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ORIGINAL RESEARCH

Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Chinese subpopulation analysis of a double-blind, randomized, placebo-controlled study

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Background: Depression in bipolar I disorder responds to the atypical antipsychotic olanzapine. This subpopulation analysis assessed whether olanzapine is superior to placebo specifically in the treatment of Chinese patients with bipolar I depression.

Methods: This was a subpopulation analysis of a 6-week, multicenter, double-blind, parallel, randomized, placebo-controlled trial among 12 Chinese study centers. Eligible inpatients and outpatients were randomized to olanzapine (5 to 20 mg/day) or placebo. Patients were primarily assessed by the Montgomery-Åsberg Depression Rating Scale total score. Secondary assessments used a range of other efficacy and safety measures. This subpopulation analysis was underpowered to show statistically significant differences between treatment groups.

Results: In total, 210 patients (mean age 32.9 years at baseline, 54.3% females) were randomized. Similar proportions of patients treated with olanzapine (75.0%) and placebo (72.9%) completed the double-blind phase. Baseline-to-endpoint least-squares mean ± standard error decrease in the Montgomery-Åsberg Depression Rating Scale total score in the olanzapine group (−13.55±0.80) was similar to that noted in the parent trial (−13.82±0.65). However, the difference between olanzapine and placebo groups was not statistically significant (P=0.44); this finding was also true for the secondary efficacy measures. A post hoc analysis showed a greater emergence of mania in the placebo group, which likely reduced the treatment difference between olanzapine and placebo in the primary efficacy measure. Safety data were consistent with the known safety profile of olanzapine, including a higher incidence of weight gain (≥7%) in the olanzapine group (24.1% vs 1.4%, P<0.001).

Conclusion: Olanzapine provides similar improvement in depression among Chinese and non-Chinese bipolar I patients. The lack of a statistically significant difference between the olanzapine and placebo groups in this Chinese subpopulation analysis may relate to an a priori lack of study power, and underestimation of the effect of olanzapine because of a greater emergence of mania in placebo-treated patients and missing data associated with a high early discontinuation rate.

Keywords: bipolar disorder, Chinese, depression, olanzapine

Introduction

Bipolar I disorder is a disabling and difficult-to-treat psychiatric disorder marked by one or more episodes of mania, or mixed states of mania and depression. Depression in bipolar I disorder is particularly problematic and is associated with subsyndromal manic symptoms,[1] a longer recovery phase,[2–4] higher rates of morbidity, and higher rates of

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suicidality than manic episodes.[5] Depression in bipolar disorder also causes substantial disability and functional impairment, even among patients with mild symptoms who do not meet criteria for clinical depression (subsyndromal depression).[6]

The atypical antipsychotic olanzapine (Zyprexa®, Eli Lilly and Company, Indianapolis, IN, USA) has been shown to be effective for the treatment of manic episodes in bipolar disorder without inducing unwanted depressogenic effects.[7,8] Indeed, studies have revealed that olanzapine is effective for the treatment of the depressive phase of bipolar I disorder both in combination with antidepressants[9,10] and as monotherapy.[9,11,12] Recently, the efficacy of olanzapine monotherapy for the treatment of depressive episodes in bipolar I disorder has been assessed in a large (N=514), international, double-blind, randomized placebo-controlled trial.[13] After 6 weeks of treatment, patients allocated to olanzapine treatment had significantly greater mean baseline-to-endpoint improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared with patients allocated to placebo (−13.8 vs −11.7, P=0.02).[13] The olanzapine group also had a significantly greater treatment response, defined as a ≥50% reduction in MADRS total score at endpoint, than the placebo group (52.5% vs 43.3%, P=0.05). A follow-up subpopulation analysis of this large trial found that olanzapine monotherapy was similarly effective in Japanese patients as in the overall, more ethnically diverse population.[14]

Despite the results of the abovementioned studies, especially that of the international, randomized trial that included many Chinese patients, there is limited evidence for the efficacy of olanzapine for the treatment of depression among Chinese patients with bipolar I disorder. A recent systematic review of the literature identified only seven studies, including four randomized controlled trials, that assessed the efficacy of olanzapine in Chinese populations with bipolar disorder.[15] In terms of managing symptoms of mania, olanzapine has been shown to have similar efficacy to that of lithium in Chinese patients with bipolar disorder.[15] In terms of managing depressive symptoms in Chinese patients with bipolar disorder, olanzapine appeared to be more effective than placebo but similar in efficacy to lithium.[13,15] However, the evidence for the similar effect of olanzapine and placebo in managing depressive symptoms is derived from the international study by Tohen et al,[13] which included a mixed population in terms of race and ethnicity.[13] Therefore, further studies and analyses appear warranted to address the efficacy of olanzapine exclusively in Chinese populations.

The primary objective of this subpopulation analysis of the trial by Tohen et al[13] was to assess whether olanzapine (5 to 20 mg/day) is superior to placebo in terms of improvement in the MADRS total score in Chinese patients with bipolar I disorder. Secondary objectives of this analysis were to compare olanzapine and placebo treatment for Chinese patients with bipolar I disorder in terms of a range of other efficacy and safety measures.

Methods

Study design

This subpopulation analysis of the parent 6-week, multicenter, double-blind, parallel, randomized, placebo-controlled, Phase 3 trial[13] evaluated whether olanzapine is superior to placebo in the treatment of Chinese patients with bipolar I depression. The parent trial recruited inpatients and outpatients from Japan, People's Republic of China, Taiwan, Korea, and the United States. Only patients recruited in People's Republic of China were included in this subpopulation analysis. A total of 12 Chinese study centers with investigators specialized in psychiatry contributed patients to this trial. The first patient enrolled into the parent trial on August 27, 2007, and the last patient completed the study on July 9, 2010.

The parent trial was approved by applicable ethical review boards and conducted in accordance with the Declaration of Helsinki and consistent with good clinical practices and applicable regulatory requirements. Ethics committees at the following sites provided ethical approval for the study: Shanghai Mental Health Center Institutional Review Board; Guangzhou Fangcun Mental Hospital Institutional Review Board; Beijing Anding Hospital Institutional Review Board; Institutional Review Board, 1st Affiliate Hospital of Harbin Medical University; Institutional Review Board, Institute of Mental Health, Beijing; Nanjing Brain Hospital Institutional Review Board; The Institutional Review Board of 1st Affiliate Hospital of Kunming Medical College; People's Hospital Wuhan University Institutional Review Board; Xiangya Medical College Institutional Review Board; Institutional Review Board, Zhejiang Medical University Affiliate; The Institutional Review Board of Xi Jing Hospital Affiliated to 4th Military Medical University; West China Hospital Institutional Review Board. Written informed consent was obtained from all patients after a description of the study to patients and before initiation of study drugs. The trial was registered with ClinicalTrials.gov (NCT00510146).

The acute phase of the parent trial was divided into a lead-in phase of 2 to 28 days (Visits 1 to 2) and a double-blind treatment phase of 6 weeks (Visits 2 to 9). Screening was undertaken at Visit 1. At Visit 2, eligible patients were randomly allocated to double-blind treatment in a 2:1 ratio to olanzapine (5 to 20 mg/day, Zyprexa®, Eli Lilly and Company) or placebo determined by a computer-generated

random sequence. Patients in the olanzapine group received olanzapine 5 mg/day once daily; after 3 to 7 days (Visit 3 or 4) at this dose, patients underwent a forced titration to 10 mg/day olanzapine once daily. On the basis of the investigator's judgement, the once-daily olanzapine dose could be increased up to 20 mg/day or decreased to 5 mg/day at subsequent once-weekly study visits.

Study subjects

Male and female patients aged ≥18 and <65 years who met diagnostic criteria for a major depressive episode and for bipolar I disorder, depressed, according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR), were eligible for randomization and double-blind treatment. In terms of key inclusion criteria, patients must have had a current Hamilton Depression Rating Scale-17 (HAMD-17) score ≥18 at Visits 1 and 2, and have experienced at least one previous manic or mixed episode, as defined in the DSM-IV-TR, before Visit 1 and within the past 6 years without currently being in a manic episode (Young Mania Rating Scale [YMRS] total score ≤8 at Visit 2). Patients were excluded principally if they had a history of serious unstable medical illness, diabetes, hemoglobin A1c ≥6.5% (or blood glucose level indicative of diabetes), serious psychiatric illness other than bipolar depression, or current rapid-cycling mood disturbance. Patients were also excluded for recent substance dependence or use of clozapine, depot antipsychotics, or central nervous system medications other than mood stabilizers. However, certain agents were allowed as concomitant medications in the acute phase of the trial. Investigators were instructed to maintain benzodiazepine use at a minimum level throughout the study. Lorazepam was permitted, if necessary, as a first-line treatment to alleviate anxiety.

Efficacy measures and objectives

Efficacy was assessed using a number of common and well-validated psychiatric measures. The primary efficacy measure was the MADRS, an investigator-rated scale for severity of depressive mood symptoms consisting of ten items, each scored from 0 to 6 in increasing order of severity.[16] Secondary efficacy measures were:

- Clinical Global Impressions-Bipolar Version (CGI-BP) Severity of Illness, an investigator-rated measure of illness severity that allows rating of mania, depression, and bipolar illness. The score ranges from 1 (normal, not ill) to 7 (very severely ill).[17]
- HAMD-17, a 17-item multiple-choice questionnaire used to rate the severity of depression by interview and observation.[18] Each question has three to five possible responses, and total scores range between 0 and 52. The higher the score, the more severe the depression.
- YMRS, an 11-item multiple choice questionnaire used by clinicians to rate the severity of mania from 0 to 60.[19] In this study, the YMRS was used to assess the potential of study drug to induce manic symptoms.
- The Mini-International Neuropsychiatric Interview (MINI), an abbreviated psychiatric structured interview, was used during screening, whereas specific efficacy modules (A, D, J, K, and L) were used to evaluate efficacy during double-blind treatment.[20]

The primary objective of this trial was based on the primary efficacy measure and assessed improvements in overall symptomatology, as measured by the mean change in the MADRS total score from baseline to last-observation-carried-forward (LOCF) endpoint, up to the end of 6 weeks of double-blind treatment. The secondary objectives of this trial were based on the secondary efficacy measures and assessed as the mean changes from baseline to LOCF endpoint for HAMD-17 score, YMRS total score, and CGI-BP Severity of Illness scores for mania, depression, and bipolar disorder. Additional severity assessments of response, remission, and recovery were conducted as part of the secondary assessment of efficacy. For these assessments, response was defined as a baseline-to-endpoint reduction of ≥50% in MADRS total score. Remission was defined a priori as at least one post-baseline MADRS total score ≤12 ("symptomatic remission") and was defined post hoc as at least one post-baseline MADRS total score ≤5 or ≤7 (as recommended by the International Society of Bipolar Disorders).[21] Recovery was defined as a MADRS total score ≤12 for ≥4 weeks at completion of the 6-week study.

In addition to these efficacy measures, data were collected on treatment adherence and use of concomitant medications such as benzodiazepines and anticholinergics. Treatment adherence was defined as the number of days the patient took the study medication as prescribed divided by his or her total number of expected days of study drug exposure during the study period.

Safety measures

All adverse events occurring during the course of the study were documented via a case report form. Treatment-emergent adverse events (TEAEs), events that first occurred or worsened after initiation of therapy, were summarized by system organ class and Medical Dictionary for Regulatory Activities preferred term. Vital signs and weight were assessed at each visit. Clinical laboratory testing and electrocardiograms

(ECGs) were assessed at Visits 1 and 9, with additional scheduled collections for clinical chemistry, lipid panel, electrolyte, and hematology measures undertaken at Visits 2 and 5. Further clinical laboratory tests were conducted any time a patient completed or discontinued the study, and when clinically indicated. The incidence and severity of extrapyramidal symptoms in various categories (parkinsonism, akathisia, dystonia, and dyskinesia) were measured by the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS). Emergence of mania, which prompted discontinuation, was defined as the first occurrence of a YMRS total score ≥15. The suicidality module of the MINI was administered at every visit during the double-blind phase to further monitor patient safety.

Statistical analysis

In the parent trial, 514 patients were randomized, with 343 into the olanzapine group and 171 into the placebo group. Sample sizes were calculated for the parent trial to allow 90% power (Type II error =0.1) to detect a treatment difference of 3.9 in the MADRS total score change from baseline. The parent trial was powered for the analysis of the primary efficacy endpoint in the global patient population, which included geographic regions in which olanzapine has not been studied in bipolar depression. Hence, a conservative effect standard deviation (SD) of 12.38, corresponding to an effect size of 0.315, was used. However, the statistical power for the Chinese subpopulation was calculated at 55% (Type II error =0.45). On this basis, the Chinese subpopulation analyses were underpowered and not expected to provide statistically significant results.

Efficacy and safety analyses were based on the intention-to-treat (ITT) population of Chinese patients, and all safety variables were analyzed using the safety population, defined as all randomized patients who received ≥1 dose of treatment. One patient randomized to the olanzapine group was thought not to have received treatment and was excluded from the safety population (although it was determined after unblinding that this patient did receive treatment). All tests of treatment effect were conducted at a two-sided significance level of 0.05, and no adjustments were made for multiple comparisons. Regarding the handling of dropouts or missing data, total scores for MADRS, YMRS, HAMD-17, DIEPSS, and MINI (suicidality module) rating scales were the sum of individual items. If >25% of items were missing, then the total score was considered missing, whereas if <25% of items were missing, then the total score was imputed from the available items.

Continuous data were assessed using analysis of covariance (ANCOVA) models of pairwise comparisons and generally included terms for treatment and the baseline measurement value as a covariate. Type III sums of squares were used to adjust for unbalanced data in the interactions of these models of variance. Importantly, an ANCOVA model was used for the primary analysis of change from baseline to endpoint in MADRS total score. Sensitivity analyses of the primary analysis were performed using observed case and a mixed-effects model repeated measures (MMRM) ANCOVA. In addition, ANCOVA models were also used for secondary efficacy measures (YMRS, HAMD-17, CGI-BP), fasting glucose and lipid levels, the suicidality model of the MINI, as well as vital signs and weight. Fisher's exact test, which is useful for categorical data and for analysis of proportions, was used to assess the incidences of discontinuation, concomitant medication usage, response rate, and adverse events. The log-rank test, based on survival distributions, was used to compare treatments for the time to discontinuation, time to response, time to first remission, time to first relapse, and time to first emergence of mania. The Cochran–Mantel–Haenszel test, for analyzing stratified categorical data, was used to analyze the rate of recovery. Finally, the Wilcoxon rank-sum test was used to analyze differences between groups for DIEPSS total scores and for laboratory analytes other than fasting glucose and lipids.

Post hoc analysis

A post hoc analysis was performed to explore the influence of the emergence of mania and consequent discontinuation on the primary efficacy measure. Initially, this involved determining the incidence of emergence of mania in the olanzapine and placebo groups for the overall population and various country-specific subpopulations. Individual changes in MADRS scores among patients who experienced mania episodes were then analyzed. To specifically explore the impact of mania emergence on MADRS reductions in the olanzapine and placebo groups, two approaches were used. Firstly, the MADRS score of the visit before mania emerged was used as the endpoint for analysis. Secondly, patients with emergence of mania were excluded from the analysis.

Results

Patient disposition and baseline characteristics

In this Chinese subpopulation analysis, a total of 210 patients (mean ± SD age 32.9±10.9 years at baseline, 54.3% females) were randomized (Figure 1). In total, 105 of 140 (75.0%) patients treated with olanzapine and 51 of 70 (72.9%) patients treated with placebo completed the acute double-blind phase. Regarding reasons for discontinuation, there was a higher

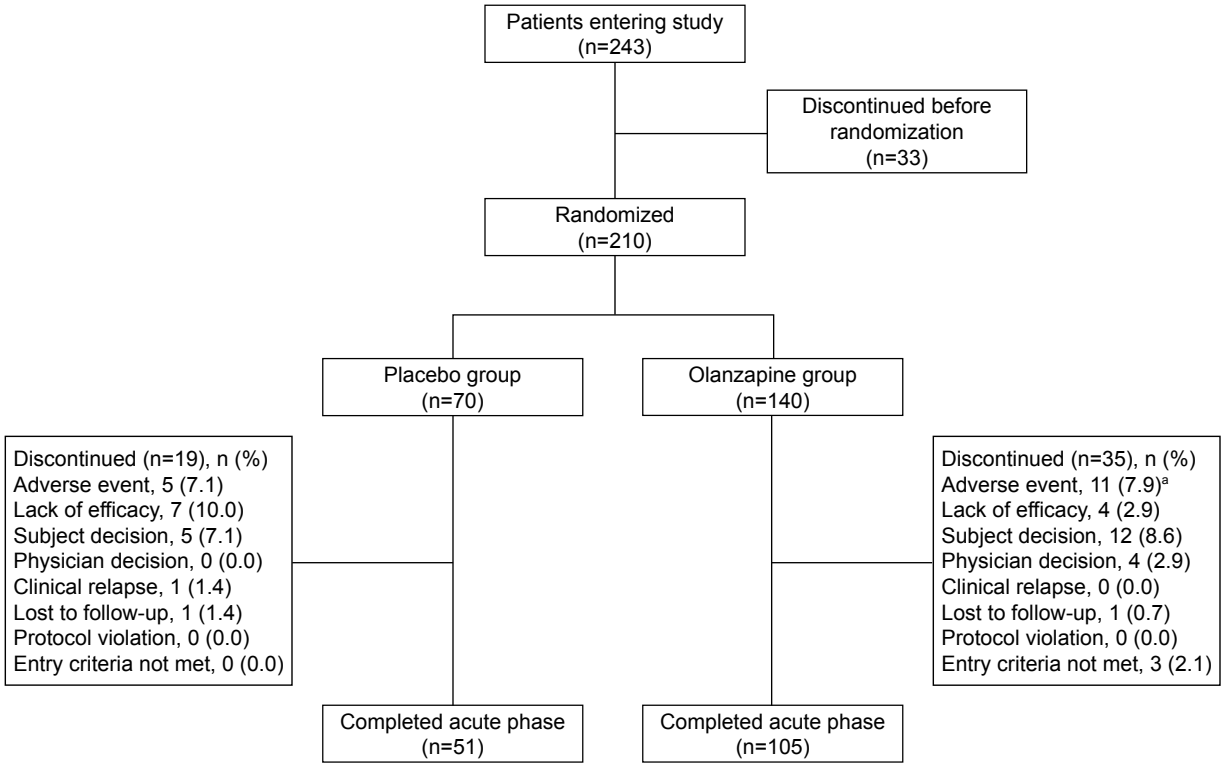

Figure 1 Patient disposition.
Note: [a]Includes one patient randomized to the olanzapine group who was excluded from the safety population but later determined to have received treatment.

lack of efficacy among placebo-treated patients (10.0%) compared with olanzapine-treated patients (2.9%, P=0.045). In relation to this, there was a statistically significant difference in time to discontinuation favoring olanzapine between treatment groups (P=0.033). The proportions of patients who discontinued for other reasons were similar in each treatment group (P>0.05). At baseline, there were no statistically significant differences between treatment groups with respect to sex, age, weight, or illness characteristics (Table 1). This Chinese subpopulation included 26 inpatients (12.4%) and 184 outpatients (87.6%). The mean ± SD daily dose for patients in the olanzapine group was 10.63±3.34 mg and both treatment groups were greater than 99% adherent during the acute phase.

Table 1 Baseline demographics and illness characteristics of Chinese study participants with bipolar depression treated with olanzapine or placebo

Characteristic	Placebo (n=70)	Olanzapine (n=140)	Total (n=210)
Female, n (%)	37 (52.9)	77 (55.0)	114 (54.3)
Age, years, mean ± SD	32.0±11.5	33.3±10.6	32.9±10.9
Age at onset of bipolar disorder, years, mean ± SD	25.6±10.3	26.6±9.7	26.3±9.9
Weight, kg, mean ± SD	64.4±12.5	62.6±11.3	63.2±11.7
Number of previous episodes, mean ± SD			
Manic	2.41±2.00	2.28±2.19	2.32±2.12
Depressive	2.40±2.20	2.69±2.18	2.60±2.18
Mixed	0.17±0.68	0.09±0.49	0.11±0.56
Illness severity scores, mean ± SD			
MADRS total	29.19±5.29	29.55±4.97	29.43±5.07
YMRS total	1.49±1.67	1.61±1.36	1.57±1.47
HAMD-17 total	22.10±3.25	22.24±2.99	22.19±3.07
CGI-BP			
Mania	1.01±0.12	1.01±0.08	1.01±0.10
Depression	4.74±0.72	4.74±0.64	4.74±0.67
Bipolar	4.73±0.74	4.71±0.64	4.72±0.67

Abbreviations: CGI-BP, Clinical Global Impressions-Bipolar Version; HAMD-17, Hamilton Depression Rating Scale-17; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

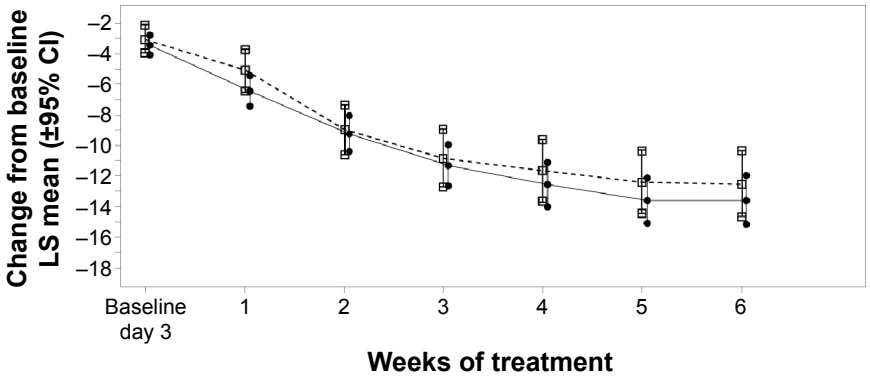

Figure 2 Visit-wise change from baseline in LS mean MADRS total score ±95% CI for entire Chinese subpopulation.
Notes: ● = olanzapine, □ = placebo.
Abbreviations: CI, confidence interval; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale.

Primary objective

Baseline-to-endpoint least-squares (LS) mean ± standard error (SE) decrease in the MADRS total score was greater in the olanzapine group compared with the placebo group, although this difference was not statistically significant (−13.55±0.80 vs −12.50±1.11, *P*=0.44).

Olanzapine showed a slightly greater LS mean decrease in the MADRS total score from baseline compared with placebo, although the differences were not statistically significant at any visit (Figure 2). Sensitivity analyses of LS mean ± SE decrease in the MADRS total score from baseline using observed case (−15.82±0.80 for olanzapine vs −13.70±1.12 for placebo at endpoint, *P*=0.125) and MMRM methods (−15.88±0.82 for olanzapine vs −13.60±1.14 for placebo at endpoint, *P*=0.106) yielded greater mean differences between treatment groups but similar results in terms of statistical significance. Results of the subgroup analysis for the primary efficacy measure by age, sex, and illness characteristics revealed no statistically significant treatment interaction for any subgroups (data not shown).

Secondary objectives

Regarding the secondary efficacy measures, baseline-to-endpoint LS mean decreases in CGI-BP depression, CGI-BP bipolar, and HAMD-17 total scores were numerically greater and increases in CGI-BP mania were smaller in the olanzapine group compared with the placebo group, but the differences were not statistically significant (Table 2). Similarly, there were no significant differences between treatment groups in terms of specific MINI syndromic criteria (data not shown). However, the baseline-to-endpoint LS mean change in YMRS total score decreased in the olanzapine group but increased in the placebo group (*P*=0.029, Table 2). In terms of additional severity of depression measures, there were no significant differences between treatment groups in symptomatic response, symptomatic remission (MADRS total score ≤12), or recovery (Table 3). Similarly, there were no statistically significant differences between groups when remission was defined as an MADRS total score of ≤5 or ≤7.

Post hoc analysis

In the overall population, emergence of mania was reported in two of 343 patients (0.6%) in the olanzapine group and five of 171 patients (2.9%) in the placebo group (*P*=0.031). In the Chinese subpopulation, emergence of mania was reported in one of 140 patients (0.7%) in the olanzapine group and three of 70 patients (4.3%) in the placebo group (*P*=0.109). In the United States subpopulation, emergence of

Table 2 Baseline to endpoint least-squares mean changes in CGI-BP, HAMD-17, and YMRS

Efficacy measure	Placebo (n=70)	Olanzapine (n=140)	*P*-value
	LS mean ± SE	LS mean ± SE	
CGI-BP mania	0.12±0.05	0.04±0.03	0.152
CGI-BP depression	−1.32±0.16	−1.44±0.11	0.523
CGI-BP bipolar	−1.23±0.15	−1.41±0.11	0.320
HAMD-17 total	−9.73±0.88	−11.50±0.63	0.102
YMRS total	0.45±0.41	−0.66±0.29	0.029

Abbreviations: CGI-BP, Clinical Global Impressions-Bipolar Version; HAMD-17, Hamilton Depression Rating Scale-17; LS, least-squares; SE, standard error; YMRS, Young Mania Rating Scale.

Table 3 Response, symptomatic remission, and recovery rates

Depression measure	Placebo (n=70)	Olanzapine (n=140)	*P*-value
	n (%)	n (%)	
Response (≥50% reduction in MADRS)	30 (42.9)	73 (52.1)	0.24
Symptomatic remission			
MADRS ≤12	30 (42.9)	70 (50.0)	0.38
MADRS ≤7	14 (20.0)	31 (22.1)	0.86
MADRS ≤5	13 (18.6)	16 (11.4)	0.20
Recovery (MADRS total score ≤12 for ≥4 weeks)	6 (8.6)	14 (10.0)	0.81

Abbreviation: MADRS, Montgomery-Åsberg Depression Rating Scale.

mania was reported in one of 60 patients (1.7%) and two of 30 patients (6.7%) in the placebo group. Hence, emergence of mania was significantly more common in placebo-treated patients than olanzapine-treated patients both in the overall population and relevant country-specific subpopulations. Emergence of mania was not recorded in either treatment group for the subpopulations in Japan (n=156), Taiwan (n=28), or Korea (n=30). For patients with emergence of mania, individual changes in MADRS total score generally decreased rapidly and to a greater extent among placebo-treated patients than among olanzapine-treated patients or compared with the overall means for the Chinese subpopulation (Figure 3). Finally, the difference in MADRS changes from baseline between olanzapine and placebo groups in the Chinese subpopulation increased when applying analyses based on the last visit before emergence of mania as the endpoint, or when excluding patients with emergence of mania (Table 4).

Safety measures

Safety data from this acute-phase study were consistent with the known safety profile of olanzapine. The rate of discontinuation due to an adverse event (7.2% for olanzapine and 7.1% for placebo for the safety population, P=1.00; Figure 1) and the rate of TEAEs (44.6% vs 38.6%, P=0.460; Table 5) were not significantly different between groups. Serious adverse events were infrequent, occurring in one patient (0.7%) in the olanzapine group (bipolar I disorder) and four patients (5.7%) in the placebo group (depression, suicidal ideation, and two cases of bipolar I disorder) (P=0.044). No statistically significant differences between olanzapine and placebo treatment were observed in extrapyramidal symptoms or suicidality total scores.

At endpoint, the olanzapine group had a greater proportion of patients with a potentially clinically significant increase (≥7%) in weight (24.1% vs 1.4% for placebo, $P<0.001$) and a significantly greater absolute mean ± SE weight increase (2.44±0.21 kg vs 0.16±0.29 kg for placebo, $P<0.001$). Other vital signs and ECG variables showed no significant differences between groups apart from a statistically significant difference in the mean ± SE change from

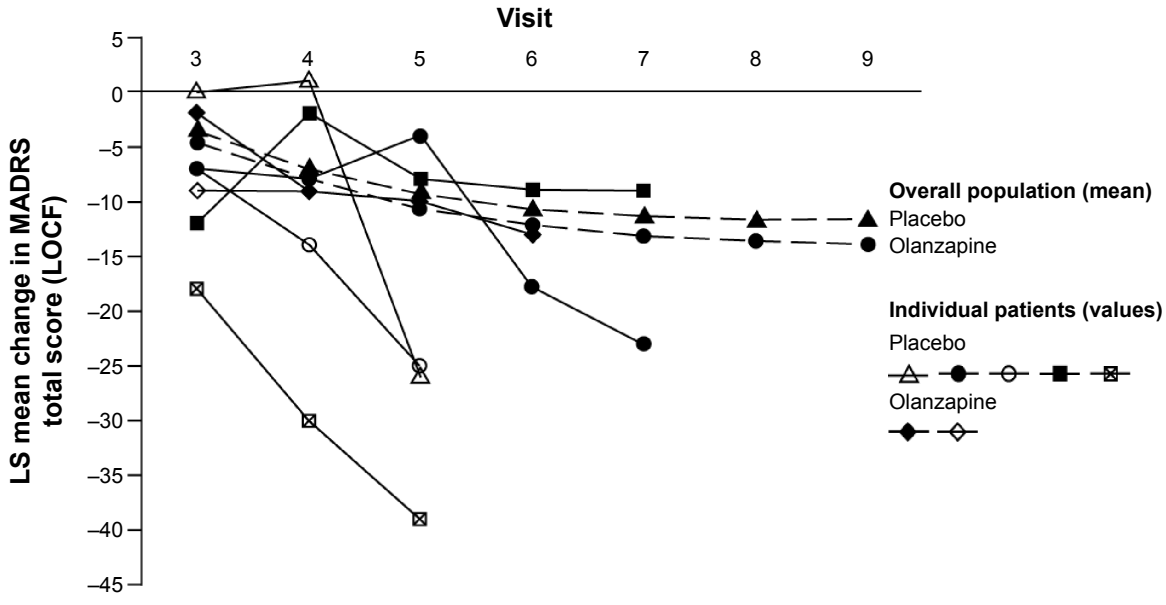

Figure 3 Visit-wise change of MADRS total score from baseline (LOCF) for individual subjects with emergence of mania in placebo and olanzapine group.
Notes: Dashed lines show the mean change for the overall population. Open symbols represent Chinese subjects; filled symbols represent US subjects.
Abbreviations: LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; LOCF, last-observation-carried-forward.

Table 4 Treatment difference between olanzapine and placebo groups in least-squares mean change in MADRS total score (95% confidence interval) using the MADRS score of the visit before mania emergence and excluding patients with emergence of mania

Exclusion condition	Overall population	Chinese subpopulation
	LS mean (95% CI)	LS mean (95% CI)
Not considering mania episode	−2.15 (−3.93, −0.36)	−1.05 (−3.75, 1.65)
Using MADRS score of the visit before mania emergence	−2.45 (−4.23, −0.68)	−1.74 (−4.42, 0.93)
Excluding patients with emergence of mania	−2.46 (−4.26, −0.66)	−1.76 (−4.48, 0.95)

Abbreviations: CI, confidence interval; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale.

baseline to endpoint standing pulse rate (olanzapine 1.05±0.58 vs placebo −1.20±0.81 beats per minute, P=0.025).

In terms of metabolic parameters, no significant differences between treatment groups were observed for categorical changes in lipid and blood glucose levels using the National Cholesterol Education Program and American Diabetes Association criteria, respectively.[22,23] However, greater baseline-to-endpoint LS mean ± SE increases in cholesterol (0.26±0.06 vs −0.08±0.09 mmol/L, P=0.002) and low density lipoprotein-cholesterol (0.19±0.05 vs −0.07±0.08 mmol/L, P=0.005) concentrations were seen in the olanzapine group compared with the placebo group. Analysis of other laboratory values showed that patients treated with olanzapine had small, but statistically larger, baseline-to-endpoint increases or decreases in a number of values compared with the placebo group (Table 6).

Table 5 Common TEAEs occurring in ≥2% of patients with any treatment

Preferred term	Placebo (n=70)	Olanzapine (n=139)	*P*-value
	n (%)	n (%)	
Patients with ≥1 TEAE	27 (38.6)	62 (44.6)	0.460
Hypersomnia	2 (2.9)	12 (8.6)	0.148
Weight increase	2 (2.9)	9 (6.5)	0.342
Abnormal hepatic function	1 (1.4)	7 (5.0)	0.273
Constipation	0 (0.0)	6 (4.3)	0.182
Dizziness	2 (2.9)	6 (4.3)	0.721
Dry mouth	1 (1.4)	5 (3.6)	0.666
Increased appetite	1 (1.4)	5 (3.6)	0.666
Somnolence	3 (4.3)	5 (3.6)	1.000
ALT increase	0 (0.0)	4 (2.9)	0.303
Asthenia	1 (1.4)	3 (2.2)	1.000
Nasopharyngitis	0 (0.0)	3 (2.2)	0.552
Palpitations	0 (0.0)	3 (2.2)	0.552
Hypersalivation	1 (1.4)	3 (2.2)	1.000
Tremor	1 (1.4)	3 (2.2)	1.000
Bipolar I disorder	3 (4.3)	1 (0.7)	0.110
URTI	4 (5.7)	1 (0.7)	0.044
Decreased appetite	2 (2.9)	0 (0.0)	0.111

Abbreviations: TEAEs, treatment-emergent adverse events; URTI, upper respiratory tract infection; ALT, alanine aminotransferase.

Discussion

In this Chinese subpopulation analysis of depressed patients with bipolar I disorder, 6 weeks of olanzapine treatment provided an LS mean ± SE decrease in MADRS total score (−13.55±0.80) similar to that seen in the overall population (−13.82±0.65).[13] Changes in secondary efficacy measures related to depression, including rates of response, remission, and recovery, showed similar levels of change in the Chinese subpopulation as in the overall population.[13] For example, the response rate, defined as an MADRS score reduction ≥50% at endpoint, in olanzapine-treated patients was 52.5% in the overall population, compared with 52.1% in the Chinese subpopulation. Further, the improvements with olanzapine treatment on key measures of depression such as MADRS, HAMD-17, and CGI-BP Depression were consistent with the findings of previous studies in patients with bipolar disorder.[9,12,24] The safety profile of olanzapine in this subpopulation analysis was also consistent with that seen in the overall population and with the known safety profile of olanzapine, including data from studies in Chinese populations.[13,15,24] These findings suggest the level of response to olanzapine in depressed Chinese patients with bipolar I disorder parallels that observed in non-Chinese patients. This observation is not surprising given that similar responsiveness to olanzapine in Chinese and non-Chinese patients has been observed in other studies of both bipolar disorder and schizophrenia.[15]

Despite the beneficial response to olanzapine seen in this Chinese population, differences between the olanzapine and placebo group in both primary and secondary efficacy measures did not reach statistical significance as they did in the overall population. The primary and most obvious reason for this was the small size of the Chinese subpopulation enrolled in this analysis, which led to a lack of statistical power to detect a statistically significant difference between olanzapine and placebo groups at the outset. However, additional post hoc data analyses conducted in response to questions related to this study raised by the China Food and Drug Administration strongly suggest that the treatment effect of olanzapine was underestimated by both the greater emergence of mania and a higher rate of early discontinuation among placebo-treated patients.[25] Emergence of mania during treatment was more common in the placebo group

Table 6 Mean change from baseline to endpoint values in laboratory analytes (except glucose and lipid panel)

Laboratory analyte	Mean ± SD change from baseline		*P*-value*
	Placebo (n=52–65)	Olanzapine (n=119–129)	
ALB, g/L	0.48±3.10	−0.66±3.08	0.023
ALT, IU/L	1.52±17.95	9.88±27.06	0.007
AST, IU/L	2.22±12.76	4.74±14.34	0.028
Basophils, $\times 10^9$/L	0.01±0.02	−0.00±0.03	0.010
Creatinine, µmol/L	−0.63±6.02	−2.93±6.76	0.015
GGT, IU/L	0.95±7.16	6.02±15.84	<0.001
Hematocrit, proportion	0.01±0.03	−0.00±0.03	0.044
Hemoglobin, mmol/L	0.14±0.40	−0.01±0.53	0.048
Hemoglobin A1c, %	−0.03±0.31	0.04±0.26	0.035
Lymphocytes, atypical, $\times 10^9$/L	0.00±0.02	−0.00±0.00	0.049
Potassium, mmol/L	−0.12±0.36	−0.00±0.36	0.013
Prolactin, µg/L	−0.57±28.60	15.23±28.89	<0.001
UA-specific gravity	0.00±0.01	−0.00±0.01	0.038
Uric acid, µmol/L	−7.28±49.67	20.03±55.31	<0.001

Note: *Wilcoxon's rank-sum test.
Abbreviations: SD, standard deviation; UA, urinalysis; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

than in the olanzapine group and mainly occurred in the Chinese subpopulation (three of five patients overall). The higher incidence of mania emergence in placebo-treated patients is understandable given that placebo cannot prevent relapse of mania as effectively as olanzapine. The large, sudden decreases in MADRS score noted mainly in patients treated with placebo most likely represented a switch from a depressive to a manic episode rather than an improvement in depression. Finally, the difference in MADRS changes from baseline between olanzapine and placebo groups increased when using the MADRS score of the visit before mania emerged or when excluding patients with emergence of mania from the analysis. Based on these analyses, it is likely that emergence of mania caused a spurious overestimate of the treatment effect for the placebo group, resulting in an underestimate of the treatment difference between the olanzapine and the placebo groups. The influence of mania emergence on this treatment difference would be specifically greater in the Chinese subpopulation given its greater contribution of patients with this outcome. Early discontinuation led to missing data, especially in the placebo group from which patients withdrew due to a lack of efficacy. Use of the LOCF method in the ITT analysis meant that missing data was imputed by assuming that the MADRS total scores remained unchanged after patients dropped out, which may have led to biased estimates toward smaller (conservative) mean differences between treatment groups. Reanalysis using the observed case method by including only patients (n=159) who completed 6 weeks of treatment found that the difference in mean change in MADRS total score between olanzapine and placebo groups increased from −1.05 to −2.12. It should be pointed out that the US National Research Council's Panel on the Handling of Missing Data in Clinical Trials has recommended that single imputation methods (such as LOCF) "should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified".[26] Instead, the MMRM model is able to provide unbiased estimates and, when reanalyzing our imputed missing data using the MMRM method, we found an increase in the treatment difference between the olanzapine and placebo groups. In summary, it appears that both the higher incidence of mania and higher rate of early discontinuation in the Chinese subpopulation compared with the overall population potentially led to an underestimation of the treatment difference between olanzapine and placebo in the Chinese subpopulation.

There are several limitations of this subpopulation analysis. As mentioned, the lack of a priori statistical power makes it difficult to interpret key findings, particularly the lack of statistically significant differences in efficacy measures between treatment arms. This subpopulation analysis is also subject to limitations of the parent trial, including stringency of the criteria used to define recovery considering the short study duration, and applicability of the results only to patients who met the inclusion criteria. Future studies should consider including patients with broader patient characteristics within the Chinese subpopulation and including study numbers at enrollment that produce sufficient statistical power.

In summary, olanzapine appears to have a similar magnitude of antidepressant treatment effect in Chinese patients with bipolar I disorder as in patients in other regions. The lack of statistically significant difference between olanzapine and placebo is primarily thought to relate to the small sample size of Chinese patients and resulting lack of statistical power in this subpopulation analysis. Further, the treatment effect of olanzapine was likely to have been underestimated by the disproportionately larger number of discontinuations related to mania episodes and large reductions in MADRS score among placebo-treated patients with emergence of mania.

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Author contributions

All authors were involved in either the design of the study (YC, SHW, HBX), or the analysis and interpretation of data for the study (all authors). All authors contributed to the drafting of the manuscript or in critical revision of the manuscript for important intellectual content. JNW provided statistical analysis for the study while YC, GW, and SHW also provided administrative, technical, or material support. GW was a trial investigator involved in the study.

Disclosure

YC, JNW, and SHW are employees of Lilly Suzhou Pharmaceutical Co., Ltd. GW has received consultancies and participated in advisory panels for Lilly Suzhou Pharmaceutical Co., Ltd. HBX has no conflicts of interest to declare in this work.

References

1. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry*. 2009;166(2):173–181.
2. Hlastala SA, Frank E, Mallinger AG, Thase ME, Ritenour AM, Kupfer DJ. Bipolar depression: an underestimated treatment challenge. *Depress Anxiety*. 1997;5(2):73–83.
3. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
4. Keller MB, Lavori PW, Coryell W, et al. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. *JAMA*. 1986;255(22):3138–3142.
5. Post RM. The impact of bipolar depression. *J Clin Psychiatry*. 2005; 66 Suppl 5:5–10.
6. Altshuler LL, Gitlin MJ, Mintz J, Leight KL, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. *J Clin Psychiatry*. 2002;63(9):807–811.
7. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. *Arch Gen Psychiatry*. 2000;57(9): 841–849.
8. Katagiri H, Takita Y, Tohen M, Higuchi T, Kanba S, Takahashi M. Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder. *Curr Med Res Opin*. 2012; 28(5):701–713.
9. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088.
10. Benazzi F, Berk M, Frye MA, Wang W, Barraco A, Tohen M. Olanzapine/fluoxetine combination for the treatment of mixed depression in bipolar I disorder: a post hoc analysis. *J Clin Psychiatry*. 2009;70(10): 1424–1431.
11. Tohen M, Kanba S, McIntyre RS, Fujikoshi S, Katagiri H. Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. *J Affect Disord*. 2014;164:57–62.
12. Tohen M, Katagiri H, Fujikoshi S, Kanba S. Efficacy of olanzapine monotherapy in acute bipolar depression: a pooled analysis of controlled studies. *J Affect Disord*. 2013;149(1–3):196–201.
13. Tohen M, McDonnell DP, Case M, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. *Br J Psychiatry*. 2012;201(5):376–382.
14. Katagiri H, Tohen M, McDonnell DP, et al. Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Japanese subpopulation analysis of a randomized, double-blind, placebo-controlled study. *BMC Psychiatry*. 2013;13:138.
15. Xue HB, Liu L, Zhang H, Montgomery W, Treuer T. Olanzapine in Chinese patients with schizophrenia or bipolar disorder: a systematic literature review. *Neuropsychiatr Dis Treat*. 2014;10:841–864.
16. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
17. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
18. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
19. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133: 429–435.
20. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22–33.
21. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5): 453–473.
22. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106(25):3143–3421.
23. American Diabetes Association. Standards of medical care in diabetes – 2014. *Diabetes Care*. 2014;37 Suppl 1:S14–S80.

24. Niufan G, Tohen M, Qiuqing A, et al. Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. *J Affect Disord*. 2008;105(1–3):101–108.
25. Eli Lilly and Company. CDE questions for olanzapine tablets monotherapy bipolar depression NDA Panel Meeting: LY170053 (Olanzapine). *Data on file*. 2014.
26. National Research Council (US) Panel on Handling Missing Data in Clinical Trials. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington (DC): National Academies Press (US); 2010.