Summary ID# 7031

Clinical Study Summary: Study F1D-MC-HGKR

Olanzapine Plus Carbamazepine Versus Carbamazepine Alone in the Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder

Date summary approved by Lilly: 27 February 2007

Brief Summary of Results

Study F1D-MC-HGKR was a Phase 3b, multicenter, randomized, double-blind study comparing the efficacy of olanzapine plus carbamazepine versus carbamazepine alone in the treatment of manic or mixed episodes associated with bipolar I disorder. The acute phase of this study was 6 weeks, followed by a 20-week open-label treatment phase. The primary objective and major secondary objectives were assessed with data from the acute phase of the study. Several additional secondary objectives assessed the maintenance of treatment effect and safety during the open-label phase.

- The last observation carried forward (LOCF) change from baseline to endpoint of the Young Mania Rating Scale (YMRS) total score was not statistically significantly different between the olanzapine plus carbamazepine and placebo plus carbamazepine treatment groups during the acute phase.
- There were no statistically significant differences between treatment groups on the Clinical Global Impressions: Bipolar Version Severity of Illness, severity of mania, severity of depression, and overall bipolar disorder (CGI-BP) scores, or Montgomery-Asberg Depression Rating Scale (MADRS) total scores during the acute phase.
- Longitudinal effects (assessed on the postbaseline YMRS total change scores and MADRS total change scores using a likelihood-based repeated measures analysis [SAS PROC MIXED]) showed no statistically significant differences between groups at any postbaseline visit for either variable during the acute phase.

- The proportions of patients in the 2 treatment groups who responded and who were remitters at endpoint using LOCF were not statistically significantly different. Likewise, the Kaplan-Meier estimated time-to-response and time-to-remission curves show that there were no statistically significant differences between groups in time to response or remission during the acute phase.
- Of the patients with both baseline and postbaseline visits (N=85), there was a statistically significant decrease from baseline to endpoint ($p<.001$) for YMRS total score during the open-label phase.
- There were no deaths during either phase of this study.
- Treatment-emergent increased alanine aminotransferase was reported statistically significantly more often for olanzapine-plus-carbamazepine-treated patients than for placebo-plus-carbamazepine-treated patients. Treatment-emergent constipation was reported statistically significantly more often by placebo-plus-carbamazepine-treated patients than by olanzapine-plus-carbamazepine-treated patients.
- There were no statistically significant differences between treatment groups in regards to the incidence of patients with treatment-emergent extrapyramidal symptom (EPS) increases during the acute phase of the study.
- Potentially clinically significant weight gain (an increase $\geq$7%) at any time was more frequently observed in olanzapine-plus-carbamazepine-treated patients (24.6%), compared with placebo-plus-carbamazepine-treated patients (3.4%). This difference between treatment groups was statistically significant.
- For olanzapine-plus-carbamazepine-treated patients, during the acute phase of the study, statistically significant changes from baseline were noted for albumin, urea nitrogen, direct bilirubin, total bilirubin, prolactin, eosinophils, hematocrit, hemoglobin, mean cell volume, and triglycerides. Statistically significant changes from baseline were noted for alkaline phosphatase, total bilirubin, mean cell volume, eosinophils, platelet count, erythrocyte count, and HDL cholesterol during the open-label phase.
- During the acute phase, placebo-plus-carbamazepine-treated patients had a statistically significantly greater mean decrease in heart rate than olanzapine-plus-carbamazepine-treated patients. Olanzapine-plus-carbamazepine-treated patients had a statistically significantly greater mean decrease in uncorrected QT intervals than placebo-plus-carbamazepine-treated patients. There were no statistically significant mean changes in electrocardiograms (ECGs) from baseline to endpoint for all patients who entered the open-label phase.
- There were no statistically significant differences between treatment groups in treatment-emergent changes in fasting glucose levels.

- No patients met the criteria for postbaseline enzyme elevation indicative of liver function damage during the acute phase or the open-label phase of the study.

Title of Study: Olanzapine Plus Carbamazepine Versus Carbamazepine Alone in the Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder	
Investigators: This multicenter study included 14 principal investigators.	
Study Centers: This study was conducted at 14 study centers in 4 countries.	
Length of Study: 1 year, 9 months, 12 days Date of first patient enrolled (assigned to therapy): 17 Sep 2004 Date of last patient completed acute phase: 01 Feb 2006 Date of last patient completed open-label phase: 28 Jun 2006	**Phase of Development:** 3b
Objectives: Primary: To assess the superiority of olanzapine (up to 30 mg per day) plus carbamazepine (400 to 1200 mg per day) versus placebo plus carbamazepine (400 to 1200 mg per day) in improving overall manic symptomatology in patients with mania (or mixed episodes) associated with bipolar I disorder. This improvement was measured by a reduction in the total score of the Young Mania Rating Scale (YMRS) from baseline to endpoint during the 6-week, double-blind treatment phase. **Secondary:** To compare the efficacy and safety of up to 6 weeks of double-blind, concomitant use of olanzapine (up to 30 mg/day) plus carbamazepine to the concomitant use of placebo plus carbamazepine, as measured by last observation carried forward (LOCF) changes from baseline to endpoint on the Montgomery-Asberg Depression Rating Scale (MADRS) total score and CGI-BP scores; longitudinal effects (assessed on the postbaseline YMRS total change scores and MADRS total change scores using a likelihood-based repeated measures analysis [SAS PROC MIXED]); analyses of the incidences of and times to response, remission, and switch to depression; the incidence and severity of treatment-emergent adverse events (TEAEs) and EPS using the Barnes Akathisia Scale, Simpson-Angus Scale, and the Abnormal Involuntary Movement Scale (AIMS); changes in vital signs, weight, laboratory analytes, and electrocardiograms (ECGs). Additional secondary objectives assessed the maintenance of treatment effect and safety of up to 20 weeks of open-label olanzapine-plus-carbamazepine treatment.	
Study Design: Study F1D-MC-HGKR (HGKR) was a global, Phase 3b, registration study designed to assess the efficacy and safety of the concomitant use of olanzapine (up to 30 mg per day) and carbamazepine (400 to 1200 mg per day) for the treatment of patients aged 18 years to 65 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for manic or mixed episodes (with or without psychotic features) associated with bipolar I disorder. The study used a multicenter, randomized, double-blind, 2-group, active-control (placebo plus carbamazepine), parallel design for 6 weeks of acute treatment (Study Period II) followed by a 20-week open-label treatment phase (olanzapine plus carbamazepine only; Study Period III).	
Number of Patients: Planned: Approximately 120 (olanzapine plus carbamazepine = 60; placebo plus carbamazepine = 60) Randomized/Entered: 118 (olanzapine plus carbamazepine = 58; placebo plus carbamazepine = 60) Completed acute phase: 85 (olanzapine plus carbamazepine = 43; placebo plus carbamazepine = 42) (refer to Figure 1 footnote for clarification regarding number of completers for the acute phase). Entered open-label phase: 86 (olanzapine plus carbamazepine only) Completed open-label phase: 62	
Diagnosis and Main Criteria for Inclusion: Patients were males or females, aged 18 years to 65 years, with a diagnosis of bipolar I disorder and who met DSM-IV-Text Revision (TR) criteria for a manic or mixed episode (with or without psychotic features), based on clinical assessment and confirmed by the Structured Clinical Interview for the DSM-IV, Axis I Disorders (SCID-I: Clinical Version), and who had a YMRS total score $\geq$20 at Visit 1 and Visit 2.	
Test Product, Dose, and Mode of Administration: Olanzapine tablets 10 to 30 mg/day, given orally, once daily in evening; carbamazepine tablets 400 to 1200 mg/day, given orally, twice daily.	
Reference Therapy, Dose, and Mode of Administration (acute phase only): Placebo capsules, given	

orally, once daily in evening; carbamazepine tablets 400 to 1200 mg/day, given orally, twice daily.
Duration of Treatment: 6 weeks in the acute phase followed by 20 weeks in the open-label phase.
Variables: Efficacy: The primary objective was measured by a reduction in the total score of the YMRS from baseline to endpoint during the 6-week, double-blind treatment phase. Secondary objectives were measured using the LOCF changes from baseline to endpoint on the MADRS total score; LOCF changes from baseline to endpoint on the CGI-BP severity of mania, depression, and overall bipolar disorder; longitudinal effects (assessed on the postbaseline YMRS total change scores and MADRS total change scores using a likelihood-based repeated measures analysis [SAS PROC MIXED]); analyses of the incidences of and times to response, remission, and switch to depression. Safety: Safety was evaluated using the incidence and severity of TEAEs; the incidence and severity of EPS using the Barnes Akathisia Scale, Simpson-Angus Scale, and the AIMS; changes in vital signs, weight, laboratory analytes, and ECGs. Pharmacokinetic: Plasma concentrations of olanzapine, carbamazepine, and carbamazepine-10, 11-epoxide.
Methods: Statistical: An intent-to-treat (ITT) principle was applied in the efficacy and safety analyses. Efficacy analyses included all randomized patients (N=118) with baseline and postbaseline observations. Efficacy data were analyzed using the LOCF method. Analysis of covariance (ANCOVA) models were used to evaluate continuous data; the models generally included the terms for treatment, investigator, and baseline value as a covariate. Fisher's exact test and the Cochran-Mantel-Haenszel (CMH) chi-square test adjusted for investigator site effect were used for analysis of proportions and incidence rates. Kaplan-Meier plots and the log-rank tests were used to compare treatment groups for time-to-event data. All tests of treatment effects were conducted at a 2-sided alpha level of 0.05, unless otherwise stated. In order to assess longitudinal effects, a likelihood-based repeated measures analysis was conducted on the postbaseline YMRS total change scores and MADRS total change scores. Pharmacokinetic: Plasma concentrations of olanzapine, carbamazepine, and carbamazepine-10, and 11-epoxide were analyzed descriptively at Visit 6 and Visit 7.

Results:

Patient Demographics

Table 1 summarizes patient baseline physical characteristics by treatment group during the acute phase. The majority of patients in both treatment groups were Caucasian. The treatment groups were comparable at baseline with respect to age, racial origin, and gender.

Table 2 summarizes physical characteristics of patients who entered the open-label phase of the study. All patients entering the open-label phase were Caucasian; the mean age was 40.7 years, with 48 (55.8%) patients being female.

There were no statistically significant differences between groups at baseline for both the primary YMRS total score and secondary CGI-BP Severity scores, and MADRS total score efficacy parameters.

Table 1. Physical Characteristics at Baseline (Acute Phase) All Randomized Patients

Variable	Pla + CBZ (N=60)	Olz + CBZ (N=58)	Total (N=118)	P-value
Sex: No. (%)				
No. Patients	60	58	118	.336*
Female	32 (53.33)	36 (62.07)	68 (57.63)	
Male	28 (46.67)	22 (37.93)	50 (42.37)	
Origin: No. (%)				
No. Patients	60	58	118	.221*
Caucasian	59 (98.33)	58(100.00)	117 (99.15)	
East Asian	1 (1.67)	0 (0.00)	1 (0.85)	
Age: yrs.				
No. Patients	60	58	118	.509**
Mean	41.25	40.08	40.67	
Median	40.65	40.84	40.77	
Standard Dev.	11.37	10.69	11.01	
Minimum	20.49	19.21	19.21	
Maximum	65.43	63.03	65.43	

*Frequencies are analyzed using a CMH chi-square test adjusted for investigator.
** Means are analyzed using a Type III sum of squares analysis of variance(ANOVA): Model=investigator treatment.

Abbreviations: CBZ = carbamazepine; Dev = deviation; N = total number of patients; No = number; Olz = olanzapine; Pla = placebo; yrs = years.

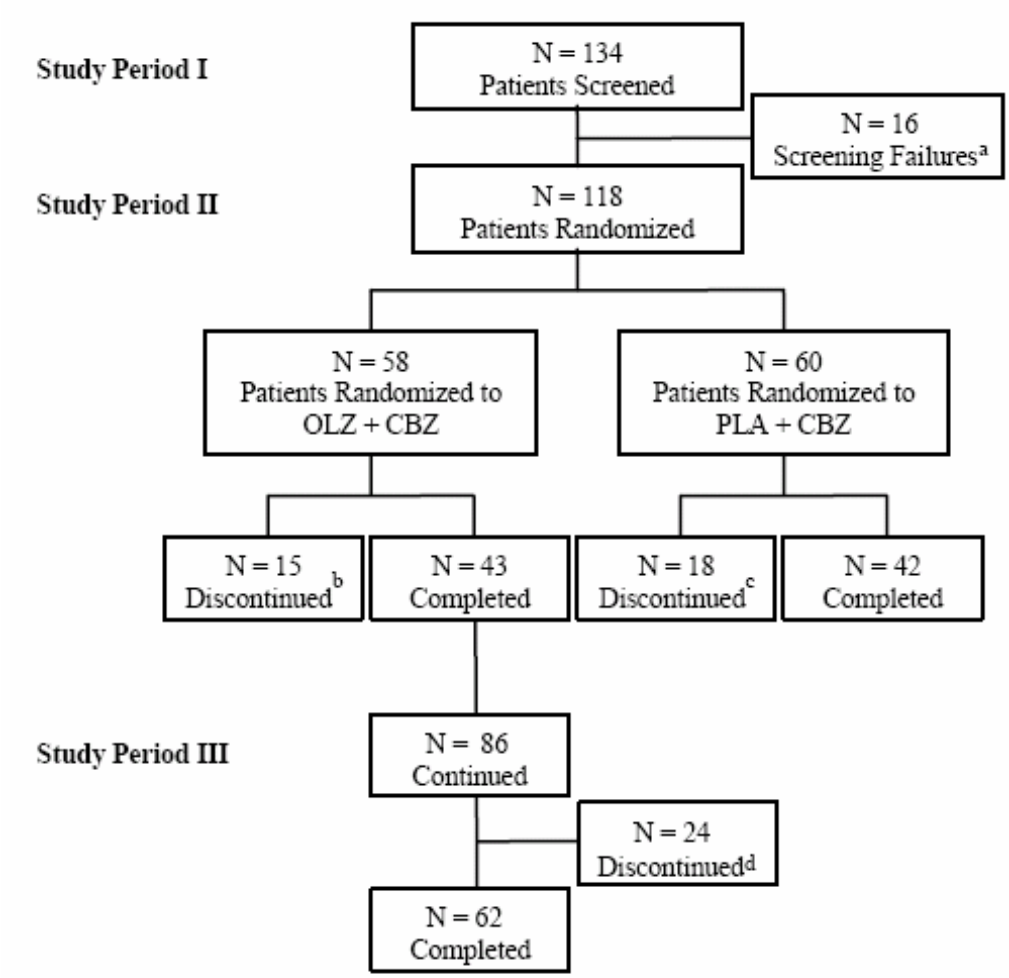
Table 2. Physical Characteristics (Open-Label Phase)

Variable	Olz + CBZ (N=86)
Sex: No. (%)	
No. Patients	86
Female	48 (55.8)
Male	38 (44.2)
Origin: No. (%)	
No. Patients	86
Caucasian	86 (100.0)
Age: yrs.	
No. Patients	86
Mean	40.66
Median	40.84
Standard Dev.	11.03
Minimum	19.21
Maximum	65.43

Abbreviations: CBZ = carbamazepine; Dev = deviation; N = total number of patients; No = number; Olz = olanzapine; yrs = years.

Patient Disposition

Figure 1 illustrates patient disposition for the entire study.



a Reasons for screening failures: entry criteria not met (13 patients), patient decision (2 patients), and AE (1 patient).
b Reasons for discontinuation: AE (5 patients), lack of efficacy (2 patients), patient decision (3 patients), protocol violation (2 patients), sponsor decision (1 patient), and physician decision (2 patients).
c Reasons for discontinuation: AE (5 patients), entry criteria not met/noncompliance (2 patients), patient decision (7 patients), protocol violation (2 patients), and lack of efficacy (2 patients).
d Reasons for discontinuation: AE (10 patients), lack of efficacy (3 patients), protocol violation (2 patients), patient decision (6 patients), sponsor decision (1 patient), and physician decision (2 patients).

Abbreviations: CBZ = carbamazepine; N = total number of patients; Olz = olanzapine; Pla = placebo.

Note: There were actually 86 patients who completed the acute phase of the study; however, 1 patient in the placebo-plus-carbamazepine group was not captured as "completed" in the acute phase database before it was locked, which is why Figure 1 shows 85 patients completing the acute phase and 86 patients continuing to the open-label phase of the study.

Figure 1. Patient disposition.

Primary Efficacy Measure

The primary variable for this study was the YMRS total score. As shown in Table 3, the LOCF change from baseline to endpoint of the YMRS total score was not statistically significantly different between the olanzapine-plus-carbamazepine and placebo-plus-carbamazepine treatment groups during the acute phase.

Table 3. LOCF Change From Baseline to Endpoint Analysis of YMRS Total Score (Acute Phase)

	LOCF Change to Endpoint				
	N	LsMean	LsMean Diff	LsMean Diff 95% CI	P-value
YMRS Total					
Pla + CBZ	59	-15.25			
Olz + CBZ	58	-15.49	-0.24	(-3.14 , 2.66)	.869

n=Patients having both baseline and post-baseline YMRS total score
P value is from Type III Sum of Squares from an analysis of covariance (ANCOVA):
model=Investigator,
Therapy and Baseline measurement
Least Square mean difference is from the same ANCOVA model

Abbreviations: CBZ = carbamazepine; CI = confidence interval; Diff = difference; LSMean = least squares mean; Olz = olanzapine.

Secondary Efficacy Measures

For the open-label phase, efficacy analyses were carried out to evaluate the maintenance of the treatment effect from the acute phase. LOCF change analysis from baseline (defined as Visit 7 in Study Period II, unless otherwise defined) to endpoint was done for YMRS total score. Of the patients with both baseline and postbaseline visits (N=85), there was a statistically significant decrease from baseline to endpoint ($p<.001$) for YMRS total score (Table 4).

Table 4. YMRS Total Score – Mean Change from Baseline to Endpoint (Open-Label Phase)

YMRS total		Baseline		Change to Endpoint		P-value
	N	Mean	SD	Mean	SD	
Olz + CBZ	85	9.56	8.36	-5.94	8.09	<.001

N = Patients having both baseline and post-baseline visits.
P-value is from one-sample t test.

Abbreviations: CBZ = carbamazepine; Olz = olanzapine; SD = standard deviation; YMRS = Young Mania Rating Scale.

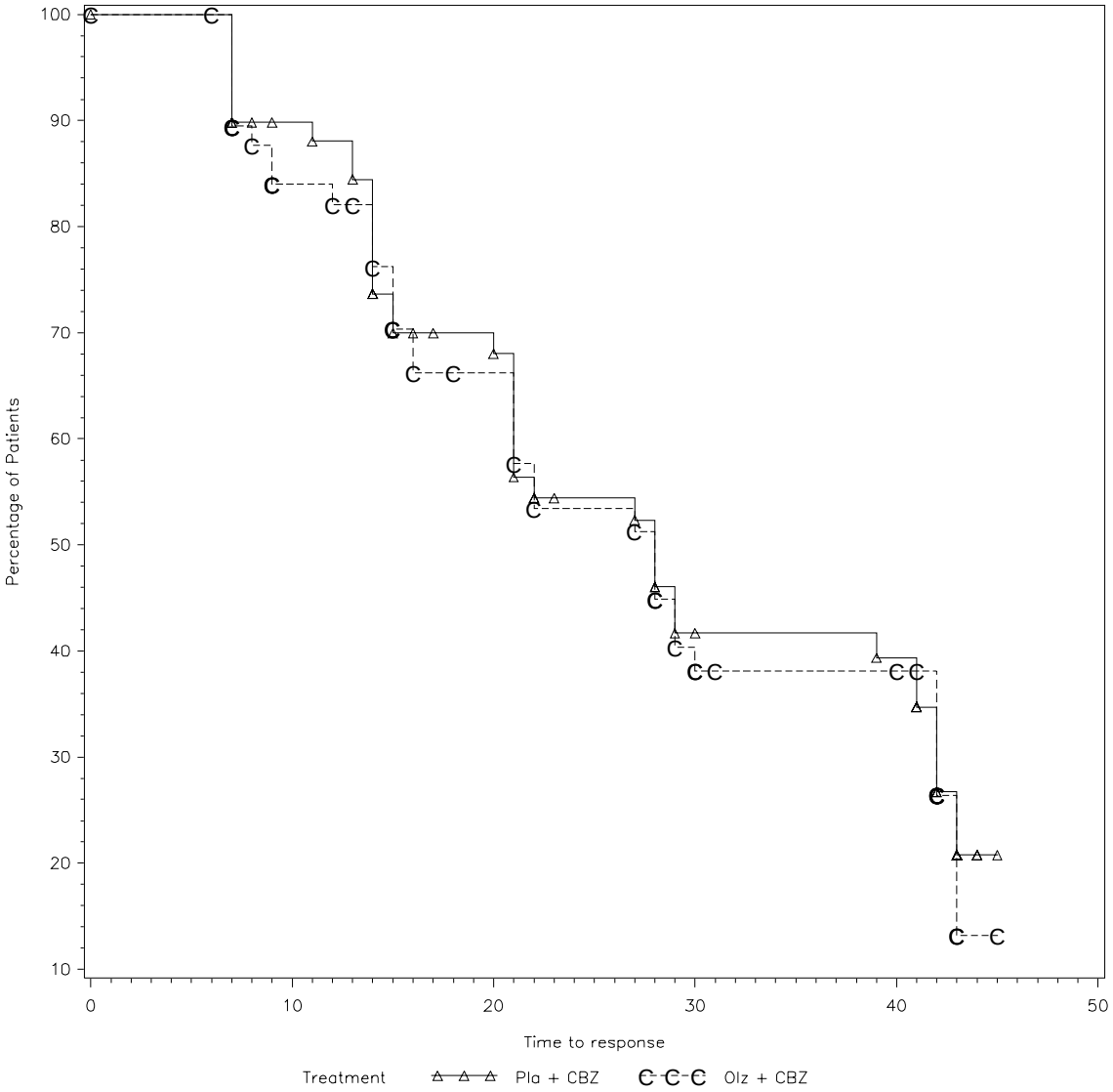
Reductions from baseline to the endpoint of the 6-week acute phase on the MADRS total score and CGI-BP severity scores were analyzed to assess the acute efficacy of olanzapine plus carbamazepine versus placebo plus carbamazepine in improving depressive symptoms and global clinical symptomatology. There were no statistically significant differences between treatment groups on any of the scores.

Longitudinal Effects

The longitudinal effects (postbaseline YMRS total change scores) were analyzed using a likelihood-based repeated measures analysis [SAS PROC MIXED]). Model includes terms for baseline, treatment, investigator, visit, and treatment-by-visit interaction. There were no statistically significant differences between groups at any postbaseline visit on change from baseline on either the YMRS total score or the MADRS total score.

Incidences of and times to response, remission, and switch to depression

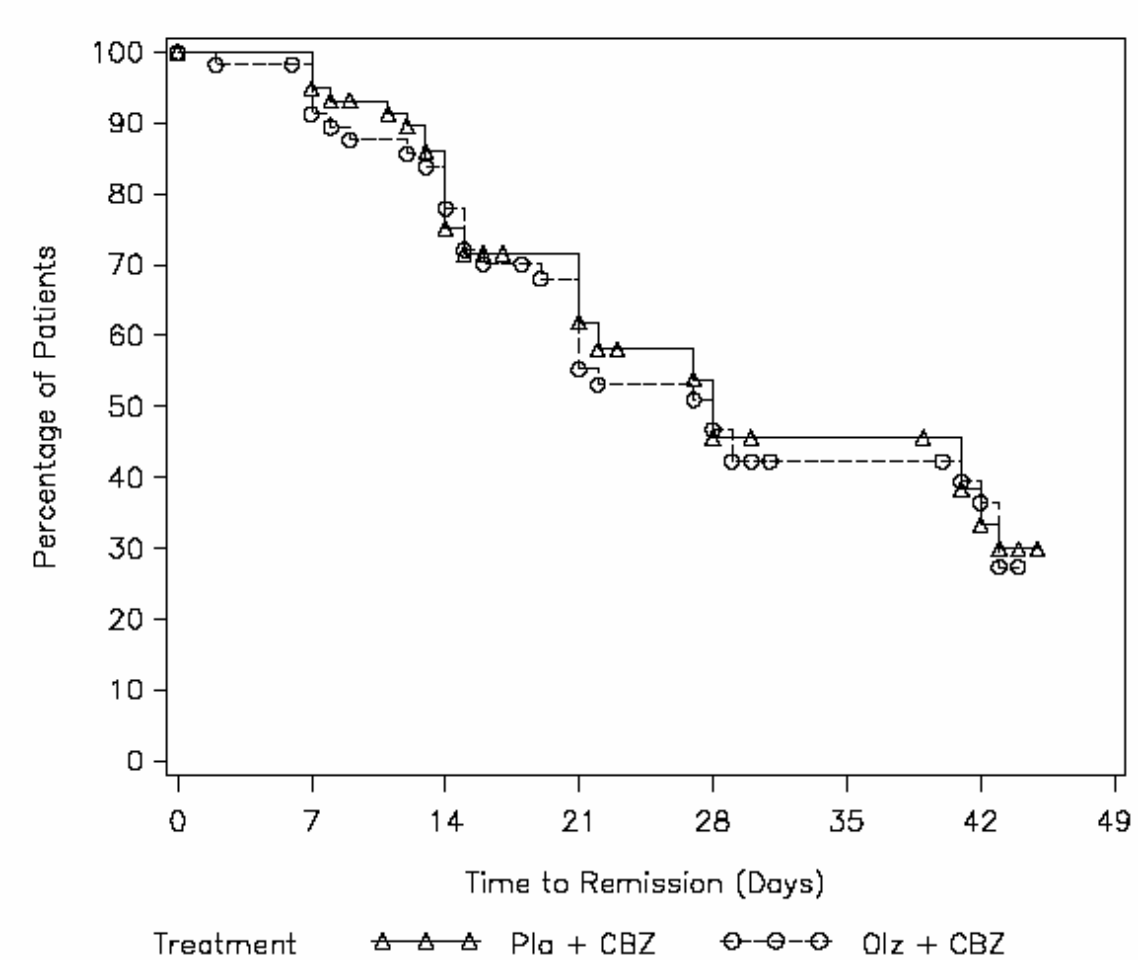
The proportion of patients who responded (and time to response), as well as proportion of patients who remitted (and time to remission), were evaluated during the double-blind acute phase to assess the acute efficacy of olanzapine plus carbamazepine versus placebo plus carbamazepine in improving clinical symptomatology. Patients with an improvement of 50% or more in YMRS total score from baseline to endpoint were classified as responders. Patients with endpoint YMRS total score $\leq$12 were considered as remitters. The analyses of time to response and time to remission were based on the time of first reaching the appropriate criterion (that is, for response, YMRS reaching 50% or more reduction on those responders; for remission, YMRS reaching $\leq$12 on those remitters). The proportion of patients in the 2 treatment groups who responded at endpoint using LOCF was not statistically significantly different. Likewise, the Kaplan-Meier estimated time-to-response curves (Figure 2) show that there were no statistically significant differences between groups in time to response.



Abbreviations: CBZ = carbamazepine; Olz = olanzapine; Pla = placebo.
Responders were patients who reached ≥50% reduction in Young Mania Rating Score (YMRS) total score from baseline at endpoint.
Nonresponders were all considered censored in the analyses.
Time to event was the time from randomization to the first visit a responder reached 50% reduction from baseline in YMRS total score at postbaseline.
Median survival time in days for placebo plus carbamazepine = 28.
Median survival time in days for olanzapine plus carbamazepine = 28.
p-value from log-rank test = .797.

Figure 2. Time to response – YMRS total score (acute phase).

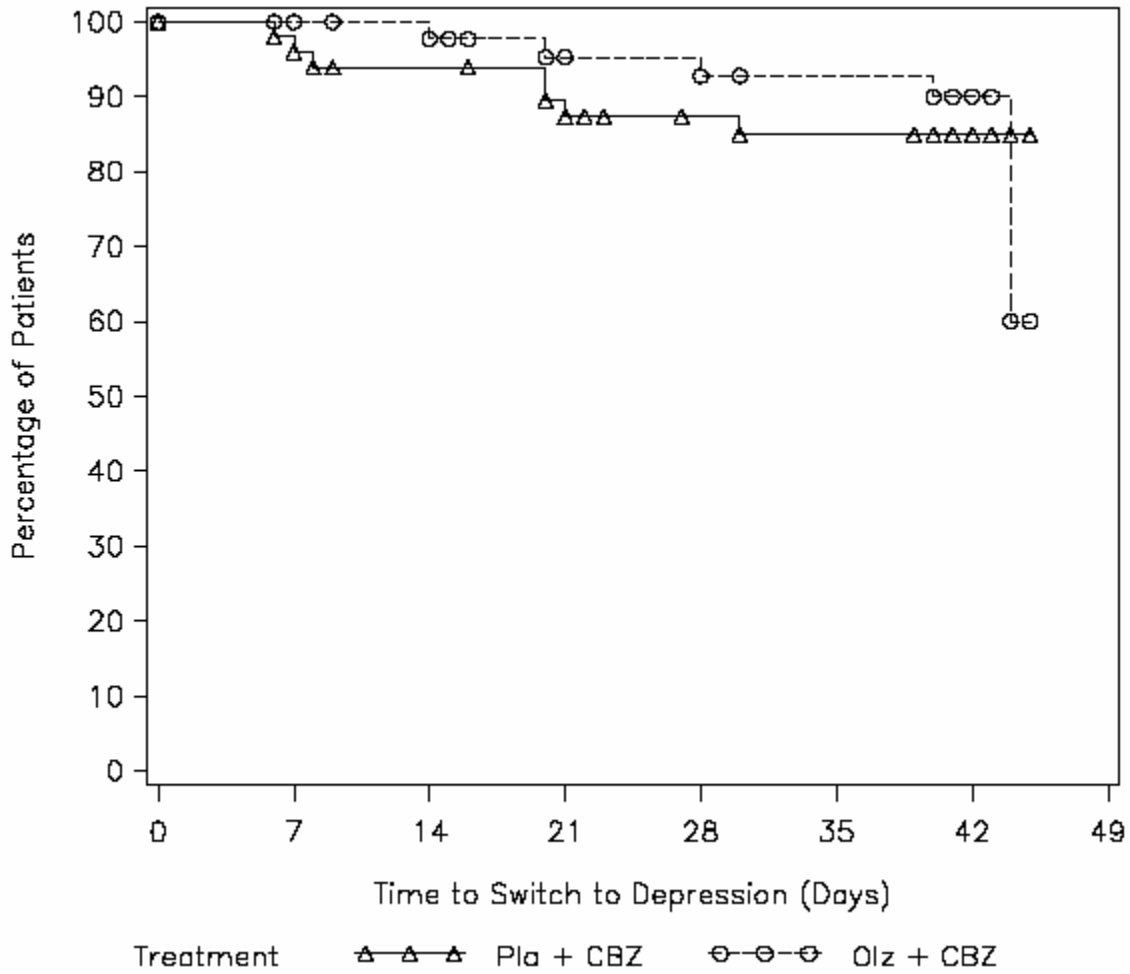
The proportion of patients in the 2 treatment groups who were remitters at endpoint using LOCF was not statistically significantly different. Likewise, the Kaplan-Meier estimated time-to-remission curves (Figure 3) show that there were no statistically significant differences between groups in time to response.



Abbreviations: CBZ = carbamazepine; Olz = olanzapine; Pla = placebo.
Remitters were patients who had Young Mania Rating Score (YMRS) total score ≤12 at endpoint.
Nonremitters were all considered censored in the analyses.
Time to event was the time from randomization to the first visit a remitter reached a YMRS total score ≤12 postbaseline.
Median time to switch in days for placebo plus carbamazepine = 28.
Median time to switch in days for olanzapine plus carbamazepine = 28.
p-value from log-rank test = .864.

Figure 3. Time to remission – YMRS total score (acute phase).

Another secondary objective was to assess the incidence of switch to depression, defined as reaching a MADRS score of 16 or more at any time postbaseline and evaluated among those patients who had a MADRS score ≤12 at baseline. Both the incidence of and time to such switches were evaluated. There were no statistically significant differences between treatment groups in either incidence of or time to switch to depression (Figure 4).



Abbreviations: CBZ = carbamazepine; Olz = olanzapine; Pla = placebo.
Time to event was the time from randomization to the first visit a patient switched from baseline Montgomery-Asberg Depression Rating Scale (MADRS) total of ≤12 to first time reached ≥16 at postbaseline.
25% time to switch in days for placebo plus carbamazepine = missing.
25% time to switch in days for olanzapine plus carbamazepine = 44.
p-value from log-rank test = .622.

Figure 4. Time to switch to depression – MADRS total score (acute phase).

A subgroup analysis of the LOCF change from baseline to endpoint during open-label phase for the YMRS total score was performed comparing acute-phase responders and nonresponders (judged at the end of the acute phase). An analysis of covariance (ANCOVA) model was used for this analysis. Within-subgroup change was analyzed using the same model. Table 5 summarizes the subgroup analyses for YMRS total score. No statistically significant difference between responders and nonresponders (p=.298) was observed for the LOCF change from baseline to endpoint for the YMRS total score. However, within-group statistically significant decreases from baseline were noted for both responders and non-responders (p<.001 for each group).

Table 5. Efficacy Subgroup Analyses (Open-Label Phase)

Endpoint: YMRS Total

Subgroup of Interest	Strata	N	Therapy	Change LsMean	Change LsMean Diff	Change LsMean Diff 95% CI	Sub-group	Within group p-Value
Responders	Yes	66	Olz+CBZ	-5.36	2.61	(-2.35, 7.56)	.298	<.001
	No	19	Olz+CBZ	-7.96				<.001

Responders are judged at the end of Acute phase.

Subgroup p-value from an ANCOVA model= baseline, subgroup.
Within group p-value from Student's t-test.

Abbreviations: CBZ = carbamazepine; CI = confidence interval; Diff = difference; LSMean = least squares mean; N = total number of patients in the category; Olz = olanzapine; YMRS = Young Mania Rating Scale.

Pharmacokinetics

Carbamazepine induced the metabolism of olanzapine, which lowered olanzapine exposure. A 30-mg olanzapine dose was administered during this study; however, the systemic olanzapine exposure was similar to that achieved by a 15-mg dose of olanzapine. The plasma concentration exposure to carbamazepine and its metabolite was unaffected whether carbamazepine was given with placebo or with olanzapine.

Safety

Adverse Events

There were no deaths during either phase of this study. Table 6 contains an overview of adverse events (AEs) during the acute phase of the study.

Table 6. Overview of Adverse Events – Number and Percentage of Patients (Acute Phase)

Adverse Event*	Pla + CBZ (N=60) n	(%)	Olz + CBZ (N=58) n	(%)
Deaths	0	(0.0)	0	(0.0)
Serious adverse events	1	(1.7)	2	(3.4)
Discontinuations due to an adverse event	5	(8.3)	5	(8.6)
Other clinically significant adverse events	2	(3.3)	10	(17.2)
Treatment-emergent adverse events	32	(53.3)	37	(63.8)

* Patients may be counted in more than one category.

Abbreviations: CBZ = carbamazepine; n = number in category; N = number of patients; Olz = olanzapine, Pla = placebo.

Table 7 summarizes treatment-emergent adverse events (TEAEs) that occurred in >2% of any treatment group during the acute phase by decreasing frequency. The most commonly reported (≥10%) TEAE in the olanzapine-plus-carbamazepine treatment group was somnolence. Increased alanine aminotransferase was observed statistically significantly more often for olanzapine-plus- carbamazepine-treated patients than for placebo-plus-carbamazepine-treated patients. Constipation was reported statistically significantly more often by placebo-plus- carbamazepine-treated patients than by olanzapine-plus-carbamazepine-treated patients.

Table 7. TEAEs by Decreasing Frequency in Olanzapine Plus Carbamazepine – Events Occurring in >2% Patients in Either Treatment Group (Acute Phase)

	Pla + CBZ			Olz + CBZ			Total			-------p-Value--------	
Event Classification	N	n	(%)	N	n	(%)	N	n	(%)	Fisher's Exact	CMH Chi-Square
Patients with >= 1 TEAE	60	32	(53.3)	58	37	(63.8)	118	69	(58.5)	.268	.228
Patients with no TEAE	60	28	(46.7)	58	21	(36.2)	118	49	(41.5)		
Somnolence	60	8	(13.3)	58	9	(15.5)	118	17	(14.4)	.797	.532
Dry mouth	60	1	(1.7)	58	5	(8.6)	118	6	(5.1)	.111	.115
Headache	60	5	(8.3)	58	5	(8.6)	118	10	(8.5)	1.00	.945
Alanine aminotransferase increased	60	0	(0.0)	58	4	(6.9)	118	4	(3.4)	.055	.050
Vision blurred	60	1	(1.7)	58	4	(6.9)	118	5	(4.2)	.203	.201
Dizziness	60	2	(3.3)	58	3	(5.2)	118	5	(4.2)	.677	.723
Rash	60	0	(0.0)	58	3	(5.2)	118	3	(2.5)	.116	.057
Sedation	60	1	(1.7)	58	3	(5.2)	118	4	(3.4)	.360	.370
Anxiety	60	1	(1.7)	58	2	(3.4)	118	3	(2.5)	.615	.544
Blood glucose increased	60	0	(0.0)	58	2	(3.4)	118	2	(1.7)	.239	.157
Increased appetite	60	1	(1.7)	58	2	(3.4)	118	3	(2.5)	.615	.701
Insomnia	60	1	(1.7)	58	2	(3.4)	118	3	(2.5)	.615	.479
Tachycardia	60	0	(0.0)	58	2	(3.4)	118	2	(1.7)	.239	.134
Tremor	60	1	(1.7)	58	2	(3.4)	118	3	(2.5)	.615	.658
Vomiting	60	0	(0.0)	58	2	(3.4)	118	2	(1.7)	.239	.157
Vaginal discharge	32	0	(0.0)	36	1	(2.8)	68	1	(1.5)	1.00	.480
Depression	60	2	(3.3)	58	1	(1.7)	118	3	(2.5)	1.00	.520
Fatigue	60	2	(3.3)	58	1	(1.7)	118	3	(2.5)	1.00	.573
Nausea	60	4	(6.7)	58	1	(1.7)	118	5	(4.2)	.365	.186
Weight increased	60	3	(5.0)	58	1	(1.7)	118	4	(3.4)	.619	.339
Acne	60	2	(3.3)	58	0	(0.0)	118	2	(1.7)	.496	.083
Constipation	60	6	(10.0)	58	0	(0.0)	118	6	(5.1)	.027	.005
Metrorrhagia	32	1	(3.1)	36	0	(0.0)	68	1	(1.5)	.471	.317

N = Number of randomized patients or number of randomized patients adjusted for gender specific event
n = Number of patients with treatment-emergent adverse event
Incidence rates of specific treatment-emergent adverse events analyzed using Fisher's Exact test as well as CMH chi-square test adjusted for investigator site.
MedDra Version: 8.0

Abbreviations: CBZ = carbamazepine; CMH = Cochran-Mantel-Haenszel; Olz = olanzapine; Pla = placebo; TEAE = treatment-emergent adverse event.

Three patients had serious adverse events (SAEs) during the acute phase of the study. Table 8 summarizes SAEs for the acute phase. No single event was experienced by more than 1 patient. The patients with depression and adenovirus infection discontinued the study, and the patient with nephrolithiasis continued in the study.

Table 8. Summary of Serious Adverse Events (Acute Phase)

	Pla + CBZ			Olz + CBZ			Total			-------p-Value--------	
Event Classification	N	n	(%)	N	n	(%)	N	n	(%)	Fisher's Exact	CMH Chi-Square
Patients with >= 1 SAE	60	1	(1.7)	58	2	(3.4)	118	3	(2.5)	.615	.528
Patients with no SAE	60	59	(98.3)	58	56	(96.6)	118	115	(97.5)		
Adenovirus infection	60	1	(1.7)	58	0	(0.0)	118	1	(0.8)	1.00	.361
Depression	60	0	(0.0)	58	1	(1.7)	118	1	(0.8)	.492	.317
Nephrolithiasis	60	0	(0.0)	58	1	(1.7)	118	1	(0.8)	.492	.317

N = Number of randomized patients or number of randomized patients adjusted for gender specific event
n = Number of patients with serious adverse event
Incidences of SAE were compared using Fisher's Exact test as well as CMH chi-square test adjusted for investigator sites.
MedDra Version: 8.0

Abbreviations: CBZ = carbamazepine; CMH = Cochran-Mantel-Haenszel; Olz = olanzapine; Pla = placebo; SAE = serious adverse event.

Table 9 summarizes SAEs for patients in the open-label phase of the study. No single SAE was experienced by more than 1 patient.

Table 9. Summary of Serious Adverse Events (Open-Label Phase)

Event Classification	Olz + CBZ N	n	(%)
Patients with >= 1 SAE	86	4	(4.7)
Patients with no SAE	86	82	(95.3)
Adenovirus infection	86	1	(1.2)
Anxiety	86	1	(1.2)
Hypersensitivity	86	1	(1.2)
Insomnia	86	1	(1.2)
Nephrolithiasis	86	1	(1.2)
Renal colic	86	1	(1.2)
Suicide attempt	86	1	(1.2)

N = Number of patients who entered open-label phase adjusted for gender specific event.
n = Number of patients with serious adverse event.

Abbreviations: CBZ = carbamazepine; CMH = Cochran-Mantel-Haenszel; Olz = olanzapine; SAE = serious adverse event.

Incidence and Severity of Extrapyramidal Symptoms (EPS)

The changes from baseline to endpoint for the Simpson-Angus total score, Barnes Akathisia global score, and the Abnormal Involuntary Movement Scale (AIMS) total score for the acute phase and the open-label phase were not statistically significantly different between groups. There was no statistically significant change from the endpoint of the acute phase to the end of the open-label phase for these assessments.

Vital Signs and Weight

There was a statistically significant change in weight from the endpoint of the acute phase to the end of the open-label phase.

Table 10 and Table 11 summarize the mean change from baseline to endpoint and a potentially clinically significant change, respectively, in weight for patients during the acute phase. Potentially clinically significant weight gain (an increase $\geq$7%) at any time was more frequently observed in olanzapine-plus-carbamazepine-treated patients (24.6%), compared with placebo-plus-carbamazepine-treated patients (3.4%). This difference between treatment groups was statistically significant.

Table 10. Vital Signs and Weight – Mean Change from Baseline to Endpoint (Acute Phase)

Variables Analyzed	Therapy	n	Change to Endpoint LsMean	LsMean Diff	LsMean Diff 95% CI	p-Value* Therapy
DIA_OR	Pla + CBZ	59	-0.2	0.6	(-1.91 , 3.12)	.633
	Olz + CBZ	58	0.3			
DIA_STN	Pla + CBZ	59	-0.4	0.6	(-2.15 , 3.47)	.642
	Olz + CBZ	58	0.1			
DIA_SUP	Pla + CBZ	59	-0.6	0.9	(-2.09 , 3.94)	.544
	Olz + CBZ	58	0.2			
PLS_OR	Pla + CBZ	59	0.9	2.4	(0.47 , 4.41)	.016
	Olz + CBZ	58	3.3			
PLS_STN	Pla + CBZ	59	-2.4	3.7	(0.36 , 7.23)	.031
	Olz + CBZ	58	1.3			
PLS_SUP	Pla + CBZ	59	-4.1	2.1	(-0.67 , 4.93)	.135
	Olz + CBZ	58	-1.9			
SYS_OR	Pla + CBZ	59	-1.5	1.6	(-1.26 , 4.51)	.266
	Olz + CBZ	58	0.0			
SYS_STN	Pla + CBZ	59	-0.5	1.0	(-2.63 , 4.68)	.580
	Olz + CBZ	58	0.4			
SYS_SUP	Pla + CBZ	59	-1.5	1.5	(-2.12 , 5.19)	.407
	Olz + CBZ	58	-0.0			
TEMP	Pla + CBZ	58	0.0	-0.1	(-0.26 , -0.01)	.040
	Olz + CBZ	57	-0.1			

Variables Analyzed	Therapy	n	Change to Endpoint LsMean	LsMean Diff	LsMean Diff 95% CI	p-Value* Therapy
WGT	Pla + CBZ	59	0.6	2.5	(1.52 , 3.56)	<.001
	Olz + CBZ	57	3.1			

Abbreviations: CBZ = carbamazepine; n = total number of patients in each treatment group having the variable in both baseline and postbaseline visits; n = Total number of patients in each treatment group having the variable in both baseline and post-baseline measures; Pla = placebo; SD = standard deviation.
* Type III Sum of Squares from analysis of covariance (ANCOVA) : model = investigator site, treatment and baseline value.

Table 11. Weight – Potentially Clinically Significant Changes (Acute Phase)

						---p-Value---	
Variable	Direction	Therapy	N	n	(%)	Fisher's exact	CMH chi-square
Weight (kg)	Gain	Pla+CBZ	59	2	(3.4)	<.001	.002
		Olz+CBZ	57	14	(24.6)		
	Loss	Pla+CBZ	59	1	(1.7)	1.00	.355
		Olz+CBZ	57	0			

Abbreviations: CBZ = carbamazepine; CMH = Cochran-Mantel-Haenszel; N = number of patients with a normal baseline and at least 1 postbaseline measure; n = number of patients with a normal baseline and an abnormal postbaseline measure; Olz = olanzapine; Pla = placebo.

Frequencies analyzed using two-tailed Fisher's exact test as well as CMH chi-square test adjusted for investigator site.

Table 12 and Table 13 summarize the mean change from baseline to endpoint and a potentially clinically significant change, respectively, in weight for patients who entered the open-label phase. There was a statistically significant increase in weight from baseline to endpoint (average weight gain of 1.86 kg, p<.001), and 15.3% patients experienced weight gain of 7% or more from baseline to endpoint.

Table 12. Weight – Mean Change from Baseline to Endpoint (Open-Label Phase)

			---Baseline---		Change to ---Endpoint---		
Variable Analyzed	Therapy	n	Mean	SD	Mean	SD	p-Value
Weight	Olz+CBZ	85	79.57	16.72	1.86	3.99	<.001

Abbreviations: CBZ = carbamazepine, n = total number of patients having the variable in both baseline and postbaseline measures, Olz = olanzapine, SD = standard deviation.

p-values are from student's t-test.

Table 13. Weight – Potentially Clinically Significant Changes (Open-Label Phase)

Variable	Direction	Therapy	N	n	(%)
Weight (kg)	Gain	Olz+CBZ	85	13	(15.3)
	Loss	Olz+CBZ	85	1	(1.2)

Abbreviations: CBZ = carbamazepine; N = number of patients with a normal baseline and at least 1 postbaseline measure; n = number of patients with a normal baseline and an abnormal postbaseline measure; Olz = olanzapine.

Laboratory Analytes

Laboratory analytes that have statistically significant changes from baseline to endpoint between treatment arms during the acute phase are presented by treatment group in Table 14.

Table 14. Laboratory Analytes – Mean Change from Baseline to Endpoint (Acute Phase)

				Change to Endpoint			
Lab Test	Lab Unit	Therapy	n	LS Mean	LS Mean Diff	LS Mean Diff 95% CI	p-Value*
Albumin	gram/Liter	Pla+CBZ	55	0.49			
		Olz+CBZ	50	-0.86	-1.34	(-2.62, -0.06)	.040
Urea Nitrogen (BUN)	millimole/Liter	Pla+CBZ	55	0.03			
		Olz+CBZ	50	0.61	0.58	(0.12, 1.04)	.014
Bilirubin, Direct	micromole/Liter	Pla+CBZ	56	-0.31			
		Olz+CBZ	56	-0.52	-0.21	(-0.40, -0.02)	.030
Bilirubin, Total	micromole/Liter	Pla+CBZ	57	-1.76			
		Olz+CBZ	58	-2.79	-1.03	(-1.90, -0.17)	.019
Prolactin	microgram/Liter	Pla+CBZ	51	-17.33			
		Olz+CBZ	48	-4.88	12.45	(4.48, 20.41)	.003
Eosinophils	Bill/L	Pla+CBZ	57	-0.04			
		Olz+CBZ	58	0.03	0.07	(0.02, 0.13)	.007
Hematocrit	Actual Count	Pla+CBZ	57	-0.00			
		Olz+CBZ	57	-0.01	-0.01	(-0.02, -0.00)	.021
Hemoglobin	mmol/Liter (Fe)	Pla+CBZ	57	0.10			
		Olz+CBZ	58	-0.11	-0.21	(-0.38, -0.03)	.019
Mean Cell Volume	femtoliter	Pla+CBZ	57	-0.10			
		Olz+CBZ	57	-1.44	-1.34	(-2.44, -0.24)	.017
Triglycerides	millimole/Liter	Pla+CBZ	57	0.02			
		Olz+CBZ	57	0.60	0.58	(0.15, 1.01)	.008

Reporting SI units

Abbreviations: CBZ = carbamazepine; CI = confidence interval; Diff = difference; Fe = iron; LSMean = least squares mean; n = Patients having both baseline and postbaseline measures; Olz = olanzapine; Pla = placebo.

* Type III Sums of Squares from an analysis of covariance (ANCOVA): model = investigator site, treatment and baseline.

Table 15 summarizes the analysis of the mean change from baseline to endpoint for laboratory parameters (that were statistically significant) in patients who entered the open-label phase.

Table 15. Laboratory Analytes – Mean Change from Baseline to Endpoint (Open-Label Phase)

				--Baseline--		Change to --Endpoint--		
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	p-Value*
Alkaline Phosphatase	Units/Liter	Olz+CBZ	85	80.52	22.94	3.35	12.42	.015
Bilirubin, Total	micromole/Liter	Olz+CBZ	85	4.54	2.42	0.81	2.71	.007
Eosinophils	Bill/L	Olz+CBZ	85	0.18	0.17	-0.06	0.15	<.001
Mean Cell Volume	femtoliter	Olz+CBZ	85	89.40	7.50	1.35	5.94	.039
Platelet Count	Bill/L	Olz+CBZ	85	273.84	61.46	-15.96	49.28	.004
Erythrocyte Count	Tril/L	Olz+CBZ	85	4.90	0.68	-0.08	0.34	.043
HDL Cholesterol - Dextran Precip.	millimole/Liter	Olz+CBZ	84	1.40	0.31	-0.06	0.26	.028

Reporting SI units.

Abbreviations: CBZ = carbamazepine; HDL = high density lipoprotein; n = patients having both baseline and postbaseline measures; Olz = olanzapine; Precip. = precipitate; SD = standard deviation.

* p-values are from student's t-test.

Changes in lipids level from fasting blood samples were closely monitored. There were no statistically significant differences between treatment groups in treatment-emergent changes in fasting glucose levels. There was a statistically significant difference between treatment groups in the category of triglycerides (normal to high), in which the olanzapine-plus-carbamazepine treatment group was statistically significantly greater (20.6%) when compared to the placebo-plus-carbamazepine treatment group (3.2%). In addition, there was a numerically, but not statistically significantly, greater difference (3 times greater) for the olanzapine-plus-carbamazepine treatment group than the placebo-

plus-carbamazepine treatment group for treatment-emergent changes in the normal to high cholesterol (25.0% versus 8.0%, Table 16).

Table 16. Summary of Treatment-Emergent Significant Changes in Blood Glucose and Lipids Level (Acute Phase)

	Pla + CBZ			Olz + CBZ			Total			p-Value	
Categories	N	n	(%)	N	n	(%)	N	n	(%)	Fisher's Exact	CMH Chi-Square
GLUCOSE, FASTING											
Normal to High	44	1	(2.3)	52	4	(7.7)	96	5	(5.2)	.371	.352
CHOLESTEROL											
Normal to Borderline	25	10	(40.0)	24	13	(54.2)	49	23	(46.9)	.396	.128
Normal to High	25	2	(8.0)	24	6	(25.0)	49	8	(16.3)	.138	.117
LDL CHOLESTEROL											
Normal to Borderline	30	11	(36.7)	26	11	(42.3)	56	22	(39.3)	.786	.318
Normal to High	30	6	(20.0)	26	7	(26.9)	56	13	(23.2)	.752	.439
HDL CHOLESTEROL-DEXTRAN PRECIP.											
Normal to Low	18	2	(11.1)	24	1	(4.2)	42	3	(7.1)	.567	.317
TRIGLYCERIDES											
Normal to Borderline	31	5	(16.1)	34	7	(20.6)	65	12	(18.5)	.754	.405
Normal to High	31	1	(3.2)	34	7	(20.6)	65	8	(12.3)	.056	.049
Normal to Extreme High	31	0	(0.0)	34	0	(0.0)	65	0	(0.0)		

Note: N=Total number of patients in each treatment group having normal value at all baseline measures and have at least one post-baseline measure.
n=Total number of patients in each treatment group having normal value at all baseline measures and have an abnormal post-baseline measure.

Note: Frequencies were analyzed using two-tailed Fisher's exact test as well as CMH chi-square test adjusted for investigator site.

Abbreviations: CBZ = carbamazepine; CMH = Cochran-Mantel-Haenszel; HDL = high density lipoprotein; LDL = low density lipoprotein; Olz = olanzapine; Pla = placebo.

During the open-label phase, fasting glucose, as well as most cholesterol and triglyceride categories, showed continued increases (Table 17).

No patients met the criteria for postbaseline enzyme elevation, indicative of liver function damage, during the acute phase or the open-label phase of the study.

Table 17. Summary of Treatment-Emergent Significant Changes in Fasting Blood Glucose and Lipid Levels from Normal to High (Open-Label Phase)

Categories	Olz + CBZ N	n	(%)
Fasting Glucose			
Normal to High (<126 mg/dL to >=126 mg/dL)	71	7	(9.9)
Total Cholesterol			
Normal to Borderline (<200 mg/dL to >=200 mg/dL & <240 mg/dL)	14	7	(50.0)
Normal to High (<200 mg/dL to >=240 mg/dL)	14	1	(7.1)
LDL Cholesterol			
Normal to Borderline (<130 mg/dL to >=130 mg/dL & <160 mg/dL)	19	17	(89.5)
Normal to High (<130 mg/dL to >=160 mg/dL)	19	1	(5.3)
HDL Cholesterol			
Normal to Low (>=50 mg/dL to <40 mg/dL)	25	1	(4.0)
Fasting Triglyceride			
Normal to Borderline high (<150 mg/dL to >=150 mg/dL & <200 mg/dL)	38	15	(39.5)
Normal to High (<150 mg/dL to >=200 mg/dL)	38	10	(26.3)
Normal to extreme High (<150 mg/dL to >=500 mg/dL)	38	1	(2.6)

Note: N = Total number of patients having normal value at all baseline measures and have at least one post-baseline measure.
n = Total number of patients having normal value at all baseline measures and have an abnormal post-baseline measure.

Abbreviations: CBZ = carbamazepine; HDL = high density lipoprotein; LDL = low density lipoprotein; Olz = olanzapine.

Electrocardiograms (ECGs)

During the acute phase, placebo-plus-carbamazepine-treated patients had a statistically significantly greater mean decrease in heart rate than olanzapine-plus-carbamazepine-treated patients. Olanzapine-plus-carbamazepine-treated patients had a statistically significant mean decrease in uncorrected QT intervals when compared with placebo-plus-carbamazepine-treated patients (Table 18). There were no such findings in ECG data during the open-label phase.

Table 18. ECG Intervals and Heart Rate – Mean Change from Baseline to Endpoint (Acute Phase)

			---Change to Endpoint---			
Variable Analyzed	Therapy	n	LS Mean	LS Mean Diff	LS Mean Diff 95% CI	p-Value
Heart Rate	Pla+CBZ Olz+CBZ	55 55	-5.04 -0.62	4.42	(0.69, 8.14)	.021
QT Interval (msec)	Pla+CBZ Olz+CBZ	55 56	5.06 -4.19	-9.25	(-17.17, -1.32)	.023

Abbreviations: CBZ = carbamazepine; CI = confidence interval; Diff = difference; LSMean = least squares mean; n = total number of patients in each treatment group having the variable in both baseline and postbaseline measures; Olz = olanzapine; Pla = placebo.

p-value and LSMean are from analysis of covariance (ANCOVA): model = investigator site, treatment and baseline value.

