Summary ID#7029

Clinical Study Summary: Study F1D-MC-HGKQ

Clinical Study Report: Olanzapine Versus Divalproex and Placebo in the Treatment of Mild to Moderate Mania Associated with Bipolar I Disorder

Date summary approved by Lilly: 17 March 2008

Brief Summary of Results

Study F1D-MC-HGKQ was a randomized, double-blind, placebo-controlled, parallel study with 4 study periods for adult patients with mild to moderate manic or mixed episode associated with bipolar I disorder. Patients were randomly assigned in a 2:2:1 ratio into 3 treatment groups: olanzapine 5 to 20 mg/day, divalproex 500 to 2500 mg/day, or placebo. Qualified patients from Study Period I (screening period) were administered double-blind study drug orally each day for 3 weeks during Study Period II (the acute phase), for 9 weeks during Study Period III (the extension phase), and were tapered down for 1 week during Study Period IV (the taper phase). At the end of Study Period II, patients who had previously received placebo were switched to olanzapine 5 to 20 mg/day; this group of patients was excluded from the formal statistical analysis of efficacy for Study Period III.

The primary objective was to compare the efficacy of olanzapine (5 to 20 mg/day) and divalproex (500 to 2500 mg/day) in improving overall manic symptomatology, as measured by reductions on the Young Mania Rating Scale (YMRS) total score from baseline to the endpoint of Study Period II. A total of 521 patients were randomized (215 olanzapine, 201 divalproex, 105 placebo); 486 received at least one dose of treatment and had at least one post-baseline efficacy assessment, and were included in the ITT population(201 olanzapine, 186 divalproex, 99 placebo). The average dose of olanzapine was 11.4 mg/day and the average dose of divalproex was 848.4 mg/day.

The results of the primary efficacy analyses showed that:

- There was no statistically significant treatment difference between the olanzapine and divalproex groups in change in YMRS total score from baseline to the endpoint of Study Period II.

The results of secondary efficacy analyses are as follows:

- For Study Period II, from baseline to endpoint, there were no statistically significant differences between the divalproex and placebo groups for mean change in YMRS total score; between any of the treatment groups in mean change in YMRS total score for the Mixed or Manic subgroups or for response rate, time to response, remission rate, or time to remission as measured by the YMRS; or for the percentage of patients who switched from not depressed to depressed or time to such a switch. Compared to divalproex, olanzapine showed statistically significantly greater reductions in mean Montgomery-Asberg Depression Rating Scale (MADRS) scores and Clinical Global Impressions-Bipolar (CGI-BP) mania, depression, and overall bipolar disorder scores. Compared to placebo, olanzapine showed statistically significantly greater reductions in YMRS total score, CGI-BP mania, depression, and overall bipolar disorder scores.
- For Study Period II-III (the combined acute and extension phases), from baseline to endpoint, there were no statistically significant differences between the olanzapine and divalproex groups in mean MADRS score, mean CGI-BP depression score, rate of and time to remission, rate of and time to switch to depression, and time to response. Compared to divalproex, olanzapine showed statistically significantly greater reductions in mean YMRS total score, mean CGI-BP mania and overall bipolar disorder scores, and response rate. The statistically significant difference between olanzapine and divalproex for mean YMRS total score was observed for all patients and for subgroups of Manic and Mixed patients.
- For Study Period III, there were no statistically significant differences between the olanzapine and divalproex treatment groups in mean YMRS total score, proportions of patients who failed to maintain a response or who experienced a relapse of mania, or the time to failure to maintain response or to relapse of mania.

The analysis of safety showed that:

- There were no deaths in the study, and no statistically significant differences between treatment groups in the percentages of patients who had serious adverse events (SAE), or adverse events (AE) leading to discontinuation during Study Period II or Study Period II-III.

- During Study Period II, the most frequently reported treated-emergent adverse event (TEAE) for olanzapine-treated patients was weight increased followed by somnolence; for divalproex-treated patients was headache followed by nausea; and for placebo-treated patients was headache followed by sedation. During Study Period II-III, the most frequently reported TEAEs for olanzapine-treated patients were again, weight increased and somnolence, and for divalproex-treated patients were headache and nausea. During Study Period III, the most frequently reported TEAEs were weight increased and somnolence (in the placebo/olanzapine group), and headache (in the olanzapine and divalproex groups). The majority of events were mild or moderate in severity.
- The TEAEs weight increased, alanine aminotransferase (ALT) increased, and somnolence occurred statistically significantly more frequently in the olanzapine group compared to the placebo group during Study Period II, and statistically significantly more frequently in the olanzapine group compared to the divalproex group during Study Periods II and II-III. The TEAE aspartate aminotransferase (AST) increased occurred statistically significantly more frequently in the olanzapine group compared to the divalproex group; nausea, vomiting, and insomnia occurred statistically significantly less frequently in the olanzapine group compared to the divalproex group during Study Period II. Nausea and vomiting occurred statistically significantly less frequently in the olanzapine group compared to the divalproex group during Study Period II-III.
- There were no statistically significant differences among treatment groups in incidence of treatment-emergent extrapyramidal symptoms.
- Olanzapine-treated patients had a statistically significantly greater mean weight increase than divalproex- or placebo-treated patients during Study Period II; and a statistically significantly greater mean weight increase than divalproex-treated patients during Study Period II-III and in Study Period III.

- During Study Period II, statistically significant differences were seen between olanzapine and divalproex for the incidence of treatment-emergent QTc prolongation, as well as treatment-emergent increases in prolactin and ALT (greater incidence of treatment-emergent increases in the olanzapine group than in the divalproex group at least once during the study); and between olanzapine and placebo for treatment-emergent increases in ALT and prolactin (greater incidence of treatment-emergent increases in the olanzapine group than placebo group at least once during the study and at endpoint for prolactin, and at least once during the study for ALT). Compared to olanzapine and placebo, statistically significantly more divalproex patients had low mean cell hemoglobin concentration (MCHC) at least once during Study Period II and at endpoint. Compared to olanzapine, statistically significantly more divalproex patients had high monocytes at least once during the study period; and statistically significantly more placebo patients had low leukocytes at endpoint.
- During Study Period III, statistically significantly more olanzapine patients had treatment-emergent increases in prolactin compared to divalproex at least once during the study and at endpoint. Compared to olanzapine, statistically significantly more divalproex patients had treatment-emergent increases in sodium (at least once during the study) and AST (at endpoint), and treatment-emergent decreases in albumin (at least once during the study) and erythrocytes (at endpoint).
- During Study Period II, statistically significantly more olanzapine patients than divalproex-treated patients experienced shifts from normal to high fasting triglycerides. During Study Period III, statistically significantly more olanzapine patients than divalproex-treated patients experienced shifts from normal to high fasting triglycerides, from borderline to high fasting total cholesterol, from impaired to high fasting glucose, and from normal/impaired to high fasting glucose.

Title of Study: Olanzapine Versus Divalproex and Placebo in the Treatment of Mild to Moderate Mania Associated with Bipolar I Disorder	
Investigator(s): This multicenter study included 68 principal investigators.	
Study Center(s): This study was conducted at 68 study centers in six countries/regions.	
Length of Study: Approximately 2 years Date of first patient enrolled: 18 October 2004 Date of last patient completed: 13 December 2006	**Phase of Development:** 4
Objectives: The primary objective of this study was to compare the efficacy of olanzapine and divalproex in improving overall manic symptomatology in patients with mild to moderate mania associated with bipolar I disorder, as measured by reductions on the Young Mania Rating Scale (YMRS) total score from baseline to the endpoint of Study Period II (the acute phase). Secondary objectives included comparing the efficacy of olanzapine and placebo, and divalproex and placebo, using the YMRS total score from baseline to the endpoint of Study Period II. If the olanzapine vs divalproex comparison was not significant, and the divalproex vs placebo comparison was significant, a noninferiority analysis of olanzapine to divalproex was to be performed. Other secondary objectives included assessing the efficacy of olanzapine compared with divalproex and placebo using various measures of the YMRS (rate of and time to response; rate of and time to remission of mania); reductions from baseline to the endpoint of Study Period II on the Montgomery-Asberg Depression Rating Scale (MADRS) total score and the Clinical Global Impressions-Bipolar Version Severity of Illness (CGI-BP Severity) score; assessing the longer-term efficacy of olanzapine compared with divalproex using reductions in the YMRS, MADRS, and CGI-BP scores from the endpoint of Study Period II to the endpoint of Study Period III (the extension phase); rate of and time to failure to maintain response during Study Period III; rate of and time relapse of mania; assessing treatment by subgroup interaction of Manic and Mixed subtypes; assessing the rate of switch to depressive episode in patients not depressed at baseline; assessing the safety of olanzapine compared to divalproex and placebo (treatment-emergent adverse events [TEAEs], vital signs and weight, laboratory evaluations, electrocardiograms [ECGs], and extrapyramidal symptoms [EPS] using the Barnes Akathisia Scale [Barnes], Abnormal Involuntary Movement Scale [AIMS], and Simpson-Angus Scale [SAS]); comparing changes in functional status and health-related quality of life based on the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and psychosocial outcomes based on the Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation (SLICE/LIFE); and evaluating Resource Utilization and Hospitalization Inventory.	
Study Design: This was a randomized, double-blind, placebo-controlled, parallel study comparing olanzapine, divalproex, and placebo in outpatients or inpatients meeting diagnostic criteria for a mild to moderate manic or mixed episode associated with bipolar I disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR). The study design consisted of 4 study periods. Study Period I was a 2- to 14-day screening period. Study Period II was a 3-week double-blind acute phase, during which patients received either olanzapine, divalproex, or placebo. Study Period III was a 9-week extension phase during which treatment continued to be given in a double-blind fashion. Patients who had previously received placebo in Study Period II were switched to olanzapine; this treatment group is referred to as the placebo/olanzapine group in discussions of Study Period II-III combined and Study Period III. This group of patients was excluded from formal statistical analysis of efficacy for Study Period III. Study Period IV was a 1-week taper phase.	
Number of Patients: Planned: 500 Randomized/Entered: 521 (215 olanzapine, 201 divalproex, 105 placebo) Completed: 231 (96 olanzapine, 82 divalproex, 53 placebo/olanzapine)	

Diagnosis and Main Criteria for Inclusion: Eligible patients were men or women, outpatients or inpatients, aged 18 through 65 years of age, with a diagnosis of bipolar I disorder and meeting DSM-IV-TR criteria for an acute manic or mixed episode (based on clinical assessment and confirmed by structured diagnostic interview using the Clinician's Version of the Structured Clinical Interview for DSM-IV [SCID-CV] plus the Rapid Cycling item from the Bipolar Specifiers obtained from the Structured Clinical Interview for DSM-IV Axis I disorders [SCID-I]; allowable diagnoses included mild or moderate manic episode and mild or moderate mixed episode) with YMRS total score of ≥20 and ≤30 and CGI-BP Mania subscore of 3 or 4 at both Visits 1 and 2 and with no major, uncontrolled physical illnesses.

Test Product, Dose, and Mode of Administration: Olanzapine 5 to 20 mg/day, given orally once daily in the evening using 5-mg and/or 10-mg capsules.

Reference Therapy, Dose, and Mode of Administration: Divalproex 500 to 2500 mg/day given orally in divided doses: twice daily (for the 500 mg dosage) or three times daily (for the 750 to 2500 mg dosages) using 250-mg capsules. Placebo given orally three times daily in capsules. To preserve the blind, all patients took the same number of capsules per day, three times daily.

Duration of Treatment: 13 weeks

Variables:

Efficacy: YMRS, MADRS, and CGI-BP.

Safety: TEAEs, clinical laboratory tests, valproic acid therapeutic blood concentrations, ECGs, vital signs and weight, EPS, SAS, Barnes, and AIMS.

Health Outcomes: Changes from baseline in the SF-36 and the SLICE/LIFE, and measurements of resource utilization (direct and indirect costs), hospitalization inventory, and medication use.

Evaluation Methods:

Population: The primary population for the analysis of efficacy was the intent-to-treat (ITT) population (defined as all randomized patients who received at least one dose of treatment and had at least one post-baseline efficacy assessment). The ITT population was used for the analysis of all efficacy endpoints. All randomized patients who received at least 1 dose of treatment were included in the safety analysis according to the actual treatment received.

Statistical Methodology: Unless otherwise stated, all statistical comparisons between treatments used two-sided statistical tests and a significance level of 5%. Data assumed to be normally distributed were summarized in terms of the mean, standard deviation (SD), median, minimum, maximum, and number of observations. Continuous data expected to be skewed (resource use variables) were presented in terms of the maximum, upper quartile, median, lower quartile, minimum, and number of observations. Categorical data were summarized in terms of frequency counts and percentages. In the categorical analysis of continuous safety data (e.g., EPS scales, laboratory analytes, vital signs), when the proportion of patients who were above or below the upper or lower limit, respectively, was of interest, only patients who had a baseline value below or equal to the upper limit or above or equal to the lower limit, as the case may be, were included.

Primary Efficacy Analysis: The primary analysis of the mean change in the YMRS total score from baseline to the end of Study Period II (Visit 5) was performed using an analysis of covariance (ANCOVA), including terms for treatment, investigator, and baseline YMRS total score (as a covariate). Main treatment effects and pairwise treatment comparisons were both analyzed for 3 treatment groups for Study Period II. This was a last-observation-carried-forward (LOCF) analysis based on the ITT population.

Secondary Efficacy Analyses and Safety Analyses: Changes in the MADRS total score and the CGI-BP Severity scores from baseline to the end of Study Period II, combination of Study Periods II and III (Study Period II-III [the combined acute and extension phases], olanzapine vs divalproex only), and Study Period III (olanzapine vs divalproex only) were analyzed in the same manner as the primary ANCOVA analysis of the YMRS total score (including baseline MADRS total score as a covariate in place of baseline YMRS total score).

(continued)

Evaluation Methods (Continued):
The rates of switch to depression in patients not depressed at baseline were summarized by treatment group for Study Periods II and III. Pairwise differences between treatments in rates of response were assessed using a Cochran-Mantel-Haenszel (CMH) test stratifying by investigator. Time to switch to depression during Study Period II and time to switch to depression during Study Period II-III were compared among treatment groups using the Kaplan-Meier product limit estimates and the log-rank test for pairwise comparisons. Overall and by preferred term, treatment differences in incidence rates of the most common TEAEs were assessed using a CMH test stratifying by investigator: all pairwise comparisons were performed for Study Period II and olanzapine versus divalproex for Study Period II-III. For laboratory values, vital signs, weight, ECGs, and EPS, changes from baseline to the endpoints of Study Period II, Study Period II-III, and Study Period III were compared pairwise by ANCOVA using treatment and investigator as fixed effects and baseline value as covariate; treatment groups were analyzed for differences in proportions of patients with treatment-emergent abnormal values (i) anytime and (ii) endpoint (the last observation) at Study Period II and Study Period III (olanzapine vs divalproex only) using a CMH test stratifying by investigator.

Sample Size: The sample size of 500 patients (200 olanzapine, 200 divalproex, and 100 placebo) provided 80% power of detecting a 3.4 point difference in the mean YMRS scores between olanzapine and divalproex. For the active treatments versus placebo, this sample size provided 80% power of detecting a 4.2 point difference in the mean YMRS scores. This was based on a significance level of 0.05, two-tailed, with an estimated standard deviation of 12.0.

Results:

Patient Demographics

Of the 521 (215 olanzapine, 201 divalproex, 105 placebo) randomized patients who entered the study, 486 (201 olanzapine, 186 divalproex, 99 placebo) patients received at least one dose of treatment and had at least one post-baseline efficacy assessment, and were included in the ITT population.

Table HGKQ.1 presents baseline demographics and severity of illness for patients in the study. There were no statistically significant differences between any of the treatment groups for the demographic characteristics in the ITT population (age, race, sex, height, or weight). Overall for all patients, the mean age was 39.6 years and the mean weight was 81.5 kg (range, 40 to 172 kg). Overall, 52.3% of patients were female and 47.7% were male. There were no statistically significant differences between treatment groups in the mean baseline severity of illness measurements (YMRS total score, CGI-BP mania score, CGI-BP depression score, CGI-BP overall bipolar disorder score, or MADRS total score) in the ITT population.

Table HGKQ.1. Baseline Demographics and Severity of Illness

Parameter	Olanzapine (N=201)	Divalproex (N=186)	Placebo/Olanzapine (1) (N=99)	Total (N=486)	p-value O vs P	p-value D vs P	p-value O vs D
Age (years) (2)							
n	201	186	99	486			
Mean	39.5	39.2	40.6	39.6	0.312	0.302	0.966
SD	11.89	11.74	12.75	12.00			
Median	40.0	38.2	39.9	39.3			
Minimum	18	18	18	18			
Maximum	65	64	65	65			
Race: n (%) (3)							
Caucasian	160 (79.6%)	152 (81.7%)	82 (82.8%)	394 (81.1%)	0.269	0.412	0.561
African	28 (13.9%)	19 (10.2%)	12 (12.1%)	59 (12.1%)			
Native American	2 (1.0%)	3 (1.6%)	0	5 (1.0%)			
East Asian	1 (0.5%)	1 (0.5%)	0	2 (0.4%)			
West Asian	0	0	1 (1.0%)	1 (0.2%)			
Hispanic	10 (5.0%)	11 (5.9%)	4 (4.0%)	25 (5.1%)			
Aboriginial and/or Torres Strait Islander	0	0	0	0			
Sex: n (%) (3)							
Female	109 (54.2%)	99 (53.2%)	46 (46.5%)	254 (52.3%)	0.232	0.191	1.000
Male	92 (45.8%)	87 (46.8%)	53 (53.5%)	232 (47.7%)			
Height (cm) (2)							
n	201	186	99	486			
Mean	170.5	170.2	170.7	170.4	0.805	0.577	0.702
SD	10.06	10.12	10.95	10.25			
Median	170.0	170.0	171.0	170.0			
Minimum	128	145	150	128			
Maximum	201	206	230	230			

(CONTINUED)

Table HGKQ.1. Baseline Demographics and Severity of Illness (Continued)

Parameter	Olanzapine (N=201)	Divalproex (N=186)	Placebo/Olanzapine (1) (N=99)	Total (N=486)	p-value O vs P	p-value D vs P	p-value O vs D
Weight (kg) (2)							
n	201	186	99	486			
Mean	82.5	81.3	79.9	81.5	0.220	0.611	0.392
SD	21.61	20.47	19.29	20.70			
Median	78.0	78.1	77.0	78.0			
Minimum	40	43	48	40			
Maximum	150	156	172	172			
Baseline YMRS Total Score (2)							
n	201	186	99	486			
Mean	23.8	23.9	23.5	23.8	0.322	0.058	0.260
SD	2.75	2.77	2.52	2.71			
Median	23.0	23.0	23.0	23.0			
Minimum	14	16	20	14			
Maximum	30	30	30	30			
Baseline CGI-BP - Mania (2)							
n	201	186	99	486			
Mean	3.7	3.7	3.7	3.7	0.792	0.545	0.673
SD	0.46	0.45	0.47	0.46			
Median	4.0	4.0	4.0	4.0			
Minimum	3	3	3	3			
Maximum	5	5	5	5			
Baseline CGI-BP - Depression (2)							
n	201	186	99	486			
Mean	1.9	2.0	2.0	2.0	0.783	0.868	0.898
SD	1.12	1.17	1.16	1.15			
Median	1.0	1.0	1.0	1.0			
Minimum	1	1	1	1			
Maximum	5	5	4	5			

(CONTINUED)

Table HGKQ.1. Baseline Demographics and Severity of Illness (Concluded)

Parameter	Olanzapine (N=201)	Divalproex (N=186)	Placebo/Olanzapine (1) (N=99)	Total (N=486)	p-value O vs P	p-value D vs P	p-value O vs D
Baseline CGI-BP - Overall Bipolar Disorder (2)							
n	201	186	99	486			
Mean	3.6	3.7	3.6	3.7	0.832	0.197	0.187
SD	0.64	0.53	0.66	0.60			
Median	4.0	4.0	4.0	4.0			
Minimum	1	1	1	1			
Maximum	5	5	5	5			
Baseline MADRS Total Score (2)							
n	201	186	99	486			
Mean	10.6	10.6	11.3	10.8	0.699	0.338	0.482
SD	7.77	7.13	7.80	7.53			
Median	8.0	9.0	9.0	9.0			
Minimum	0	0	0	0			
Maximum	37	32	32	37			

Abbreviations: ANOVA = analysis of variance; CGI-BP = Clinical Global Impressions-Bipolar; CMH = Cochran-Mantel-Haenszel; D = divalproex; MADRS = Montgomery-Asberg Depression Rating Scale; N = total number of patients; n = number of patients assessed; O = olanzapine; P = placebo; SD = standard deviation; YMRS = Young Mania Rating Scale.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Analyzed using ANOVA with terms for treatment and investigator.
(3) Analyzed using CMH test stratifying by investigator.

Patient Disposition

Of the 521 patients randomized, 215 were randomized to the olanzapine group, 201 to the divalproex group, and 105 to the placebo group. Of these, 74.0% of olanzapine-treated, 75.1% of divalproex-treated, and 73.3% of placebo-treated patients completed Study Period II (the acute phase). Table HGKQ.2 presents a summary of reasons for discontinuation from the study. The percentage of patients who discontinued from Study Period II due to an adverse event (AE) was statistically significantly greater in the olanzapine group (7.4%) compared to the divalproex (3.0%) and placebo groups (1.0%) (p=0.045 olanzapine vs divalproex, p=0.014 olanzapine vs placebo). The percentage of patients who discontinued due to patient decision was statistically significantly smaller (p=0.017) in the olanzapine group (5.6%) compared to the divalproex group (11.9%).

During Study Period II-III (the combined acute and extension phases), the percentage of patients who discontinued due to patient decision was statistically significantly smaller (p=0.033) in the olanzapine group (14.4%) compared to the divalproex group (22.4%). The percentage of patients who discontinued due to lost-to-follow up was statistically significantly greater (p=0.044) in the olanzapine group (14.0%) compared to the divalproex group (8.5%).

A total of 387 patients entered Study Period III (the extension phase) (159, 150, and 78 patients in the olanzapine, divalproex, and placebo/olanzapine groups, respectively). Of these, 240 patients completed Study Period III (101 [47.0%], 86 [42.8%], and 53 [50.5%] patients in the olanzapine, divalproex, and placebo/olanzapine groups, respectively).

A total of 268 patients entered Study Period IV (the taper phase) (112 [70.4%], 99 [66.0%], and 57 [73.1%] patients in the olanzapine, divalproex, and placebo/olanzapine groups, respectively). Of these, 231 patients completed the study; 96 (60.4%), 82 (54.7%), and 53 (67.9%) patients in the olanzapine, divalproex, and placebo/olanzapine groups, respectively.

Table HGKQ.2. Reasons for Discontinuation

	Olanzapine n (%)	Divalproex n (%)	Placebo/Olanzapine (1) n (%)	Total n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Number of patients who prematurely discontinued during Study Period II	56 (26.0)	50 (24.9)	28 (26.7)	134 (25.7)	0.978	0.739	0.710
Primary reason for discontinuation during Study Period II:							
Adverse event/death	16 (7.4)	6 (3.0)	1 (1.0)	23 (4.4)	0.014	0.297	0.045
Lack of efficacy	3 (1.4)	4 (2.0)	2 (1.9)	9 (1.7)	0.675	0.890	0.728
Patient decision	12 (5.6)	24 (11.9)	11 (10.5)	47 (9.0)	0.127	0.500	0.017
Protocol entry criteria not met	2 (0.9)	1 (0.5)	3 (2.9)	6 (1.2)	0.165	0.071	0.639
Protocol violation	3 (1.4)	1 (0.5)	1 (1.0)	5 (1.0)	0.726	0.502	0.320
Sponsor decision	3 (1.4)	4 (2.0)	1 (1.0)	8 (1.5)	0.849	0.519	0.632
Physician decision	2 (0.9)	3 (1.5)	2 (1.9)	7 (1.3)	0.519	0.853	0.637
Lost to follow-up	15 (7.0)	7 (3.5)	7 (6.7)	29 (5.6)	0.829	0.148	0.075
Number of patients who prematurely discontinued during Study Period II and III	114 (53.0)	115 (57.2)	52 (49.5)	281 (53.9)			0.452
Primary reason for discontinuation during Study Period II and III:							
Adverse event/death	28 (13.0)	19 (9.5)	6 (5.7)	53 (10.2)			0.293
Lack of efficacy	8 (3.7)	13 (6.5)	2 (1.9)	23 (4.4)			0.181
Patient decision	31 (14.4)	45 (22.4)	17 (16.2)	93 (17.9)			0.033
Protocol entry criteria not met	2 (0.9)	1 (0.5)	3 (2.9)	6 (1.2)			0.639
Protocol violation	5 (2.3)	6 (3.0)	2 (1.9)	13 (2.5)			0.846
Sponsor decision	7 (3.3)	9 (4.5)	1 (1.0)	17 (3.3)			0.496
Physician decision	3 (1.4)	5 (2.5)	3 (2.9)	11 (2.1)			0.455
Lost to follow-up	30 (14.0)	17 (8.5)	18 (17.1)	65 (12.5)			0.044

(CONTINUED)

Table HGKQ.2. Reasons for Discontinuation (Concluded)

	Olanzapine n (%)	Divalproex n (%)	Placebo/Olanzapine (1) n (%)	Total n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Number of patients who prematurely Discontinued during Study Period III	58 (36.5)	64 (42.7)	25 (32.1)	147 (38.0)			
Primary reason for discontinuation during Study Period III:							
Adverse event/death	12 (7.5)	13 (8.7)	5 (6.4)	30 (7.8)			
Lack of efficacy	5 (3.1)	9 (6.0)	0	14 (3.6)			
Patient decision	19 (11.9)	21 (14.0)	6 (7.7)	46 (11.9)			
Protocol entry criteria not met	0	0	0	0			
Protocol violation	2 (1.3)	5 (3.3)	1 (1.3)	8 (2.1)			
Sponsor decision	4 (2.5)	5 (3.3)	0	9 (2.3)			
Physician decision	1 (0.6)	2 (1.3)	2 (2.6)	5 (1.3)			
Lost to follow-up	15 (9.4)	9 (6.0)	11 (14.1)	35 (9.0)			

Abbreviations: CMH = Cochran-Mantel-Haenszel; D = divalproex; n = number of patients discontinued from the study; O = olanzapine; P = placebo.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Pairwise frequencies are compared using CMH test stratifying by investigator.

Efficacy Results

Table HGKQ.3 presents a summary of primary and secondary efficacy results for Study Period II.

Primary Efficacy Results:

The primary efficacy analysis was to compare the efficacy of olanzapine and divalproex in improving overall manic symptomatology, as measured by reduction in the YMRS total score from baseline to the endpoint of Study Period II. There was no statistically significant treatment difference in mean change in YMRS total score between the olanzapine (-9.4) and divalproex (-8.2) groups during Study Period II.

Secondary Efficacy Results (Study Period II):

During Study Period II, olanzapine showed statistically significantly greater reductions in mean MADRS score (p=0.045), CGI-BP mania score (p=0.038), CGI-BP depression score (p=0.040), and CGI-BP overall bipolar disorder score (p=0.014) compared to divalproex. Olanzapine showed statistically significantly greater reductions in mean YMRS total score (p=0.034), CGI-BP mania score (p=0.031), CGI-BP depression score (p=0.036), and CGI-BP overall bipolar disorder score (p=0.005) compared to placebo. There were no statistically significant treatment differences between the divalproex and placebo groups for any of the key efficacy parameters. There were no statistically significant differences between treatment groups in mean change in YMRS total score for either the Mixed or the Manic subgroup, or in the percentages of patients who had a response (defined as ≥50% reduction from baseline in the YMRS total score), achieved remission (defined as YMRS total score of ≤12), or switched from not depressed (MADRS score of ≤12) to depressed (MADRS score of ≥16 or hospitalization due to deterioration in clinical symptoms of depression). Furthermore, there were no statistically significant differences between treatment groups in time to response, time to remission, or time to switch to depression.

Table HGKQ.3. Efficacy Results at End of Study Period II (the Acute Phase)

Variable	Olanzapine (N=201)	Divalproex (N=186)	Placebo (N=99)	p-Values O vs D	p-Values O vs P	p-Values D vs P
LS Mean Change from Baseline						
YMRS – Total	-9.4	-8.2	-7.4	0.143	0.034	0.373
YMRS – Total Manic Subgroup	(n=143) -9.4	(n=132) -8.4	(n=68) -7.1	0.314	0.059	0.301
YMRS – Total Mixed Subgroup	(n=57) -10.5	(n=54) -9.3	(n=30) -8.5	0.378	0.206	0.591
MADRS	-3.3	-2.1	-2.4	0.045	0.209	0.686
CGI-BP – Mania	-1.0	-0.8	-0.7	0.038	0.031	0.665
CGI-BP – Depr.	-0.3	-0.2	-0.1	0.040	0.036	0.700
CGI-BP – Overall	-0.8	-0.6	-0.5	0.014	0.005	0.461
Response – n (%)	82 (40.8)	75 (40.3)	31 (31.3)	0.653	0.063	0.140
Median Time to Response – days	24	22	23	0.532	0.136	0.306
Remission – n (%)	86 (42.8)	75 (40.3)	35 (35.4)	0.360	0.175	0.519
Median Time to Remission – days	--	22	--	0.329	0.209	0.653
Switch to Depr. – n/N (%)	13/134 (9.7)	13/127 (10.2)	10/67 (14.9)	0.448	0.397	0.227
Med. Time to Switch to Depr. – days	--	--	28	0.886	0.495	0.575

Abbreviations: ANCOVA = analysis of covariance; CGI-BP = Clinical Global Impressions-Bipolar; CMH = Cochran-Mantel-Haenszel; Depr. = Depression; D = divalproex; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; Med. = Median; N = total number of patients; n = number of patients assessed or with observations analyzed; O = olanzapine; P = placebo; YMRS = Young Mania Rating Scale.

Definitions: Response = ≥50% reduction from baseline in the YMRS total score; Remission = YMRS total score of ≤12; Switch to depression = switch from MADRS score of ≤12 (not depressed) to MADRS score of ≥16 or hospitalization due to deterioration of clinical symptoms of depression.

Analysis methods: Continuous variables (YMRS, MADRS, CGI-S) were analyzed using ANCOVA with terms for treatment and investigator and baseline score as a covariate. Categorical variables (response, remission, switch to depression) were analyzed using CMH test stratifying by investigator; and median times based on Kaplan-Meier estimates, with p-values for times determined using log-rank test.

Secondary Efficacy Results (Study Period II-III):

Table HGKQ.4 presents a summary of efficacy results for Study Period II-III, combining data from Study Period II and Study Period III (baseline to Visit 10). Patients who had previously received placebo in Study Period II were switched to olanzapine 5 to 20 mg/day at the beginning of Study Period III, and in the context of Study Period II-III are referred to as the placebo/olanzapine group. Treatment comparisons were performed between olanzapine and divalproex only. Data from the placebo/olanzapine group were summarized; no treatment comparison was performed.

During Study Period II-III, olanzapine showed statistically significantly greater reductions in mean YMRS total score (p=0.004), YMRS total score for both the Manic subgroup (p=0.034) and the Mixed subgroup (p=0.020), CGI-BP mania score (p=0.008), and CGI-BP overall bipolar disorder score (p=0.023) compared to divalproex. There were no statistically significant differences between the olanzapine and divalproex groups in mean change in MADRS score or CGI-BP depression score, or in percentages of patients who switched from not depressed to depressed. A statistically significantly greater percentage of olanzapine-treated patients had a response compared to divalproex-treated patients (p=0.044). There was no statistically significant difference between the olanzapine and divalproex groups in the percentages of patients who achieved remission. There were no statistically significant differences between treatment groups in time to response, time to remission, or time to switch to depression.

Table HGKQ.4. Efficacy Results of End of Study Period II-III (the Combined Acute and Extension Phases)

Variable	Olanzapine (N=201)	Divalproex (N=186)	p-Values Olanzapine vs Divalproex
LS Mean Change from Baseline			
YMRS – Total	-13.3	-10.7	0.004
YMRS – Total: Manic Subgroup	-13.9 (n=143)	-11.4 (n=132)	0.034
YMRS – Total: Mixed Subgroup	-14.2 (n=57)	-11.0 (n=54)	0.020
MADRS	-2.3	-2.2	0.883
CGI-BP – Mania	-1.5	-1.2	0.008
CGI-BP – Depression	-0.2	-0.2	0.910
CGI-BP – Overall	-1.2	-0.9	0.023
Response – n (%)	133 (66.2)	106 (57.0)	0.044
Median Time to Response – days	28	34	0.139
Remission – n (%)	133 (66.2)	112 (60.2)	0.164
Median Time to Remission – days	28	28	0.459
Switch to Depression – n/N (%)	22/134 (16.4)	22/127 (17.3)	0.396
Median Time to Switch to Depression – days	--	--	0.796

Abbreviations: ANCOVA = analysis of covariance; CGI-BP = Clinical Global Impressions-Bipolar; CMH = Cochran-Mantel-Haenszel; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; N = total number of patients; n = number of patients assessed or with observation; YMRS = Young Mania Rating Scale.

Definitions: Response = ≥50% reduction from baseline in the YMRS total score; Remission = YMRS total score of ≤12; Switch to depression = switch from MADRS score of ≤12 (not depressed) to MADRS score of ≥16 or hospitalization due to deterioration of clinical symptoms of depression.

Analysis methods: Continuous variables (YMRS, MADRS, CGI-BP) were analyzed using ANCOVA with terms for treatment and investigator and baseline score as a covariate. Categorical variables (response, remission, switch to depression) were analyzed using CMH test stratifying by investigator; median times based on Kaplan-Meier estimates, with p-values for times determined using log-rank test.

Secondary Efficacy Results (Study Period III):

Table HGKQ.5 presents a summary of efficacy results for Study Period III. Patients who had previously received placebo in Study Period II were switched to olanzapine 5 to 20 mg/day, and in the context of Study Period III are referred to as the placebo/olanzapine group. Treatment comparisons were performed between olanzapine and divalproex only. Data from the placebo/olanzapine group were summarized; no treatment comparison was performed.

During Study Period III, there were no statistically significant differences between the olanzapine and divalproex groups in mean change in YMRS total score, the percentages of patients who failed to maintain a response (defined as returned to a YMRS total score of ≥20 and/or hospitalization due to deterioration in clinical symptoms of mania during Study Period III), or the percentages of patients who experienced a relapse of mania

(defined as achieving a YMRS total score ≥15 and/or hospitalization due to a deterioration in clinical symptoms of mania during Study Period III).

Table HGKQ.5. Efficacy Results of Study Period III (the Extension Phase)

Variable	Olanzapine	Divalproex	Placebo/ Olanzapine	p-Values O vs D
LS Mean Change from End of Acute Phase YMRS – Total	-4.8 (n=154)	-3.2 (n=144)	--	0.057
Failure to Maintain a Response – n/N (%)	6/64 (9.4)	7/79 (10.1)	1/28 (3.6)	0.826
Median Time to Failure to Maintain a Response – days	--	--	--	0.819
Relapse – n/N (%)	12/65 (18.5)	9/67 (13.4)	3/32 (9.4)	0.305
Median Time to Relapse of Mania – days	--	--	--	0. 517
Switch to Depression – n/N (%)	--	--	7/57 (12.3)	--

Abbreviations: ANCOVA = analysis of covariance; CMH = Cochran-Mantel-Haenszel; D = divalproex; LS = least squares; O = olanzapine; MADRS = Montgomery-Asberg Depression Rating Scale; N = total number of patients; n = number of patients assessed or with observation; YMRS = Young Mania Rating Scale.

Placebo/olanzapine group received placebo during Study Period II and olanzapine (5 to 20 mg/day) during Study Period III.

Definitions: Response = ≥50% reduction from baseline in the YMRS total score; Failure to maintain a response = returned to a YMRS total score of ≥20 and/or hospitalization due to deterioration in clinical symptoms of mania during Study Period III (the extension phase); Relapse of mania = achieved a YMRS total score ≥15 and/or hospitalized due to a deterioration in clinical symptoms of mania during Study Period III (the extension phase); Switch to depression = switch from MADRS score of ≤12 (not depressed) to MADRS score of ≥16 or hospitalization due to deterioration of clinical symptoms of depression.

Analysis methods: YMRS was analyzed using ANCOVA with terms for treatment and investigator and Study Period II endpoint score as a covariate. Categorical variables (failure to maintain a response, relapse, switch to depression) were analyzed using CMH test stratifying by investigator; and median times based on Kaplan-Meier estimates, with p-values for times determined using log-rank test.

Safety Results

Dose:

During Study Period II, olanzapine 10 mg was the most common dose, followed by olanzapine 15 mg, in patients treated with olanzapine; and divalproex 750 mg was the most common dose in patients treated with divalproex. The average dose of olanzapine was 11.4 mg/day and the average dose of divalproex was 848.4 mg/day.

Divalproex sodium is a stable coordination compound of sodium valproate and valproic acid. The doses of divalproex chosen for this study (500 to 2500 mg/day) are consistent with approved dosages of divalproex in the treatment of psychiatric disorders, as recommended in the approved labeling. The mean valproic acid concentration for the

divalproex group was 61.3 μg/mL at end of Study Period II and 45.7 μg/mL at end of Study Period III. The percentage of patients who were below the therapeutic range (therapeutic range: 50 to 125 μg/ml) varied from 35.4% to 57.1% at any particular visit.

There were no statistically significant differences in mean total YMRS scores between valproic acid concentration levels (above/within range, below range, or missing) at any visit. However, greater reductions in total YMRS scores from baseline to endpoint were found in patients who had valproic acid concentration <50 μg/mL compared to patients who had valproic acid concentration ≥50 μg/mL in both Study Period II and Study Period II-III. Statistically significantly larger ($p<0.05$) mean doses of divalproex were seen in the subgroup of patients who had valproic acid concentration levels above/within range compared to the other subgroups during Study Period II (missing level); end of Study Period II (below range); and during Study Period III (below range and missing level).

The doses of olanzapine chosen for this study are consistent with approved dosages in the treatment of psychiatric disorders, with a recommended dosage of olanzapine of 5 to 20 mg/day.

Treatment-Emergent Adverse Events:

Table HGKQ.6 shows the most common treatment-emergent adverse events (TEAEs) (≥5.0% incidence) reported by all patients in the study for Study Period II, Study Period II-III, and Study Period III.

During Study Period II, TEAEs were reported in 52.6%, 48.3%, and 46.7% of olanzapine, divalproex, and placebo patients, respectively. The most commonly reported TEAEs among olanzapine-treated patients were weight increased, somnolence, increased appetite, sedation, and dry mouth. Of these, the TEAEs weight increased and somnolence occurred statistically significantly more frequently in the olanzapine group compared to the placebo group ($p<0.05$), and in the olanzapine group compared to the divalproex group ($p<0.02$). The TEAEs nausea and insomnia occurred statistically significantly less frequently in the olanzapine group compared to the divalproex group ($p<0.01$).

During Study Period II-III, TEAEs were reported in 62.3% and 61.7% of olanzapine and divalproex patients, respectively. The most commonly reported TEAEs among olanzapine-treated patients were weight increased, somnolence, increased appetite, headache, sedation, dry mouth, and fatigue. Of these, the TEAEs weight increased and somnolence occurred statistically significantly more frequently in the olanzapine group compared to the divalproex group ($p\leq0.004$). The TEAEs nausea and vomiting occurred statistically significantly less frequently in the olanzapine group compared to the divalproex group ($p<0.03$).

During Study Period III, TEAEs were reported in 47.2%, 46.3%, and 59.0% of olanzapine, divalproex, and placebo/olanzapine patients, respectively. The most commonly reported TEAEs among olanzapine-treated patients were weight increased and

headache. During Study Period IV, TEAEs were reported in 4.5%, 5.1%, and 8.8% of olanzapine, divalproex, and placebo/olanzapine patients, respectively. No individual TEAE was reported by ≥5.0% of patients in any treatment group during Study Period IV.

Table HGKQ.6. Treatment-Emergent Adverse Events Occurring in at Least 5.0% of Patients in Any Treatment Group (or with Statistically Significant Difference Between Groups) by Decreasing Frequency

Preferred Term	Olanzapine (N=215) n (%)	Divalproex (N=201) n (%)	Placebo/Olanzapine (1) (N=105) n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study period II (Acute Phase)						
Any Adverse Event	113 (52.6)	97 (48.3)	49 (46.7)	0.260	0.996	0.138
HEADACHE	9 (4.2)	18 (9.0)	9 (8.6)	0.114	0.903	0.071
WEIGHT INCREASED	19 (8.8)	8 (4.0)	3 (2.9)	0.049	0.663	0.016
SOMNOLENCE	19 (8.8)	5 (2.5)	3 (2.9)	0.045	0.793	0.004
NAUSEA	2 (0.9)	17 (8.5)	3 (2.9)	0.173	0.063	<0.001
INCREASED APPETITE	12 (5.6)	11 (5.5)	2 (1.9)	0.110	0.135	0.820
SEDATION	12 (5.6)	7 (3.5)	5 (4.8)	0.849	0.525	0.260
DRY MOUTH	12 (5.6)	5 (2.5)	3 (2.9)	0.224	0.895	0.092
INSOMNIA	2 (0.9)	11 (5.5)	4 (3.8)	0.116	0.451	0.008
ALANINE AMINOTRANSFERASE INCREASED	8 (3.7)	0	0	0.042	-	0.004
ASPARTATE AMINOTRANSFERASE INCREASED	5 (2.3)	0	0	0.128	-	0.032
VOMITING	1 (0.5)	7 (3.5)	4 (3.8)	0.012	0.830	0.039
Study period II-III (Combined Acute and Extension Phases)						
Any Adverse Event	134 (62.3)	124 (61.7)				0.502
WEIGHT INCREASED	28 (13.0)	12 (6.0)				0.003
HEADACHE	16 (7.4)	23 (11.4)				0.249
SOMNOLENCE	24 (11.2)	8 (4.0)				0.004
NAUSEA	3 (1.4)	21 (10.4)				<0.001
INCREASED APPETITE	17 (7.9)	14 (7.0)				0.581
SEDATION	14 (6.5)	8 (4.0)				0.208
DRY MOUTH	14 (6.5)	7 (3.5)				0.116
INSOMNIA	5 (2.3)	13 (6.5)				0.053
FATIGUE	13 (6.0)	6 (3.0)				0.101
DIARRHEA	4 (1.9)	11 (5.5)				0.057
TREMOR	4 (1.9)	10 (5.0)				0.103
VOMITING	2 (0.9)	10 (5.0)				0.022

(CONTINUED)

Table HGKQ.6. Treatment-Emergent Adverse Events Occurring in at Least 5.0% of Patients in Any Treatment Group (or with Statistically Significant Difference Between Groups) by Decreasing Frequency (Concluded)

Study period III (Extension Phase)

Preferred Term	Olanzapine (N=159) n (%)	Divalproex (N=149) n (%)	Placebo/Olanzapine (1) (N=78) n (%)
Any Adverse Event	75 (47.2)	69 (46.3)	46 (59.0)
WEIGHT INCREASED	12 (7.5)	7 (4.7)	8 (10.3)
SOMNOLENCE	7 (4.4)	3 (2.0)	7 (9.0)
UPPER RESPIRATORY TRACT INFECTION	0	1 (0.7)	6 (7.7)
HEADACHE	10 (6.3)	9 (6.0)	3 (3.8)
FATIGUE	5 (3.1)	0	4 (5.1)

Abbreviations: CMH = Cochran-Mantel-Haenszel; D = divalproex; N = total number of patients; n = number of patients reporting adverse event; O = olanzapine; P = placebo.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Rates of adverse events among treatment groups compared using CMH test stratifying by investigator.
Patients reporting more than one adverse event within the table row are counted only once within that row.

Treatment-Emergent Adverse Events Considered by Site Investigators to Be Possibly Related to Study Medication:

During Study Period II, TEAEs considered by site investigators to be possibly related to study medication were reported in 34.0%, 26.4%, and 29.5% of olanzapine, divalproex, and placebo patients, respectively. Related TEAEs that were reported in ≥5.0% of olanzapine-treated patients were: somnolence, weight increased, increased appetite, and sedation; nausea was the only related TEAE reported at this frequency in divalproex-treated patients.

During Study Period II-III, TEAEs considered by site investigators to be possibly related to study medication were reported in 42.3% of olanzapine patients and 35.8% of divalproex patients. Related TEAEs reported in ≥5.0% of olanzapine-treated patients were weight increased, somnolence, increased appetite, sedation, dry mouth, and fatigue; and in divalproex-treated patients, nausea and increased appetite.

During Study Period III, TEAEs considered by site investigators to be possibly related to study medication were reported in 25.8%, 21.5%, and 30.8% of olanzapine, divalproex, and placebo/olanzapine patients, respectively. Related TEAEs reported in ≥5.0% of olanzapine-treated patients were weight increased.

During Study Period IV, 1 (1.8%) patient had a TEAE considered to be possibly related to study drug (viral infection in the placebo/olanzapine group).

Deaths and Other Serious Adverse Events:

There were no deaths in the study.

During Study Period II, serious adverse events (SAEs) were reported in 2.3%, 0.5%, and 1.0% of patients in the olanzapine, divalproex, and placebo groups, respectively. The most common SAE was mania, occurring in 2 (0.9%) olanzapine patients. No other SAE was experienced by >1 patient within a treatment group. There were no statistically significant differences between treatment groups.

During Study Period II-III, SAEs were reported in 3.3% of olanzapine and 3.5% of divalproex patients. There were 2 SAEs reported in >1 patient: mania, in 2 (0.9%) olanzapine and 2 (1.0%) divalproex patients; and suicidal ideation, in 2 (0.9%) olanzapine patients and 1 (0.5%) divalproex patient. There were no statistically significant differences between treatment groups.

During Study Period III, SAEs were reported in 1.3%, 4.7%, and no patients in the olanzapine, divalproex, and placebo/olanzapine groups, respectively. During Study Period IV, SAEs were reported in 0.9% of olanzapine patients and no divalproex or placebo/olanzapine patients. No SAEs were reported in >1 patient during Study Periods III or IV.

Adverse Events Leading to Discontinuation from the Study:

Table HGKQ.7 presents a summary of the incidence of AEs resulting in discontinuation of the study.

During Study Period II, AEs leading to discontinuation were reported in 8.4%, 5.5%, and 2.9% of patients in the olanzapine, divalproex, and placebo groups, respectively. AEs leading to discontinuation reported by >1 patient within a treatment group were alanine aminotransferase (ALT) increased, hepatic enzyme increased, and somnolence (each in 2 [0.9%] olanzapine patients) and somnolence, sedation, and nausea (each in 2 [1.0%] divalproex patients). There were no statistically significant differences between treatment groups.

During Study Period II-III, AEs leading to discontinuation were reported in 11.2% of olanzapine and 9.0% of divalproex patients. AEs leading to discontinuation reported by >1 patient within a treatment group were ALT increased, hepatic enzyme increased, sedation, somnolence, suicidal ideation, and weight increased (each in 2 [0.9%] olanzapine patients) and sedation, somnolence, mania, and nausea (each in 2 [1.0%] divalproex patients). There were no statistically significant differences between treatment groups.

During Study Period III, AEs leading to discontinuation were reported in 4.4%, 5.4%, and 3.8% of patients in the olanzapine, divalproex, and placebo/olanzapine groups, respectively. Mania was reported in 2 (1.3%) divalproex patients; no other AE leading to discontinuation was reported in >1 patient within a treatment group. During Study Period IV, no AEs leading to discontinuation were reported.

Table HGKQ.7. Adverse Events Leading to Discontinuation by Decreasing Frequency Within the Drug Treatment Group

Preferred Term	Olanzapine (N=215) n (%)	Divalproex (N=201) n (%)	Placebo/Olanzapine (1) (N=105) n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study period II						
Any Adverse Event Resulting in Discontinuation	18 (8.4)	11 (5.5)	3 (2.9)	0.060	0.379	0.254
ALANINE AMINOTRANSFERASE INCREASED	2 (0.9)	0	0	0.307	-	0.126
HEPATIC ENZYME INCREASED	2 (0.9)	0	0	0.371	-	0.180
SOMNOLENCE	2 (0.9)	2 (1.0)	0	0.345	0.320	0.944
AGITATION	1 (0.5)	0	0	0.491	-	0.330
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (0.5)	0	0	0.517	-	0.355
BLOOD TRIGLYCERIDES INCREASED	1 (0.5)	0	0	0.480	-	0.317
HEPATITIS TOXIC	1 (0.5)	0	0	0.517	-	0.355
HYPERGLYCAEMIA	1 (0.5)	0	0	0.480	-	0.386
HYPERTRIGLYCERIDAEMIA	1 (0.5)	0	0	0.480	-	0.264
MANIA	1 (0.5)	0	0	0.414	-	0.414
PNEUMONIA	1 (0.5)	0	0	0.414	-	0.414
PSYCHOTIC DISORDER	1 (0.5)	0	0	0.414	-	0.414
SEDATION	1 (0.5)	2 (1.0)	0	0.517	0.317	0.543
SUICIDAL IDEATION	1 (0.5)	0	1 (1.0)	0.718	0.157	0.248
WEIGHT INCREASED	1 (0.5)	1 (0.5)	0	0.517	0.480	0.941
ABDOMINAL PAIN	0	1 (0.5)	0	-	0.484	0.279
BLOOD CREATINE PHOSPHOKINASE INCREASED	0	0	1 (1.0)	0.123	0.153	-
DEPRESSION	0	1 (0.5)	0	-	0.527	0.317
NAUSEA	0	2 (1.0)	0	-	0.319	0.124
NEUTROPHIL COUNT DECREASED	0	1 (0.5)	0	-	0.527	0.371
PAIN IN EXTREMITY	0	1 (0.5)	0	-	0.480	0.304
RESTLESSNESS	0	0	1 (1.0)	0.114	0.114	-

[continued]

Table HGKQ.7. Adverse Events Leading to Discontinuation by Decreasing Frequency Within the Drug Treatment Group (Continued)

Preferred Term	Olanzapine (N=215) n (%)	Divalproex (N=201) n (%)	p-value (2)
Study period II-III			
Any Adverse Event Resulting in Discontinuation	24 (11.2)	18 (9.0)	0.520
ALANINE AMINOTRANSFERASE INCREASED	2 (0.9)	0	0.126
HEPATIC ENZYME INCREASED	2 (0.9)	0	0.180
SEDATION	2 (0.9)	2 (1.0)	0.968
SOMNOLENCE	2 (0.9)	2 (1.0)	0.944
SUICIDAL IDEATION	2 (0.9)	1 (0.5)	0.566
WEIGHT INCREASED	2 (0.9)	1 (0.5)	0.636
AGITATION	1 (0.5)	0	0.330
BIPOLAR DISORDER	1 (0.5)	0	0.355
BIPOLAR I DISORDER	1 (0.5)	0	0.355
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (0.5)	0	0.355
BLOOD TRIGLYCERIDES INCREASED	1 (0.5)	0	0.317
HEPATITIS C	1 (0.5)	0	0.414
HEPATITIS TOXIC	1 (0.5)	1 (0.5)	0.842
HYPERGLYCAEMIA	1 (0.5)	0	0.386
HYPERTRIGLYCERIDAEMIA	1 (0.5)	0	0.264
MANIA	1 (0.5)	2 (1.0)	0.460
PNEUMONIA	1 (0.5)	0	0.414
PSYCHOTIC DISORDER	1 (0.5)	0	0.414
ABDOMINAL PAIN	0	1 (0.5)	0.279
ASPARTATE AMINOTRANSFERASE INCREASED	0	1 (0.5)	0.273
DEPRESSION	0	1 (0.5)	0.317
INFLUENZA	0	1 (0.5)	0.304
NAUSEA	0	2 (1.0)	0.124
NEUTROPHIL COUNT DECREASED	0	1 (0.5)	0.371
PAIN IN EXTREMITY	0	1 (0.5)	0.304
TREMOR	0	1 (0.5)	0.317

[continued]

Table HGKQ.7. Adverse Events Leading to Discontinuation by Decreasing Frequency Within the Drug Treatment Group (Concluded)

Preferred Term	Olanzapine (N=159) n (%)	Divalproex (N=149) n (%)	Placebo/Olanzapine (1) (N=78) n (%)
Study period III			
Any Adverse Event Resulting in Discontinuation	7 (4.4)	8 (5.4)	3 (3.8)
BIPOLAR DISORDER	1 (0.6)	0	0
BIPOLAR I DISORDER	1 (0.6)	0	0
HEPATITIS C	1 (0.6)	0	0
HYPERGLYCAEMIA	1 (0.6)	0	0
SEDATION	1 (0.6)	0	0
SUICIDAL IDEATION	1 (0.6)	1 (0.7)	0
WEIGHT INCREASED	1 (0.6)	0	1 (1.3)
ASPARTATE AMINOTRANSFERASE INCREASED	0	1 (0.7)	0
BLOOD TRIGLYCERIDES INCREASED	0	0	1 (1.3)
DEPRESSION	0	1 (0.7)	0
HEPATITIS TOXIC	0	1 (0.7)	0
HYPERSOMNIA	0	0	1 (1.3)
INFLUENZA	0	1 (0.7)	0
MANIA	0	2 (1.3)	0
TREMOR	0	1 (0.7)	0

Abbreviations: CMH = Cochran-Mantel-Haenszel; D = divalproex; N = total number of patients; n = number of patients with adverse event leading to discontinuation; O = olanzapine; P = placebo.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Rates of adverse events compared between Olanzapine and Divalproex treatment groups using CMH test stratifying by investigator.

Other Clinically Significant Adverse Events:

Most of the AEs that met criteria for clinical significance, defined as any nonserious TEAEs that could be considered potentially serious or clinically significant by a clinician, and determined to be clinically significant for analysis purposes via critical review of AE and other study data by sponsor physicians, were reported in 1 patient in any treatment group, and included the non-hepatic events of hypotension, myocardial ischemia, and anemia (divalproex patients); hypersomnia and hyperglycemia (olanzapine patients); and blood glucose increased (placebo patient). Syncope was reported in 2 (1.0%) divalproex patients.

Clinically significant hepatic AEs (identified as clinically significant via sponsor physician review of AE and other study data) were reported in the study and included ALT increased (5 [2.3%] olanzapine and 2 [1.0%] divalproex patients); aspartate aminotransferase (AST) increased (3 [1.4%] olanzapine and 3 [1.5%] divalproex patients); hepatic enzyme increased (3 [1.4%] olanzapine patients); gamma-glutamyltransferase (GGT) increased (2 [0.9%] olanzapine and 1 [0.5%] divalproex patients); blood creatine phosphokinase (CPK) increased (2 [1.0%] divalproex patients); hepatitis toxic (1 [0.5%] olanzapine and 1 [0.5%] divalproex patients); and blood alkaline phosphatase increased (1 [0.5%] olanzapine patient).

Extrapyramidal Symptoms:

Extrapyramidal symptoms (EPS) measured during the study included treatment-emergent akathisia (defined using the Barnes), treatment-emergent parkinsonism (defined using the Simpson-Angus Scale [SAS]), and treatment-emergent dyskinesia (defined using the Abnormal Involuntary Movement Scale [AIMS]). Table HGKQ.8 shows the incidence of EPS during Study Periods II, II-III, and III.

There were no statistically significant differences between any of the treatment groups in the percentages of patients with treatment-emergent akathisia, parkinsonism, or dyskinesia during the study. There was a statistically significant difference in change from baseline to endpoint during Study Period II-III in SAS score between the olanzapine (0.1) and divalproex (-0.1) groups (p=0.035). There was a statistically significant difference in change from baseline to endpoint during Study Period II in AIMS score between the olanzapine (-0.1) and placebo (0.1) groups (p=0.037).

Table HGKQ.8. Treatment-Emergent Extrapyramidal Symptoms

Variable	Olanzapine (N=215) n (%)	Divalproex (N=201) n (%)	P/O (N=105) n (%)	p-Values O vs P	p-Values D vs P	p-Values O vs D
Study Period II (Acute Phase)						
Akathisia	8 (3.7)	5 (2.5)	2 (1.9)	0.442	0.820	0.412
Parkinsonism	0	0	1 (1.0)	0.206	0.157	--
Dyskinesia	2 (0.9)	1 (0.5)	1 (1.0)	0.962	0.611	0.510
Study Period II-III (Combined Acute and Extension Phases)						
Akathisia	11 (5.1)	6 (3.0)	--	--	--	0.311
Parkinsonism	5 (2.3)	1 (0.5)	--	--	--	0.130
Dyskinesia	3 (1.4)	1 (0.5)	--	--	--	0.242
Study Period III (Extension Phase)						
Akathisia	5 (2.3)	2 (1.0)	--	--	--	0.454
Parkinsonism	5 (2.3)	1 (0.5)	--	--	--	0.073
Dyskinesia	3 (1.4)	0	--	--	--	0.076

Abbreviations: AIMS = Abnormal Involuntary Movement Scale; CMH = Cochran-Mantel-Haenszel; D = divalproex; N = total number of patients; n = number of patients reporting extrapyramidal symptoms; O = olanzapine; P = placebo; SAS = Simpson-Angus Scale.

Definitions: Akathisia = Barnes item 4 score of ≥2 at any post-baseline visit at specified study period and baseline Barnes item 4 score of <2; Parkinsonism = total SAS score of >3 at any post-baseline visit at specified study period and baseline total SAS score ≤3; Dyskinesia =score of ≥3 on any one of the AIMS item 1 through 7, or a score of ≥2 on any two of the AIMS items 1 through 7, at any post-baseline visit at specified study period without either criteria at baseline.

Placebo/olanzapine group received placebo during Study Period II and olanzapine (5 to 20 mg/day) during Study Period III.

Analysis methods: P-values were obtained using CMH test stratifying by investigator.

Clinical Laboratory Values:

Table HGKQ.9 summarizes the incidence of patients with treatment-emergent changes in laboratory findings at any time during double-blind treatment and at endpoint during Study Period II for the following analytes: ALT, AST, total bilirubin, fasting cholesterol, fasting glucose, prolactin, segmented neutrophils, white blood cell (WBC) count, and any additional analytes with findings that were statistically significant between treatment groups. The treatment-emergent changes in laboratory values were based on predefined reference ranges.

Table HGKQ.10 summarizes the incidence of patients with treatment-emergent changes in laboratory findings at any time during double-blind treatment and at endpoint during Study Period III for the aforementioned analytes and any additional analytes with findings that were statistically significant between treatment groups.

Table HGKQ.9. Treatment-Emergent Changes in Laboratory Values During Study Period II (the Acute Phase)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)		p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Chemistry									
Fasting ALT/SGPT (Units/Liter)									
Normal/low lab parameter values at baseline and at least one SPII value	195		181		94				
High at anytime (3)	11	(5.6)	0		0		0.020	-	0.001
High at Endpoint (4)	5	(2.6)	0		0		0.124	-	0.016
Normal/high lab parameter values at baseline and at least one SPII value	195		185		95				
Low at anytime (3)	1	(0.5)	2	(1.1)	0		0.527	0.371	0.540
Low at Endpoint (4)	1	(0.5)	1	(0.5)	0		0.527	0.527	0.937
Fasting AST/SGOT (Units/Liter)									
Normal/low lab parameter values at baseline and at least one SPII value	192		184		94				
High at anytime (3)	6	(3.1)	1	(0.5)	1	(1.1)	0.328	0.666	0.062
High at Endpoint (4)	2	(1.0)	0		0		0.379	-	0.194
Normal/high lab parameter values at baseline and at least one SPII value	193		184		94				
Low at anytime (3)	0		1	(0.5)	0		-	0.480	0.264
Low at Endpoint (4)	0		0		0		-	-	-
Fasting Total Bilirubin (micromole/Liter)									
Normal/low lab parameter values at baseline and at least one SPII value	196		184		94				
High at anytime (3)	1	(0.5)	0		0		0.414	-	0.248
High at Endpoint (4)	1	(0.5)	0		0		0.414	-	0.248
Normal/high lab parameter values at baseline and at least one SPII value	177		171		89				
Low at anytime (3)	20	(11.3)	17	(9.9)	5	(5.6)	0.256	0.187	0.848
Low at Endpoint (4)	4	(2.3)	7	(4.1)	2	(2.2)	0.666	0.494	0.310

(CONTINUED)

Table HGKQ.9. Treatment-Emergent Changes in Laboratory Values During Study Period II (the Acute Phase) (Continued)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)		p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Chemistry (continued)									
Fasting Cholesterol (millimole/Liter)									
Normal/low lab parameter values at baseline and at least one SPII value	195		182		94				
High at anytime (3)	3	(1.5)	3	(1.6)	2	(2.1)	0.595	0.704	0.856
High at Endpoint (4)	2	(1.0)	1	(0.5)	0		0.379	0.480	0.655
Normal/high lab parameter values at baseline and at least one SPII value	194		181		93				
Low at anytime (3)	4	(2.1)	5	(2.8)	3	(3.2)	0.595	0.931	0.492
Low at Endpoint (4)	2	(1.0)	3	(1.7)	1	(1.1)	0.981	0.620	0.486
Fasting Glucose (millimole/Liter)									
Normal/low lab parameter values at baseline and at least one SPII value	195		185		95				
High at anytime (3)	2	(1.0)	0		0		0.226	-	0.141
High at Endpoint (4)	2	(1.0)	0		0		0.226	-	0.141
Normal/high lab parameter values at baseline and at least one SPII value	189		183		94				
Low at anytime (3)	4	(2.1)	4	(2.2)	2	(2.1)	0.792	0.857	0.987
Low at Endpoint (4)	0		2	(1.1)	1	(1.1)	0.264	0.832	0.101
Prolactin (microgram/Liter)									
Normal/low lab parameter values at baseline and at least one SPII value	143		141		70				
High at anytime (3)	48	(33.6)	15	(10.6)	8	(11.4)	0.002	0.743	<0.001
High at Endpoint (4)	48	(33.6)	15	(10.6)	8	(11.4)	0.002	0.743	<0.001
Normal/high lab parameter values at baseline and at least one SPII value	179		176		90				
Low at anytime (3)	1	(0.6)	0		0		0.480	-	0.317
Low at Endpoint (4)	1	(0.6)	0		0		0.480	-	0.317

(CONTINUED)

Table HGKQ.9. Treatment-Emergent Changes in Laboratory Values During Study Period II (the Acute Phase) (Continued)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)		p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Hematology									
Neutrophils (BILL/L)									
Normal/low lab parameter values at baseline and at least one SPII value	196		179		97				
High at anytime (3)	11	(5.6)	5	(2.8)	1	(1.0)	0.070	0.322	0.174
High at Endpoint (4)	5	(2.6)	4	(2.2)	0		0.098	0.119	0.884
Normal/high lab parameter values at baseline and at least one SPII value	197		184		97				
Low at anytime (3)	4	(2.0)	3	(1.6)	3	(3.1)	0.506	0.343	0.708
Low at Endpoint (4)	2	(1.0)	1	(0.5)	2	(2.1)	0.384	0.241	0.578
Leukocytes (WBC) (BILL/L)									
Normal/low lab parameter values at baseline and at least one SPII value	197		185		100				
High at anytime (3)	7	(3.6)	4	(2.2)	2	(2.0)	0.477	0.951	0.404
High at Endpoint (4)	4	(2.0)	3	(1.6)	0		0.179	0.174	0.925
Normal/high lab parameter values at baseline and at least one SPII value	198		184		98				
Low at anytime (3)	1	(0.5)	2	(1.1)	3	(3.1)	0.063	0.230	0.579
Low at Endpoint (4)	0		1	(0.5)	3	(3.1)	0.012	0.075	0.361

(CONTINUED)

Table HGKQ.9. Treatment-Emergent Changes in Laboratory Values During Study Period II (the Acute Phase) (Concluded)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)		p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Hematology (continued)									
Mean Cell Hemoglobin Concentration (MCHC) (mmol/Liter (Fe))									
Normal/high lab parameter values at baseline and at least one SPII value	187		172		94				
Low at anytime (3)	5	(2.7)	16	(9.3)	3	(3.2)	0.768	0.020	0.003
Low at Endpoint (4)	1	(0.5)	10	(5.8)	1	(1.1)	0.695	0.029	0.001
Monocytes (BILL/L)									
Normal/low lab parameter values at baseline and at least one SPII value	194		178		98				
High at anytime (3)	0		5	(2.8)	0		-	0.099	0.030

Abbreviations: ALT/SGPT = alanine aminotransferase; AST/SGOT = aspartate aminotransferase; BILL = billion; CMH = Cochran-Mantel-Haenszel; D = divalproex; Fe = iron; L = liter; MCHC = mean cell hemoglobin concentration; N = total number of patients; n = number of patients with normal/abnormal laboratory values; O = olanzapine; P = placebo; SPII = Study Period II; WBC = white blood cell.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Obtained using CMH test stratifying by investigator.
(3) Treatment-emergent abnormal value observed at least once during the study period.
(4) Treatment-emergent abnormal value observed at last observation during the study period. Baseline is the period from screening until the time of first dose of Study Period II.

Table HGKQ.10. Treatment-Emergent Changes in Laboratory Values During Study Period III (the Extension Phase)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Chemistry								
Fasting ALT/SGPT (Units/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	149		139					
High at anytime (3)	8	(5.4)	3	(2.2)				0.269
High at Endpoint (4)	2	(1.3)	2	(1.4)				0.656
Normal/high lab parameter values at baseline and at least one SPIII value	149		142					
Low at anytime (3)	1	(0.7)	1	(0.7)				0.937
Low at Endpoint (4)	1	(0.7)	0					0.264
Fasting AST/SGOT (Units/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	148		141					
High at anytime (3)	5	(3.4)	6	(4.3)				0.658
High at Endpoint (4)	1	(0.7)	6	(4.3)				0.029
Normal/high lab parameter values at baseline and at least one SPIII value	148		141					
Low at anytime (3)	0		1	(0.7)				0.264
Low at Endpoint (4)	0		1	(0.7)				0.264
Fasting Total Bilirubin (micromole/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	150		141					
High at anytime (3)	2	(1.3)	1	(0.7)				0.590
High at Endpoint (4)	1	(0.7)	1	(0.7)				1.000
Normal/high lab parameter values at baseline and at least one SPIII value	135		131					
Low at anytime (3)	14	(10.4)	13	(9.9)				0.742
Low at Endpoint (4)	7	(5.2)	4	(3.1)				0.570

(CONTINUED)

Table HGKQ.10. Treatment-Emergent Changes in Laboratory Values During Study Period III (the Extension Phase) (Continued)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Chemistry (continued)								
Fasting Cholesterol (millimole/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	150		139					
High at anytime (3)	0		1	(0.7)				0.371
High at Endpoint (4)	0		1	(0.7)				0.371
Normal/high lab parameter values at baseline and at least one SPIII value	149		138					
Low at anytime (3)	5	(3.4)	5	(3.6)				0.986
Low at Endpoint (4)	1	(0.7)	2	(1.4)				0.679
Fasting Glucose (millimole/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	149		142					
High at anytime (3)	1	(0.7)	0					0.414
High at Endpoint (4)	1	(0.7)	0					0.414
Normal/high lab parameter values at baseline and at least one SPIII value	144		141					
Low at anytime (3)	4	(2.8)	4	(2.8)				0.782
Low at Endpoint (4)	3	(2.1)	1	(0.7)				0.314
Prolactin (microgram/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	103		96					
High at anytime (3)	29	(28.2)	9	(9.4)				0.004
High at Endpoint (4)	29	(28.2)	9	(9.4)				0.004
Normal/high lab parameter values at baseline and at least one SPIII value	130		122					
Low at anytime (3)	0		0					-
Low at Endpoint (4)	0		0					-

(CONTINUED)

Table HGKQ.10. Treatment-Emergent Changes in Laboratory Values During Study Period III (the Extension Phase) (Continued)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Chemistry (continued)								
Fasting Sodium (millimole/Liter)								
Normal/low lab parameter values at baseline and at least one SPIII value	150		142					
High at anytime (3)	0		4	(2.8)				0.020
Fasting Albumin (gram/Liter)								
Normal/high lab parameter values at baseline and at least one SPIII value	147		139					
Low at anytime (3)	2	(1.4)	9	(6.5)				0.027
Hematology								
Neutrophils (BILL/L)								
Normal/low lab parameter values at baseline and at least one SPIII value	151		138					
High at anytime (3)	17	(11.3)	6	(4.3)				0.067
High at Endpoint (4)	5	(3.3)	2	(1.4)				0.469
Normal/high lab parameter values at baseline and at least one SPIII value	153		142					
Low at anytime (3)	5	(3.3)	7	(4.9)				0.554
Low at Endpoint (4)	1	(0.7)	3	(2.1)				0.275

(CONTINUED)

Table HGKQ.10. Treatment-Emergent Changes in Laboratory Values During Study Period III (the Extension Phase) (Concluded)

	Olanzapine (N=215) n (%)		Divalproex (N=201) n (%)		Placebo/Olanzapine (1) (N=105) n (%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Hematology (continued)								
Leukocytes (WBC) (BILL/L)								
Normal/low lab parameter values at baseline and at least one SPIII value	152		141					
High at anytime (3)	10	(6.6)	5	(3.5)				0.299
High at Endpoint (4)	1	(0.7)	2	(1.4)				0.593
Normal/high lab parameter values at baseline and at least one SPIII value	153		142					
Low at anytime (3)	3	(2.0)	3	(2.1)				0.991
Low at Endpoint (4)	2	(1.3)	2	(1.4)				0.963
Erythrocyte Count (RBC) (TRIL/L)								
Normal/high lab parameter values at baseline and at least one SPIII value	153		142					
Low at Endpoint (4)	0		3	(2.1)				0.011

Abbreviations: ALT/SGPT = alanine aminotransferase; AST/SGOT = aspartate aminotransferase; BILL = Billion; CMH = Cochran-Mantel-Haenszel; D = divalproex; L = liter; N = total number of patients; n = number of patients with normal/abnormal laboratory values; O = olanzapine; P = placebo; RBC = red blood cell; SPIII = Study Period III; TRIL = trillion; WBC = white blood cell.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Obtained using CMH test stratifying by investigator.
(3) Treatment-emergent abnormal value observed at least once during the study period.
(4) Treatment-emergent abnormal value observed at last observation during the study period.
Baseline is the period from screening until the time of first dose of Study Period II.

Glucose and Lipid Levels:

In additional analyses of treatment-emergent changes in blood glucose levels (based on American Diabetes Association criteria) and lipid levels (based on National Cholesterol Education Program criteria), which were conducted to provide more in-depth information about these kinds of changes, several statistically significant treatment differences in change from baseline were observed:

During Study Period II, fasting triglycerides changed from normal to high (normal <1.69 mmol/L; borderline ≥1.69 mmol/L and <2.26 mmol/L; high ≥2.26 mmol/L; extreme high ≥5.65 mmol/L) in 12% of olanzapine patients and 4% of divalproex patients (p=0.019). During Study Period III, fasting glucose changed from impaired to high (normal <5.56 mmol/L; impaired ≥5.56 mmol/L and <7.0 mmol/L; high ≥7.0 mmol/L) in 14% of olanzapine and 2% of divalproex patients (p=0.049); and from normal/impaired to high in 6% of olanzapine and 1% of divalproex patients (p=0.019). Fasting total cholesterol changed from borderline to high (normal <5.17 mmol/L; borderline ≥5.17 mmol/L and <6.21 mmol/L; high ≥6.21 mmol/L) in 33% of olanzapine and 12% of divalproex patients (p=0.036). Fasting triglycerides changed from normal to high in 18% of olanzapine and 4% of divalproex patients (p=0.001).

Vital Signs and Weight:

Vital signs were reviewed to assess the incidence of patients with potentially clinically significant treatment-emergent orthostatic hypotension (defined as ≥20 mmHg decrease in systolic blood pressure and ≥10 bpm increase in orthostatic pulse going from supine to standing). Weight was reviewed to assess the incidence of patients with potentially clinically significant changes (defined as an increase or decrease ≥7%). Table HGKQ.11 shows the incidence of patients with potentially clinically significant treatment-emergent orthostatic hypotension or weight increases at any time during the double-blind treatment, as well as incidence of any other vital signs findings that occurred at a statistically significantly different incidence between treatment groups .

During Study Period II, there was a statistically significant difference from baseline to endpoint between the olanzapine and divalproex group in the proportion of patients with potentially clinically significant decreases in supine systolic blood pressure (occurred in more patients in the divalproex group [2%] than in the olanzapine group [none], p=0.048).

During Study Period III, there was a statistically significant difference from baseline to endpoint between the olanzapine and divalproex groups in the proportion of patients with potentially clinically significant increases in weight (occurred in more patients in the olanzapine group [23%] than in the divalproex group [10%], [p=0.003]).

Mean changes from baseline to endpoint were also assessed for these analytes. In Study Period II, there were statistically significant differences (p<0.001) from baseline to endpoint between the olanzapine and divalproex groups for mean changes in weight,

body mass index (BMI), standing pulse rate, and supine pulse rate (greater change from baseline in the olanzapine group than divalproex). There were statistically significant differences ($p \leq 0.001$) from baseline to endpoint between the olanzapine and placebo groups for mean changes in weight, BMI, standing pulse rate, and supine pulse rate (greater change from baseline in the olanzapine group than in the placebo group). During this study period, mean weight (based on the least squares means) increased from baseline by 1.28 kg for olanzapine, 0.24 kg for divalproex, and 0.31 kg for placebo.

In Study Period II-III, there were statistically significant differences ($p<0.05$) from baseline to endpoint between the olanzapine and divalproex groups for mean changes in weight, BMI, standing pulse rate, and supine pulse rate (greater increase from baseline in the olanzapine group than divalproex). During Study Period II-III, mean weight (based on the least squares means) increased from baseline by 2.04 kg for olanzapine and 0.23 kg for divalproex.

Table HGKQ.11. Potentially Clinically Significant Changes in Vital Signs and Weight

Parameter	Olanzapine (N=215) n(%)	Divalproex (N=201) n(%)	Placebo/Olanzapine (1) (N=105) n(%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study Period II						
Weight						
Number of patients (4)	202	188	100			
Potentially CS low	1 (0.5)	1 (0.5)	0	0.524	0.480	0.866
Potentially CS high	13 (6.4)	5 (2.7)	1 (1.0)	0.056	0.378	0.064
Orthostatic hypotension						
Normal at baseline (3)	198	184	100			
Potentially CS change	7 (3.5)	2 (1.1)	1 (1.0)	0.251	0.846	0.079
Supine systolic BP (mm Hg) (Low: <= 90 and decrease >= 20 High: >= 180 and increase >= 20)						
Normal/High at baseline (3)	201	184	100			
Potentially CS low	0	3 (1.6)	1 (1.0)	0.176	0.621	0.048
Study Period III						
Weight						
Number of patients (4)	157	144				
Potentially CS low	3 (1.9)	2 (1.4)				0.897
Potentially CS high	36 (22.9)	14 (9.7)				0.003
Orthostatic hypotension						
Normal at baseline (3)	157	143				
Potentially CS change	8 (5.1)	3 (2.1)				0.068

Abbreviations: BP = blood pressure; CMH = Cochran-Mantel-Haenszel; CS = clinically significant; D = divalproex; N = total number of patients; n = number of patients with potentially clinically significant change in vital signs or weight; O = olanzapine; P = placebo.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Obtained using CMH test stratifying by investigator.
(3) At least one baseline and corresponding treatment period value and no potentially CS change at Visit 2.
(4) Patients with at least one baseline and corresponding treatment period value.

Electrocardiograms:

Electrocardiogram data were reviewed to assess the incidence of patients with potentially clinically significant treatment-emergent QTc interval measurements, defined 8 different ways and corrected using both Bazett's and Fridericia's methods: (1) in men, QTc ≥430 ms; in women, QTc ≥450 ms; (2) in men, QTc ≥450 ms; in women, QTc ≥470 ms; (3) QTc ≥450 ms; (4) QTc ≥480 ms; (5) QTc ≥500 ms; (6) increase ≥30 ms relative to baseline; (7) increase ≥60 ms relative to baseline; and (8) increase ≥75 ms relative to baseline.

Table HGKQ.12 shows the incidence of potentially clinically significant prolonged ECG QTc intervals during Study Period II and Study Period III. In general, olanzapine patients had a higher incidence of treatment-emergent prolonged QTc compared to divalproex, and some of the comparisons were statistically significant, particularly during Study Period II and when using Bazett's correction method.

In addition, there was a statistically significant difference between groups in the proportion of patients with potentially clinically significant PR interval values (2 [1.2%] patients in the olanzapine group and no patients in the divalproex group during Study Period II, p=0.047).

Table HGKQ.12. Potentially Clinically Significant Values of Prolonged ECG QTc Intervals

Criteria for identifying patients with potentially clinically significant values	Olanzapine (N=215) n(%)	Divalproex (N=201) n(%)	Placebo/Olanzapine (1) (N=105) n(%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study Period II						
QTc Bazett (ms)						
Number of patients (3)	145	141	71			
1. In men, >=430 ms; in women, >=450 ms	19 (13.1)	7 (5.0)	7 (9.9)	0.394	0.094	0.019
Number of patients (3)	174	160	84			
2. In men, >=450 ms; in women, >=470 ms	11 (6.3)	2 (1.3)	1 (1.2)	0.071	0.896	0.013
Number of patients (3)	160	152	81			
3. QTc >= 450 ms	15 (9.4)	3 (2.0)	3 (3.7)	0.134	0.345	0.010
Number of patients (3)	176	163	88			
4. QTc >=480 ms	4 (2.3)	1 (0.6)	0	0.154	0.480	0.224
Number of patients (3)	176	163	88			
5. QTc >=500 ms	1 (0.6)	0	0	0.511	-	0.370
Number of patients (4)	176	163	88			
6. Increase >=30 ms relative to baseline	15 (8.5)	1 (0.6)	1 (1.1)	0.026	0.560	0.001
Number of patients (4)	176	163	88			
7. Increase >=60 ms relative to baseline	0	0	0	-	-	-
Number of patients (4)	176	163	88			
8. Increase >=75 ms relative to baseline	0	0	0	-	-	-

[continued]

Table HGKQ.12. Potentially Clinically Significant Values of Prolonged ECG QTc Intervals (Continued)

Criteria for identifying patients with potentially clinically significant values	Olanzapine (N=215) n(%)	Divalproex (N=201) n(%)	Placebo/Olanzapine (1) (N=105) n(%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study Period II (continued)						
QTc Fridericia (ms)						
Number of patients (3)	168	153	81			
1. In men, >=430 ms; in women, >=450 ms	9 (5.4)	3 (2.0)	4 (4.9)	0.894	0.069	0.127
Number of patients (3)	176	161	87			
2. In men, >=450 ms; in women, >=470 ms	4 (2.3)	0	1 (1.1)	0.486	0.172	0.046
Number of patients (3)	173	158	87			
3. QTc >= 450 ms	6 (3.5)	1 (0.6)	3 (3.4)	0.987	0.086	0.060
Number of patients (3)	176	163	88			
4. QTc >=480 ms	1 (0.6)	0	0	0.511	-	0.370
Number of patients (3)	176	163	88			
5. QTc >=500 ms	0	0	0	-	-	-
Number of patients (4)	176	163	88			
6. Increase >=30 ms relative to baseline	7 (4.0)	1 (0.6)	2 (2.3)	0.466	0.202	0.049
Number of patients (4)	176	163	88			
7. Increase >=60 ms relative to baseline	0	0	0	-	-	-
Number of patients (4)	176	163	88			
8. Increase >=75 ms relative to baseline	0	0	0	-	-	-

[continued]

Table HGKQ.12. Potentially Clinically Significant Values of Prolonged ECG QTc Intervals (Continued)

Criteria for identifying patients with potentially clinically significant values	Olanzapine (N=215) n(%)	Divalproex (N=201) n(%)	Placebo/Olanzapine (1) (N=105) n(%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study Period III						
QTc Bazett (ms)						
Number of patients (3)	102	101				
1. In men, >=430 ms; in women, >=450 ms	18 (17.6)	6 (5.9)				0.013
Number of patients (3)	117	113				
2. In men, >=450 ms; in women, >=470 ms	7 (6.0)	2 (1.8)				0.126
Number of patients (3)	111	106				
3. QTc >= 450 ms	12 (10.8)	2 (1.9)				0.009
Number of patients (3)	118	115				
4. QTc >=480 ms	0	0				-
Number of patients (3)	118	115				
5. QTc >=500 ms	0	0				-
Number of patients (4)	118	115				
6. Increase >=30 ms relative to baseline	13 (11.0)	4 (3.5)				0.079
Number of patients (4)	118	115				
7. Increase >=60 ms relative to baseline	1 (0.8)	0				0.617
Number of patients (4)	118	115				
8. Increase >=75 ms relative to baseline	0	0				-

[continued]

Table HGKQ.12. Potentially Clinically Significant Values of Prolonged ECG QTc Intervals (Concluded)

Criteria for identifying patients with potentially clinically significant values	Olanzapine (N=215) n(%)	Divalproex (N=201) n(%)	Placebo/Olanzapine (1) (N=105) n(%)	p-value (2) O vs P	p-value (2) D vs P	p-value (2) O vs D
Study Period III (continued)						
QTc Fridericia (ms)						
Number of patients (3)	116	109				
1. In men, >=430 ms; in women, >=450 ms	4 (3.4)	1 (0.9)				0.320
Number of patients (3)	118	113				
2. In men, >=450 ms; in women, >=470 ms	1 (0.8)	0				0.617
Number of patients (3)	117	110				
3. QTc >= 450 ms	3 (2.6)	0				0.175
Number of patients (3)	118	115				
4. QTc >=480 ms	0	0				-
Number of patients (3)	118	115				
5. QTc >=500 ms	0	0				-
Number of patients (4)	118	115				
6. Increase >=30 ms relative to baseline	2 (1.7)	2 (1.7)				0.758
Number of patients (4)	118	115				
7. Increase >=60 ms relative to baseline	0	0				-
Number of patients (4)	118	115				
8. Increase >=75 ms relative to baseline	0	0				-

Abbreviations: D = divalproex; CMH = Cochran-Mantel-Haenszel; N = total number of patients; n = number of patients with potentially clinically significant values of prolonged QTc intervals; O = olanzapine; P = placebo; QTc = corrected QT interval.
(1) Received Placebo during Study Period II and Olanzapine (5 to 20 mg/day) during Study Period III.
(2) Obtained using CMH test stratifying by investigator.
(3) Number of patients not meeting the criterion at the last baseline visit and with QTc data at the corresponding period.
(4) Number of patients with a baseline QTc interval measurement with QTc data at the corresponding period.

Health Outcomes

SF-36:

Table HGKQ.13 presents changes from baseline scores for the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) subscale at the endpoint of Study Period II. There were statistically significant differences between the olanzapine and divalproex groups for mean changes in the Mental Component (greater increase in the olanzapine group, p=0.039), and between the olanzapine and placebo groups for mean changes in Physical Functioning (reduced in olanzapine patients and increased in placebo patients, p=0.047) and the Physical Component (reduced in olanzapine patients and no change in placebo patients, p=0.020).

Table HGKQ.14 presents changes from baseline scores for the SF-36 subscale at the endpoint of Study Period II-III. There was a statistically significant difference between the olanzapine and divalproex groups for mean change in Vitality (greater increase in the olanzapine group, p=0.044).

Table HGKQ.13. Health Outcomes – SF-36 Scores – Study Period II (the Acute Phase)

Variable	Olanzapine (N=161)	Divalproex (N=149)	Placebo (N=79)	p-Values O vs D	p-Values O vs P	p-Values D vs P
LS Mean Change from Baseline						
Physical Functioning	-0.4	-0.3	0.4	0.647	0.047	0.112
Bodily Pain	-0.3	-0.3	0.0	0.910	0.256	0.224
Role Limitations due to Physical Problems	0.1	0.0	0.1	0.914	0.789	0.724
Role Limitations due to Emotional Problems	0.3	0.1	0.2	0.182	0.591	0.569
General Health Procedures	0.2	0.2	-0.1	0.831	0.198	0.275
Mental Health	0.7	0.4 (n=148)	0.2	0.340	0.162	0.554
Social Function	0.0	0.0	0.2	0.904	0.104	0.089
Vitality	1.2	0.7 (n=148)	0.8	0.081	0.245	0.767
Physical Component Score	-1.4	-1.0 (n=148)	0.0	0.433	0.020	0.101
Mental Component Score	3.0	1.6 (n=148)	1.7	0.039	0.115	0.883

Abbreviations: ANCOVA = analysis of covariance; D = divalproex; LS = least squares; N = total number of patients; n = number of patients assessed; O = olanzapine; P = placebo; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey.

Analysis methods: P-values were obtained using ANCOVA that includes terms for treatment and investigator and baseline score as a covariate.

Table HGKQ.14. Health Outcomes – SF-36 Scores – Study Period II-III (the Combined Acute and Extension Phases)

Variable	Olanzapine (N=162)	Divalproex (N=149)	p-Values O vs D
LS Mean Change from Baseline			
Physical Functioning	0.4	-0.2	0.095
Bodily Pain	-0.6	-0.2	0.054
Role Limitations due to Physical Problems	0.0	0.1	0.599
Role Limitations due to Emotional Problems	0.3	0.3	0.560
General Health Procedures	0.3	0.1	0.554
Mental Health	0.5	0.1	0.215
Social Function	0.0	0.1	0.102
Vitality	1.4	0.8	0.044
Physical Component Score	-0.9	-0.5	0.387
Mental Component Score	2.7	1.6	0.158

Abbreviations: ANCOVA: analysis of covariance; D = divalproex; LS = least squares; N = total number of patients; O = olanzapine; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey.
Analysis methods: P-Values were obtained using ANCOVA that includes terms for treatment and investigator and baseline score as a covariate.

SLICE/LIFE:

For the summary of Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation (SLICE/LIFE) in Study Period II, there was a statistically significant greater mean decrease in the placebo group compared to the divalproex group for Student Work Impairment (p=0.032).

No statistically significant differences were found between groups for the mean number of outpatient resources overall or by country during Study Period II and Study Period II-III.

The mean total time of hospitalization was approximately 3 and 6 days in each group for Study Period II and Study Period II-III, respectively, with no statistically significant differences between groups. A statistically significantly greater proportion of olanzapine patients were hospitalized at least once compared to either of the other two groups (3.0% olanzapine, none divalproex, none placebo; p=0.009 olanzapine vs divalproex and p=0.036 olanzapine vs placebo) in Study Period II.

There were no statistically significant differences between any of the treatment groups in concomitant medication parameters during Study Period II. There were no statistically significant differences between the olanzapine and divalproex treatment groups in concomitant medication parameters during Study Period II-III, except for anticholinergic use. There was a statistically significantly greater proportion of patients using anticholinergics in the olanzapine group (4.5%) compared to the divalproex group (0.5%); p=0.023.