because of lack of efficacy or significant adverse events (AEs).

In addition, subjects were required to have discontinued use of previous psychotropic agents (including anticonvulsants) for a minimum of 1 week; lithium for a minimum of 2 weeks; monoamine oxidase inhibitors, fluoxetine, or the OFC for a minimum of 4 weeks; and any depot neuroleptic agent for a minimum of 6 months before being randomized into the study. Women of childbearing age agreed to use birth control. All subjects provided written informed consent.

Study Design

Studies 1 and 2 were 6-week, randomized, double-blind, multicenter, flexible-dose, placebo-controlled studies conducted in the United States evaluating the efficacy and safety of oral ziprasidone in outpatient subjects aged 18 years and older with bipolar I disorder. The first study recruited participants from 56 of 70 investigational sites in 25 states, whereas the second recruited at 45 sites from a total of 48 sites in 22 states. Fifteen states contributed to both trials.

Study 1 (A1281136, July 2005–February 2008)

Subjects were randomly assigned to a ziprasidone fixed-flexible dosing group (20–40 mg twice daily [bid] or 60–80 mg bid) or placebo in a 1:1:1 ratio as follows:

- Ziprasidone low-dose (40–80 mg/d): subjects started dosing at 20 mg bid on days 1 to 6, then flexible dosing started on day 7 (20–40 mg bid [20 mg bid or 40 mg bid at the discretion of the investigator]) for the remainder of the 6-week study.
- Ziprasidone high-dose (120–160 mg/d): subjects started at 20 mg bid on days 1 to 2, then 40 mg bid on days 3 to 4, then 60 mg bid on days 5 to 6, then flexible dosing started on day 7 (60–80 mg bid [60 mg bid or 80 mg bid at the discretion of the investigator]) for the remainder of the 6-week study.
- Placebo: subjects were given placebo with the same flexible dosing schedule as ziprasidone for the entire 6-week study.

Study 2 (A1281139, February 2006–March 2008)

Subjects were randomly assigned to a ziprasidone flexible-dose treatment group or placebo in a 1:1 ratio as follows:

- Ziprasidone flexible-dose treatment group: subjects were started at 20 mg bid fixed dose on days 1 and 2, 40 mg bid on days 3 to 6, and flexible dosing starting on day 7 (ie, 20–80 mg bid, adjustable by 20 mg bid at each visit) for the remainder of the 6-week study.
- Placebo: subjects were given placebo with the same flexible dosing schedule as ziprasidone for the entire 6-week study.

Concomitant Medication

For agitation or intolerable anxiety, lorazepam up to 2 mg/d was allowed during the screening period and the first 2 weeks of double-blind treatment up to 4 days per week. For insomnia, nonbenzodiazepine sleep agents (all approved agents, eg, zolpidem up to 10 mg/d, eszopiclone up to 3 mg/d, zaleplon up to 20 mg/d, or ramelteon up to 8 mg/d) were allowed during the screening period and the first 2 weeks of double-blind treatment up to 4 days per week and for the remainder of the study up to 2 days per week. Benztropine (up to 6 mg/d) for extrapyramidal symptoms and propranolol (up to 120 mg/d) for akathisia were allowed only on an as-needed basis and not on a continuous daily basis prophylactically to treat extrapyramidal symptoms/akathisia. These medications were not allowed within the 12 hours before cognitive testing. All other psychoactive medications were prohibited during the subject's participation in the study.

Efficacy, Safety, and Post Hoc Analyses

Efficacy

The primary efficacy measure in both studies was the change in MADRS total score[20] from baseline to week 6 (end of the study). Response on the MADRS scale was defined as a 50% or greater reduction from baseline in the MADRS total score. Secondary efficacy measures included baseline and postbaseline measurement of the range of depressive symptoms (using HAM-D score), anxiety (HAM-A score), mania (using YMRS), global clinical severity, and global improvement of symptoms (via Clinical Global Impression [CGI] of Severity and CGI of Improvement scores, respectively); global assessment of functioning; change in quality of life, enjoyment, or satisfaction; occupational/psychosocial impact of symptoms; and cognition.

Safety

Safety and tolerability assessments included AEs, vital signs, laboratory tests, serum prolactin, and weight. Movement disorder symptoms were measured using the Simpson-Angus Scale (SAS),[21] the Barnes Akathisia Scale (BAS),[22] and the Abnormal Involuntary Movement Scale (AIMS).

Post Hoc Analyses

Post hoc analyses were performed for both studies to obtain a better understanding of potential reasons for study failure such as high placebo response and rating inconsistencies. Specifically, comparisons were made between the MADRS scores and HAM-D-17 scores at baseline and between MADRS actual scores and predicted MADRS scores (ie, MADRS scores derived from HAM-D scores using the formula developed by Zimmerman et al[23]). Subgroup analyses to study the influence of baseline illness severity (as measured by the MADRS score) were also performed.

Statistical Analysis

The safety population for both studies included all randomized subjects who were administered at least 1 dose of double-blind study medication. The intent-to-treat (ITT) population for both studies included all subjects included in the safety population and for whom at least 1 postbaseline primary efficacy evaluation was obtained. The primary efficacy analysis in both studies used the ITT population.

Efficacy

Similar mixed-model repeated-measures (MMRM) analyses were used for the primary efficacy evaluation in both studies. The primary comparisons of interest in both studies were the mean changes from baseline to week 6 in MADRS score between ziprasidone and placebo. In study 1, the specific treatment comparisons of interest were ziprasidone 120 to 160 mg/d versus placebo and ziprasidone 40 and 80 mg/d versus placebo. The primary analysis was based on the ITT population using observed cases (OCs) data. The Hochberg procedure for adjusting for multiple treatment comparisons was used only for the change from baseline MADRS score (at each time point) in the MMRM analysis only. The MMRM model in both studies included fixed categorical effects of treatment, rapid cycling, center, visit, previous hospitalization status (with or without previous bipolar manic or mixed-manic episode hospitalization), and treatment-by-visit interaction, as well as fixed continuous effect of baseline MMRS total score in the model. The subject effect was included as a random effect. The restricted maximum likelihood estimation method was used for the MMRM analysis with a sandwich estimator of the variance-covariance matrix of the fixed-effects parameters. An unstructured variance-covariance matrix was used. The assumptions of the MMRM analyses were evaluated. In addition, changes from baseline in MADRS total score at each visit week (last observation carried forward [LOCF] at week 6 and OC data at each visit week) were analyzed with an analysis of covariance (ANCOVA) model that included the following model terms: treatment, rapid cycling, center, previous hospitalization status, and baseline score as a covariate.

For the secondary efficacy evaluations in both studies, the MMRM model described above for the MADRS total score was applied to the change from baseline in CGI of severity and CGI of improvement scores. Change from baseline in HAM-D-17 at each visit week was analyzed using the ANCOVA model described above for the MADRS total score.

The Cochran-Mantel-Haenszel test stratified by study center and rapid cycling strata was used in both studies to compare response rates between ziprasidone and placebo, where response based on the MADRS scales was defined as a more than 50% reduction from the baseline MADRS total score.

Safety

Standard safety summaries of AEs, vital signs, laboratory tests, serum prolactin, and weight were generated. Analysis of the change from baseline to the end of the study in SAS total score, BAS global clinical assessment of akathisia, AIMS total score, AIMS global severity score, and AIMS incapacitation score was performed using the same ANCOVA model described above in the analysis of the MADRS total score.

Post Hoc Analyses

Additional post hoc analyses were conducted for both studies to outline possible reasons for study failure. These included:

(1) Comparison of the distribution of MADRS total scores and HAM-D-17 scores at baseline using graphical displays of MADRS total scores and the HAM-D-17 scores at baseline with the inclusion cutoff highlighted for both scales.

(2) Analysis comparing the actual and predicted (ie, derived from HAM-D-17) MADRS total scores at both baseline and the end of the study (using LOCF data) were performed as a measure of rating reliability. Specifically, predicted MADRS total scores were calculated from the HAM-D-17 total scores using the formula developed by Zimmerman et al[23] (as $\text{MADRS}_{\text{predicted}}$ total score = 1.43 × HAM-D-17 total score + 0.87). A summary of the divergence (calculated for each subject as actual MADRS total score − predicted MADRS total score) was reported at baseline and at the end of the study.

(3) To study the influence of baseline illness severity, the primary MMRM efficacy analysis was repeated within subgroups based on baseline MADRS score categories. The protocol eligibility criterion called for a score of least 20 on the HAM-D-17 at baseline, which corresponds to a predicted MADRS score greater than 29.5. Hence, the subgroups eligible (≥29.5) versus ineligible (<29.5) were created for this analysis. Of note is that, as the conversion calculation gave a cutoff score of 29.5, and it is not possible for MADRS score to be other than an integer, the criterion of 29 or less was used.

(4) To characterize placebo response by site, graphical displays showing placebo response rates at the end of the study for each site (for sites with at least 10 subjects enrolled) are presented.

RESULTS

Of treated subjects, a total of 102 (61.8%) of 165, 91 (53.2%) of 171, and 111 (66.1%) of 168 subjects in the ziprasidone 40- to 80-mg/d group, ziprasidone 120- to 160-mg/d group, and placebo group, respectively, completed study 1. For study 2, of the treated subjects a total of 112 (60.5%) of 185 and 134 (68.4%) of 196 ziprasidone and placebo subjects, respectively, were completers. The overall mean daily dose of ziprasidone for study 1 was 113.1 (±27.2) mg/d for the higher dose group and 53.9 (±15.3) mg/d for the lower dose group; for study 2, the overall mean daily dose of ziprasidone was 83.9 (±29.6) mg/d. Of the treated subjects, the proportion of study entrants hospitalized for mania did not differ significantly between groups in study 1 (range, 82.5%–84.8%) and in study 2 (range, 80.6%–85.4%). In study 1, benzodiazepine (lorazepam) usage was reported by 10.9%, 8.2%, and 8.9% in the 40- to 80-mg/d, 120- to 160-mg/d, and placebo groups, respectively. In study 2, benzodiazepine usage was reported by 10.3% and 6.6% in the ziprasidone and placebo groups, respectively.

Primary Efficacy Analysis

The primary efficacy analysis (MMRM) indicated that both the high- and low-dose ziprasidone groups in study 1 and the ziprasidone group in study 2 failed to demonstrate statistical superiority over placebo in change from baseline MADRS score at week 6 (Fig. 1). In both studies, the results from the ANCOVA

analyses of week 6 data (both LOCF and OC data) were generally consistent with the primary MMRM analysis results.

Secondary Efficacy Analysis

In both studies, MADRS response rates (≥50% improvement from baseline MADRS scores) were similar to placebo, ranging from 46% to 53% of subjects (Table 1). In study 1, response rates at the end of the study for subjects indicated by the MADRS scores were 52.5%, 45.8%, and 49.4% for lower dose ziprasidone, higher dose ziprasidone, and placebo, respectively. In study 2, response rates at the end of the study were 52.8% for ziprasidone subjects and 51.1% for placebo subjects. The ziprasidone groups did not demonstrate a statistically significant difference over placebo in response rates in either study.

Results of the ANCOVA analysis of the secondary efficacy end point, change from baseline in the HAM-D-17 total score, showed no significant difference between ziprasidone and placebo in both studies (unadjusted $P > 0.05$ for all comparisons between ziprasidone and placebo). In study 1, the least squares (LS) mean (SE) for change from baseline to the end of the study (OC) were −10.5 (0.9) (n = 151), −11.5 (0.95) (n = 150) in the ziprasidone high- and low-dose groups, respectively, and −10.6 (0.95) (n = 153) in the placebo group. In study 2, the LS mean (SE) for change from baseline to the end of the study (OC) were −6.9 (1.4) (n = 168) and −7.1 (1.3) (n = 181) in the ziprasidone and placebo groups, respectively. Response rates based on the HAM-D-17 total score (response defined as ≥50% reduction from baseline HAM-D-17 total score) also showed no significant difference between ziprasidone and placebo groups in both studies (nominal $P > 0.05$ for all comparisons between ziprasidone and placebo).

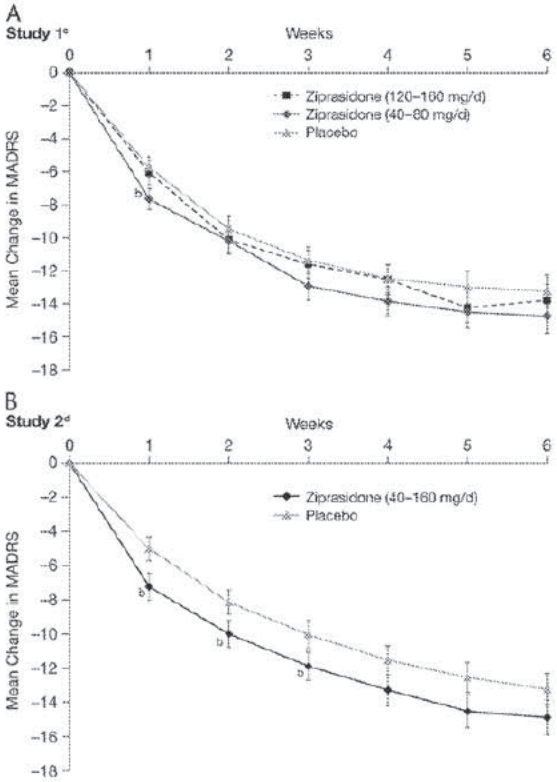

FIGURE 1. Primary efficacy analysis[a] comparing ziprasidone versus placebo (intent-to-treat [ITT] population, observed cases). [a]The mixed-model repeated-measures (MMRM) with model terms: treatment, rapid cycling, center, visit, previous hospitalization status, treatment by visit interaction, and baseline as covariate. [b]$P < 0.05$. [c]Baseline Montgomery-Åsberg Depression Rating Scale (MADRS) scores were 27.1 (ziprasidone 120–160 mg/d), 28.7 (ziprasidone 40–80 mg/d), and 28.9 (placebo). [d]Baseline MADRS scores were 28.6 (ziprasidone 40–160 mg/d) and 28.2 (placebo). Week 6 results represent the primary efficacy analysis.

Safety and Tolerability

In study 1, the most frequently reported treatment-emergent AEs (all causalities) in the higher dose ziprasidone group (at twice the rate of placebo) were somnolence (17.5%) and sedation (11.7%). In the lower dose ziprasidone group, the most frequently reported AE was somnolence (15.2%). In study 2, among subjects randomized to the ziprasidone group, the 3 most frequently reported AEs were somnolence (13.5%), sedation (11.9%), and headache (11.4%) compared with nausea and headache (each 10.7%) and diarrhea (7.7%) for subjects in the placebo group. In both studies, mean changes in vital sign values, body mass index, weight, and waist circumference were similar among treatment groups. Clinically significant weight gain or loss was not commonly observed. Vital signs among the treatment groups did not change appreciably from baseline to the end of the study.

For both studies, changes from baseline across treatment groups and across movement scales were very small and not clinically relevant, although some differences did reach statistical significance. In study 1, significant changes from baseline were observed at the end of the study for the comparison between the ziprasidone higher dose treatment group and placebo group for SAS total score (nominal $P = 0.0277$). In study 2, the LS mean change (SE) from baseline to the end of the study in SAS total score was −0.07 (0.08) and −0.23 (0.07) in the ziprasidone and placebo groups, respectively; this difference was significant (nominal $P = 0.0174$). The LS mean change (SE) from baseline to the end of the study in BAS total score was 0.08 (0.17) and −0.37 (0.16) in the ziprasidone and placebo groups, respectively; this difference was significant (nominal $P = 0.0033$). The LS mean change (SE) from baseline to the end of the study in AIMS total score was 0.01 (0.09) and −0.00 (0.08) in the ziprasidone and placebo groups, respectively; this difference was not significant (nominal $P = 0.8399$).

Post Hoc Analyses

Results of the post hoc analyses conducted for both studies to examine potential reasons for study failure are described below.

Distribution of HAM-D-17 and MADRS Scores at Baseline

In both studies, baseline HAM-D-17 scores determined subject inclusion, but a distribution of these scores does not fully correspond to baseline MADRS scores—a similar measure of depression and the primary efficacy measure in both studies. Figures 2 and 3 illustrate the distribution of actual HAM-D-17 and MADRS scores, respectively, at baseline. Whereas HAM-D-17 scores show the inclusion of appropriate study subjects, MADRS scores suggest the inclusion of many individuals with depression of lesser severity than was required by study inclusion criteria.

The actual baseline MADRS scores of 29 or less show that most of the subjects in both studies (52.9% of 486 in study 1 and 50.5% of 370 in study 2) had scores below the threshold considered to be the minimal severity threshold required for

TABLE 1. Results From Clinical Studies of Atypical Antipsychotics for the Treatment of Bipolar I Depression

Study	Duration, wk	Discontinuation Rate (Discontinued/Randomized), %	Response* Rate, %	Change in MADRS Score at Last Assessment	
				n	LS Mean (SE)
Study 1	6				
Placebo		57/174 (32.8)	49	162	−13.3 (1.0)
Ziprasidone 40–80 mg/d		63/176 (35.8)	53	158	−14.8 (0.97)
Ziprasidone 120–160 mg/d		80/186 (43.0)	46	166	−13.8 (1.0)
Study 2	6				
Placebo		62/200 (31.0)	51	190	−13.2 (0.9)
Ziprasidone 40–160 mg/d		73/192 (38.0)	53	180	−14.9 (1.0)
Thase et al, 2006[7]	8				
Placebo		58/168 (34.5)	45	161	−11.9 (0.99)
Quetiapine 300 mg/d		71/172 (41.3)	60	155	−16.9 (0.99)
Quetiapine 600 mg/d		79/169 (46.7)	58	151	−16.0 (1.01)
Calabrese et al, 2005[6]	8				
Placebo		74/181 (40.9)	36	169	−10.3
Quetiapine 300 mg/d		60/181 (33.1)	58	172	−16.4
Quetiapine 600 mg/d		82/180 (45.5)	58	170	−16.7
Tohen et al[5]	8				
Placebo		232/377 (61.5)	30	355	−11.9 (0.8)
Olanzapine/fluoxetine		31/86 (36.0)	56	82	−18.5 (1.3)
Olanzapine		191/370 (51.6)	39	351	−15.0 (0.7)
Thase et al (study 1)[9,25]	8				
Placebo		66/188 (35.1)	39	177	−10.6
Aripiprazole		87/186 (46.8)	43	162	−11.9
Thase et al (study 2)[9,25]	8				
Placebo		56/188 (29.8)	44	176	−11.5
Aripiprazole		77/187 (41.2)	45	175	−12.3

*50% decrease in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline. SE data missing when unavailable.
LS indicates least squares; SE, standard error.

study enrollment. Furthermore, 12 (3%, study 1) and 19 (5%, study 2) subjects at baseline would be considered in remission at baseline according to their MADRS scores (MADRS scores ≤12). At the time of last observation, 98 (20%) and 54 (15%) subjects had MADRS scores of 4 or less in study 1 and study 2, respectively, including 28 and 12 subjects, respectively, with an MADRS score of 0.

Comparison of Actual and Predicted MADRS Score at Both Baseline and at the End of the Study

The mean (±SD) and median (minimum, maximum) of the divergence between actual and predicted MADRS scores observed at baseline were −7.90 (± 5.52) and −8.09 (−28.63, 13.54), and −8.63 (± 6.18) and −8.32 (−34.34, 7.1), for studies 1 and 2, respectively. In a quarter of subjects, the predicted MADRS score was more than 11 and 12.3 points greater than the actual MADRS score in studies 1 and 2, respectively. In 10% of subjects, the derived MADRS score was more than 15 and 16.6 points greater than the actual MADRS score in studies 1 and 2, respectively. At the end of the study, the mean and median divergences were markedly less than at baseline, at 4.67 (± 4.99) and −4.3 (23.33, 9.84) for study 1, and −4.29 (± 5.69) and −4.31 (−22.04, 21.11) for study 2. In a quarter of the subjects, the predicted MADRS score was more than 7.8 (study 1) and 7.9 (study 2) points greater than the actual MADRS score; in 10% of subjects, the predicted MADRS score was more than 11.3 (study 1) and 12.1 (study 2) points greater than the actual MADRS score.

Influence of Baseline Illness Severity

Results of the primary efficacy MMRM analysis repeated for each of the 2 subgroups (ineligible vs eligible based on baseline MADRS total scores <29.5 and ≥29.5) are presented in Table 2. Not unexpectedly, subjects with lower baseline MADRS scores experienced less change during the course of the study than subjects with higher MADRS scores. Results in the 2 subgroups based on baseline MADRS scores were consistent with the results from the primary efficacy MMRM analysis. In study 1, the placebo response rate in the ineligible group was greater than the proportion in the eligible group (57.1% vs 41.0%); in study 2, however, the placebo response rate in the eligible group was greater than that in the ineligible group (54.8% vs 47.4%). For both studies, there were no meaningful differences between the response rates for ziprasidone subjects in the ineligible group versus the eligible group.

Placebo Response

Among the 21 sites in study 1 that had at least 10 subjects, placebo response rates greater than 40% were observed in 14 sites (66.7%); and among the 15 sites in study 2 that had at least 10 subjects, placebo response rates greater than 40% were observed in 13 sites (86.7%) (Fig. 4, A and B).

DISCUSSION

Randomized clinical trials can generate positive or negative results or they can fail to provide meaningful results. Positive

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