

Summary ID#1028

Clinical Study Summary: Study F1D-MC-HGEH[c]

Title of Study: Olanzapine versus Placebo in the Treatment of Mania Associated with Bipolar I Disorder	
Investigator(s): This multicenter study included 16 principal investigators.	
Study Center(s): This study was conducted at 16 study centers.	
Length of Study: 18 October 1996 through 22 August 1997 (last double-blind visit date)	Phase of Development: 3
<p>Objectives: The primary objective of this study was to assess the efficacy of olanzapine in a dose range of 5, 10, 15, or 20 mg/day compared with placebo in the treatment of patients diagnosed with manic or mixed episode associated with bipolar I disorder in improving overall symptomatology as measured by reductions from baseline of the Young Mania Rating Scale (YMRS) total score after 3 weeks of therapy.</p> <p>Secondary objectives included: 1) assessing the efficacy of olanzapine compared with placebo in improving clinical symptomatology in patients diagnosed with manic episode associated with bipolar I disorder after 3 weeks of therapy; 2) to assess the safety of acute, as well as long-term open-label, treatment with olanzapine; and 3) to assess the efficacy of open-label olanzapine in long-term treatment of patients with bipolar I disorder in improving clinical symptomatology.</p>	
Study Design: This protocol was designed as 2 randomized, double-blind, placebo-controlled, parallel studies with a placebo comparator.	
<p>Number of Patients:</p> <p>Randomized in acute phase: 70 olanzapine, 69 placebo</p> <p>Open-label phase: 113 olanzapine</p>	
Diagnosis and Main Criteria for Inclusion: Patients must have had an initial total score (at Visits 1 and 2) on the YMRS of at least 20 and a diagnosis of bipolar I disorder displaying an acute manic or mixed episode (with or without psychotic features) for at least 2 weeks prior to Visit 1, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as determined by the Structured Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Patient Version (SCID-P).	
Test Product, Dose, and Mode of Administration: Olanzapine 5, 10, 15, or 20 mg/day, given once per day as 5-mg tablets	
<p>Duration of Treatment: Olanzapine, 56 weeks; placebo, 3 weeks</p> <p>Qualified patients from Study Period I (screening period) were assigned by random allocation at Visit 2 to 1 of 2 treatment groups: olanzapine (5, 10, 15, or 20 mg/day) or placebo. Randomization was performed at a 1:1 ratio. Study Period II was the 3-week, double-blind acute therapy period. Study Period III was the open-label extension period. Patients who showed no improvement from baseline on their YMRS total score after 1 or 2 weeks could transfer into Study Period III at Visit 3 or Visit 4. All other patients continued into Study Period III at the conclusion of Study Period II (Visit 5) regardless of YMRS score.</p>	
Reference Therapy, Dose, and Mode of Administration: Placebo, given once per day as 5-mg tablets	

Variables:

Efficacy: Last observation carried forward (LOCF) change from baseline to endpoint in the YMRS score served as the primary efficacy criterion.

Secondary efficacy assessments included reductions from baseline on the Hamilton Depression Rating Scale-21 (HAMD-21), the Clinical Global Impressions - Bipolar Severity of Illness (CGI-BP Severity), and the Positive and Negative Symptom Scale (PANSS) (total, positive, and negative).

Safety: Safety evaluations were based on records of vital signs, treatment-emergent adverse events (TEAEs), extrapyramidal symptoms (EPS), and laboratory analytes. Measures for EPS included the Simpson-Angus Scale for parkinsonism, the Barnes Akathisia Scale for akathisia, and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia.

Evaluation Methods:

Statistical: Analysis of variance was used to evaluate continuous data, and the model generally included the terms for treatment, investigator, and the treatment-by-investigator interaction. Fisher's exact test was used to evaluate categorical data. Analyses were performed on an intent-to-treat basis. All tests of hypotheses were tested at a 2-sided significance level of 0.05. Treatment-by-investigator interactions and heterogeneity across investigative sites were tested at a significance level of 0.10.

Summary:**Patient Disposition**

Table HGEH.1 summarizes the disposition of the patients randomized to therapy in the acute phase of the study and the reasons the patients discontinued from the study. Of the 139 patients randomized, 69 patients were randomized to the placebo treatment group, and 70 were randomized to the olanzapine treatment group. A significantly greater proportion of olanzapine-treated patients (61.4%) than placebo-treated patients (34.8%) completed the acute phase ($p=.002$). In addition, the percentage of patients who discontinued from the acute phase due to lack of efficacy was significantly smaller ($p=.024$) in the olanzapine treatment group (28.6%) than in the placebo treatment group (47.8%). No olanzapine-treated patient discontinued the acute phase for an adverse event, while 2.9% of the placebo-treated patients discontinued for an adverse event.

Table HGEH.1. Patient Disposition – Acute Phase

Reason for Discontinuation	Placebo (N=69) n (%)	Olz (N=70) n (%)	Total (N=139) n (%)	p-Value*
Reporting Interval Complete	24 (34.8)	43 (61.4)	67 (48.2)	.002
Adverse Event	2 (2.9)	0	2 (1.4)	.245
Lack of Efficacy	33 (47.8)	20 (28.6)	53 (38.1)	.024
Lost to Follow-up	1 (1.4)	0	1 (0.7)	.496
Patient Decision	4 (5.8)	6 (8.6)	10 (7.2)	.745
Criteria not met / Compliance	1 (1.4)	1 (1.4)	2 (1.4)	1.00
Sponsor Decision	3 (4.3)	0	3 (2.2)	.120
Physician Decision	1 (1.4)	0	1 (0.7)	.496

*Frequencies analyzed using the Fisher's Exact Test

Table HGEH.2 summarizes the disposition of the patients in the open-label phase of the study and the reasons the patients discontinued. The number of patients who discontinued from the study due to adverse events was 7 (6.2%). The number of patients who discontinued from the open-label phase of the study due to lack of efficacy was 14 (12.4%).

Table HGEH.2. Patient Disposition – Open-Label Phase

Reason for Discontinuation	Olz (N=113) n (%)
Protocol Complete	45 (39.8)
Adverse Event	7 (6.2)
Lack of Efficacy	14 (12.4)
Lost to Follow-up	6 (5.3)
Patient Decision	22 (19.5)
Criteria not met / Compliance	13 (11.5)
Physician Decision	6 (5.3)

Patient Characteristics

Table HGEH.3 summarizes the physical characteristics of patients in the acute phase of the study. Patients had a mean age of 39.49 years; 72.7% were Caucasian, and 51.8% were male. The treatment groups were comparable at baseline with respect to mean age, ethnic origin, and sex.

Table HGEH.3. Physical Characteristics – Acute Phase

Variable	Placebo (N=69)	Olz (N=70)	Total (N=139)	p-Value
Sex: No. (%)				
No. Patients	69	70	139	.735*
Male	37 (53.6)	35 (50.0)	72 (51.8)	
Female	32 (46.4)	35 (50.0)	67 (48.2)	
Origin: No. (%)				
No. Patients	69	70	139	.776*
Caucasian	48 (69.6)	53 (75.7)	101 (72.7)	
African Descent	15 (21.7)	13 (18.6)	28 (20.1)	
Hispanic	5 (7.2)	4 (5.7)	9 (6.5)	
Other Origin	1 (1.4)	0	1 (0.7)	
Age: years.				
No. Patients	69	70	139	.959**
Mean	38.72	40.25	39.49	
Median	40.08	39.77	40.08	
Standard Dev.	10.35	11.59	10.98	
Minimum	18.88	18.15	18.15	
Maximum	62.58	64.48	64.48	

* Frequencies are analyzed using a Fisher's exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

Table HGEH.4 summarizes the physical characteristics of patients in the open-label phase of the study. Patients had a mean age of 38.61 years; 51.3% were male, and most (74.3%) were Caucasian.

Table HGEH.4. Physical Characteristics – Open-Label Phase

Variable	Olz (N=113)
Sex: No. (%)	
No. Patients	113
Male	58 (51.3)
Female	55 (48.7)

Origin: No. (%)

No. Patients	113
Caucasian	84 (74.3)
African Descent	22 (19.5)
Hispanic	6 (5.3)
Other Origin	1 (0.9)

Age:years.

No. Patients	113
Mean	38.61
Median	39.12
Standard Dev.	10.85
Minimum	18.15
Maximum	64.48

Illness Characteristics

Table HGEH.5 summarizes the illness characteristics of patients in the acute phase of the study. In the acute phase, 82.7% of the patients were bipolar manic, and 17.3% were bipolar mixed. Overall, 32.4% of the patients were rapid cyclers, and 53.2% were currently psychotic. Of those psychotic patients, 85.1% experienced mood-congruent psychotic features. The treatment groups were comparable at baseline with respect to all variables measured.

Table HGEH.5. Illness Characteristics – Acute Phase

Variable	Placebo (N=69)	Olz (N=70)	Total (N=139)	p-Value
Current Episode-Bplr Mixed(M) vs Bplr Manic(P)				
No. Patients	69	70	139	1.00*
M	12 (17.4)	12 (17.1)	24 (17.3)	
P	57 (82.6)	58 (82.9)	115 (82.7)	
Current Episode - Psychotic vs Nonpsychotic				
No. Patients	69	70	139	.866*
N	33 (47.8)	32 (45.7)	65 (46.8)	
Y	36 (52.2)	38 (54.3)	74 (53.2)	
Psychosis Mood-Congruent vs Mood-Incongruent				
No. Patients	36	38	74	.108*
N	8 (22.2)	3 (7.9)	11 (14.9)	
Y	28 (77.8)	35 (92.1)	63 (85.1)	
Length of Current Episode (Days)				
No. Patients	69	70	139	.227**
Mean	53.65	51.06	52.35	
Median	32.00	31.50	32.00	
Standard Dev.	48.47	51.16	49.68	
Minimum	7.00	14.00	7.00	
Maximum	212.00	292.00	292.00	
Age of Onset of Illness				
No. Patients	68	69	137	.373**
Mean	23.29	25.78	24.55	
Median	20.50	24.00	22.00	
Standard Dev.	8.30	10.09	9.30	
Minimum	7.00	10.00	7.00	
Maximum	53.00	50.00	53.00	
Unspecified	1	1	2	
Number of prev. episodes of mania - lifetime				
No. Patients	65	64	129	.815**
Mean	19.49	17.44	18.47	
Median	8.00	10.00	10.00	
Standard Dev.	32.52	24.80	28.86	
Minimum	0.00	0.00	0.00	
Maximum	200.00	130.00	200.00	
Unspecified	4	6	10	

Number of prev. episodes of depression - lifetime

No. Patients	65	66	131	.629**
Mean	18.11	13.06	15.56	
Median	5.00	4.50	5.00	
Standard Dev.	34.68	24.32	29.90	
Minimum	0.00	0.00	0.00	
Maximum	175.00	130.00	175.00	
Unspecified	4	4	8	

Number of previous mixed episodes - lifetime

No. Patients	66	65	131	.297**
Mean	10.95	6.54	8.76	
Median	1.50	1.00	1.00	
Standard Dev.	35.45	15.17	27.33	
Minimum	0.00	0.00	0.00	
Maximum	264.00	100.00	264.00	
Unspecified	3	5	8	

Number of rapid cyclers

No. Patients	69	70	139	.208*
N	43 (62.3)	51 (72.9)	94 (67.6)	
Y	26 (37.7)	19 (27.1)	45 (32.4)	

Y = Yes, N = No, U = Unknown, - = Not Applicable

* Frequencies are analyzed using a Fisher's exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

Table HGEH.6 summarizes the illness characteristics of patients in the open-label phase of the study. Of the 113 patients who continued into the open-label phase, 82.3% were bipolar manic, and 17.7% were bipolar mixed. Overall, 34.5% of the patients had a rapid-cycling course, and 54.0% were currently psychotic. Of those psychotic patients, 88.5% experienced mood-congruent psychotic features.

Table HGEH.6. Illness Characteristics – Open-Label Phase

Variable	Olz (N=113)

Current Episode-Bplr Mixed(M) vs Bplr Manic(P)	
No. Patients	113
M	20 (17.7)
P	93 (82.3)
Current Episode - Psychotic vs Nonpsychotic	
No. Patients	113
N	52 (46.0)
Y	61 (54.0)
Psychosis Mood-Congruent vs Mood-Incongruent	
No. Patients	61
N	7 (11.5)
Y	54 (88.5)
Length of Current Episode (Days)	
No. Patients	113
Mean	53.98
Median	33.00
Standard Dev.	51.13
Minimum	7.00
Maximum	292.00
Age of Onset of Illness	
No. Patients	111
Mean	24.23
Median	22.00
Standard Dev.	8.94
Minimum	10.00
Maximum	50.00
Unspecified	2

Number of prev. episodes of mania - lifetime

No. Patients	103
Mean	19.94
Median	10.00
Standard Dev.	31.47
Minimum	0.00
Maximum	200.00
Unspecified	10

Number of prev. episodes of mania - last 12 months

No. Patients	112
Mean	2.87
Median	1.00
Standard Dev.	5.02
Minimum	0.00
Maximum	36.00
Unspecified	1

Number of prev. episodes of depression - lifetime

No. Patients	105
Mean	17.43
Median	5.00
Standard Dev.	32.52
Minimum	0.00
Maximum	175.00
Unspecified	8

Number of prev. episodes of depression - last 12 m

No. Patients	112
Mean	1.96
Median	0.00
Standard Dev.	4.14
Minimum	0.00
Maximum	24.00
Unspecified	1

Number of previous mixed episodes - lifetime

No. Patients	105
Mean	9.42
Median	1.00
Standard Dev.	30.05
Minimum	0.00
Maximum	264.00
Unspecified	8

Number of previous mixed episodes - last 12 month

No. Patients	111
Mean	1.69
Median	0.00
Standard Dev.	4.02
Minimum	0.00
Maximum	30.00
Unspecified	2

Number of rapid cyclers

No. Patients	113
N	74 (65.5)
Y	39 (34.5)

Y = Yes, N = No, U = Unknown, - = Not Applicable

Efficacy Results

Table HGEH.7 shows summary statistics and statistical evaluations of change from baseline to endpoint in efficacy and quality-of-life measures for the acute phase of the study. The primary efficacy analysis was the LOCF change from baseline to Week 3 of therapy in YMRS total scores. The olanzapine (Olz) treatment group experienced a statistically significantly greater mean improvement in YMRS total score than the placebo (Pla) treatment group ($p=.019$). The Olz treatment group also had a statistically significantly greater mean improvement in the CGI-BP Severity of mania score ($p=.019$), the PANSS total score ($p=.019$), and the PANSS positive score ($p=.040$) compared with the placebo treatment group.

Table HGEH.7. Mean Change Scores – Acute Phase

Measure	Therapy	n	Baseline		Change to Endpoint		p-Value
			Mean	SD	Mean	SD	
YMRS total score	Olz	70	28.66	6.71	-10.26	13.43	.019
	Pla	66	27.65	6.46	-4.88	11.64	
HAM-D-21 total score	Olz	69	12.58	7.15	-2.90	6.74	.871
	Pla	65	13.98	6.69	-3.00	6.00	
PANSS total score	Olz	70	71.04	18.74	-11.06	16.98	.019
	Pla	64	70.97	21.04	-3.09	18.37	
PANSS positive score	Olz	70	20.90	6.59	-4.67	6.57	.040
	Pla	64	20.72	7.01	-2.00	7.10	
PANSS negative score	Olz	70	13.51	5.45	-0.90	4.26	.397
	Pla	64	13.94	5.69	-0.19	4.23	
CGI overall score	Olz	70	4.46	0.88	-0.89	1.39	.150
	Pla	66	4.68	0.83	-0.59	1.30	
CGI mania score	Olz	70	4.51	0.86	-1.07	1.60	.019
	Pla	66	4.62	0.87	-0.48	1.37	
CGI depression score	Olz	70	1.71	0.97	0.06	1.17	.144
	Pla	66	2.11	1.29	-0.30	1.15	

Abbreviations: CGI = Clinical Global Impressions; HAM-D-21 = Hamilton-Depression Rating Scale-21; n = number; Olz = olanzapine; PANSS = Positive and Negative Symptom Scale; Pla = placebo; SD = standard deviation; YMRS = Young Mania Rating Scale.

Table HGEH.8 shows summary statistics and statistical evaluations of change from baseline to endpoint in efficacy measures for the open-label phase of the study. The YMRS total scores statistically significantly decreased from baseline to endpoint. In addition, 60.6% of patients were classified as responders in the open-label phase. Response was defined as a decrease of 50% or more in YMRS total score from baseline to endpoint. Patients achieving a YMRS score of 12 or less at any time in the open-label phase were considered to be in remission of mania. The remission criterion for mania was met in 97 of 109 (89.0%) patients at some point during open-label therapy. The majority of these remissions occurred within the first 25 days of open-label therapy. A relapse to mania was defined as achieving a YMRS score of 15 or more after a period of symptomatic remission at any time in the open-label phase. The relapse criterion for mania was met in 22 of 94 (23.4%) patients at some point during open-label therapy.

The HAMD-21 total scores were statistically significantly reduced from baseline during the open-label phase. A relapse of depression was defined to be a patient achieving a HAMD-21 total score of 15 or more after a period of symptomatic remission at any time in the open-label phase. The relapse criterion for depression was met in 17 of 95 (17.9%) patients at some point during open-label therapy.

Statistically significant changes from baseline to endpoint were also seen during the open-label phase in CGI-BP Severity of mania scores; CGI-BP Severity of overall bipolar scores; and PANSS total, positive, and negative scores.

Table HGEH.8. Efficacy Scores

Mean Change from Baseline to Endpoint – Open-Label Phase

		-----Baseline-----		Change to -----Endpoint-----		p-Value	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Within Group
YMRSTOT	Olz	109	19.28	14.34	-11.80	13.46	<.001
HAMD21TO	Olz	109	10.08	7.05	-3.69	7.31	<.001
CS_MANIA	Olz	110	3.63	1.60	-1.52	1.65	<.001
CS_DEPR	Olz	110	1.80	1.11	0.10	1.53	0.495
CS_OVER	Olz	110	3.67	1.55	-1.17	1.57	<.001
PANSSTOT	Olz	109	61.61	25.04	-14.60	22.90	<.001
PANSSPS	Olz	109	16.61	8.58	-5.73	7.96	<.001
PANSSNG	Olz	109	12.84	5.88	-1.89	5.61	<.001
CS_DEPR	CGI-BP Severity of Depression						
CS_MANIA	CGI-BP Severity of Mania						
CS_OVER	CGI-BP Severity of Overall Bipolar Illness						
HAMD21TO	HAMD21TO: Total Score						
PANSSNG	PANSS Negative Total						
PANSSPS	PANSS Positive Total						
PANSSTOT	PANSS Total						
YMRSTOT	Y-MRSTOT: Total						

Safety ResultsDose:

The mean modal dose of olanzapine during the acute phase of the study was 14.9 mg/day. The mean modal dose during the open-label phase of the study was 13.8 mg/day.

Treatment-Emergent Adverse Events:

Table HGEH.9 shows TEAEs ($\geq 10\%$ incidence, or $p < 0.05$) reported by all patients in the acute phase of the study, ordered by decreasing frequency within the olanzapine treatment group. The most commonly reported TEAEs among olanzapine-treated patients were somnolence, dry mouth, dizziness, agitation, asthenia, headache, anxiety, depression, constipation, pain, and weight gain. The TEAEs somnolence, dry mouth, dizziness, and weight gain occurred statistically significantly more frequently in the olanzapine treatment group than in the placebo treatment group. No other TEAE occurred at a rate statistically significantly different between the olanzapine and placebo treatment groups.

**Table HGEH.9. Treatment-Emergent Adverse Events
by Decreasing Frequency – Olanzapine, Acute Phase**

Event Classification	Placebo			Olanzapine			Total			Fishers Exact p-Value
	N	n	(%)	N	n	(%)	N	n	(%)	
PATIENTS WITH ≥ 1 TESS	69	62	89.9%	70	64	91.4%	139	126	90.6%	.779
PATIENTS WITH NO TESS	69	7	10.1%	70	6	8.6%	139	13	9.4%	.779
SOMNOLENCE	69	12	17.4%	70	23	32.9%	139	35	25.2%	.050
DRY MOUTH	69	6	8.7%	70	18	25.7%	139	24	17.3%	.012
DIZZINESS	69	4	5.8%	70	16	22.9%	139	20	14.4%	.007
AGITATION	69	16	23.2%	70	13	18.6%	139	29	20.9%	.537
ASTHENIA	69	5	7.2%	70	13	18.6%	139	18	12.9%	.075
HEADACHE	69	11	15.9%	70	12	17.1%	139	23	16.5%	1.000
ANXIETY	69	7	10.1%	70	10	14.3%	139	17	12.2%	.606
DEPRESSION	69	8	11.6%	70	9	12.9%	139	17	12.2%	1.000
CONSTIPATION	69	2	2.9%	70	8	11.4%	139	10	7.2%	.097
PAIN	69	3	4.3%	70	8	11.4%	139	11	7.9%	.208
WEIGHT GAIN	69	1	1.4%	70	8	11.4%	139	9	6.5%	.033
DYSPEPSIA	69	2	2.9%	70	6	8.6%	139	8	5.8%	.275

Olanzapine; N = total number of patients; n = number of patients reporting event.

Table HGEH.10 shows the most common TEAEs ($\geq 10\%$ incidence) reported by patients in the open-label phase of the study.

**Table HGEH.10. Treatment-Emergent Adverse Events by Decreasing Frequency –
Open-Label Phase**

Event Classification	N	n	(%)
PATIENTS WITH ≥ 1 TESS	113	100	88.5%
PATIENTS WITH NO TESS	113	13	11.5%
DEPRESSION	113	39	34.5%
SOMNOLENCE	113	36	31.9%
WEIGHT GAIN	113	36	31.9%
INCREASED APPETITE	113	22	19.5%
ASTHENIA	113	20	17.7%
RHINITIS	113	20	17.7%
DRY MOUTH	113	17	15.0%
INSOMNIA	113	17	15.0%
PAIN	113	16	14.2%
HEADACHE	113	15	13.3%
AGITATION	113	12	10.6%
ANXIETY	113	12	10.6%

Extrapyramidal Symptoms:

In both phases of the study, treatment-emergent parkinsonism was defined as a change in Simpson-Angus total score from ≤ 3 at baseline to a score > 3 at any postbaseline visit, and treatment-emergent akathisia was defined as a score of < 2 at baseline to a score of ≥ 2 at any postbaseline visit.

Table HGEH.11 shows the incidence of treatment-emergent EPS for patients in the acute phase of the study. For each measure, only patients with both a baseline and at least 1 postbaseline measure were included. The numbers and percentages of patients with treatment-emergent parkinsonism were 7 of 62 (11.3%) olanzapine-treated patients and 4 of 59 (6.8%) placebo-treated patients. There was no statistically significant difference in these percentages ($p=.531$). The numbers and percentages of patients treatment-emergent akathisia were 9 of 58 (15.5%) olanzapine-treated patients and 4 of 53 (7.5%) placebo-treated patients. There was no statistically significant difference in these percentages ($p=.244$).

Table HGEH.11. Treatment-Emergent Extrapyramidal Symptoms – Acute Phase

EPS	Pla N	Pla n	Pla (%)	Olz N	Olz n	Olz (%)	p-Value
Parkinsonism	59	4	6.8%	62	7	11.3%	.531
Akathisia	53	4	7.5%	58	9	15.5%	.244

Abbreviations: EPS = extrapyramidal symptoms; N = number of patients with at least 1 baseline and 1 postbaseline measure; n = number of patients with treatment-emergent symptoms; Olz = olanzapine; Pla = placebo.

Table HGEH.12 shows the incidence of treatment-emergent EPS for patients in the open-label phase of the study. For each measure, only patients with both a baseline and at least 1 postbaseline measure were included. The number of patients with treatment-emergent parkinsonism at any time during the open-label extension was 7 of 81 (8.6%), and this rate is lower than that of the olanzapine-treated patients during the acute phase of the study. The number of patients with treatment-emergent akathisia at any time during the open-label extension was 10 of 73 (13.7%), and this rate is lower than that of the olanzapine-treated patients during the acute phase of the study.

Long-term treatment-emergent dyskinetic symptoms were defined as a score of 3 or more on any 1 of the AIMS items 1 through 7 or a score of 2 or more on any 2 of the AIMS items 1 through 7 without either of these criteria at baseline. The numbers and percentages of patients with long-term treatment-emergent dyskinetic symptoms at any postbaseline visit were 3 of 105 (2.9%).

Table HGEH.12. Treatment-Emergent Extrapyramidal Symptoms – Open-Label Study Phase

EPS	N	n	Olz (%)
Parkinsonism	81	7	8.6%
Akathisia	73	10	13.7%
Dyskinesia	105	3	2.9%

Abbreviations: EPS = extrapyramidal symptoms; N = number of patients with baseline and postbaseline measures; n = number of patients with treatment-emergent symptoms; Olz = olanzapine.

Clinical Laboratory Values:

A treatment-emergent abnormal value was defined as a change from normal at baseline to abnormal at any time during the acute phase. A treatment-emergent high value was defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the acute phase. A treatment-emergent low value was defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the acute phase.

Table HGEH.13 summarizes the analysis of treatment-emergent abnormal, high, or low laboratory values (based on Lilly reference ranges) at any time among patients in the acute phase. The only statistically significant differences between treatment groups occurred in alanine transaminase (ALT/SGPT) and inorganic phosphorus. Patients in the Olz treatment group had a statistically significantly ($p < .001$) larger incidence of increased ALT/SGPT than patients in the placebo treatment group (17.6% versus 0%). Patients in the Olz treatment group had a statistically significantly ($p = .030$) larger incidence of increased inorganic phosphorus than patients in the placebo treatment group (17.9% versus 5.1%).

Table HGEH.13. Treatment-Emergent Abnormal, High, or Low Laboratory Values at Any Time – Acute Phase

Name of Lab Test	Direction	Placebo			Olz			Fisher's Exact p-Value
		N	n	(%)	N	n	(%)	
ALT/SGPT	High	61	0	0.0%	68	12	17.6%	<.001
AST/SGOT	High	61	0	0.0%	69	3	4.3%	.247
BILIRUBIN, TOTAL	High	62	0	0.0%	68	0	0.0%	
CHOLESTEROL	High	62	2	3.2%	70	1	1.4%	.600
EOSINOPHILS	High	61	0	0.0%	66	2	3.0%	.497
GLUCOSE, NON-FASTING	High	60	1	1.7%	70	1	1.4%	1.00
INORGANIC PHOSPHORUS	High	59	3	5.1%	67	12	17.9%	.030
NEUTROPHILS, SEGMENTED	Low	62	1	1.6%	66	1	1.5%	1.00
UA-WBC	ABNM	56	4	7.1%	63	2	3.2%	.418

Abbreviations: ABNM = abnormal; ALT/SGPT = alanine transaminase; AST/SGOT = aspartate transaminase; Olz = olanzapine.

Table HGEH.14 summarizes treatment-emergent abnormal, high, or low values at any time during the open-label phase. Increased ALT/SGPT (17.0%) and abnormal urinary protein (12.0%) were the most common (incidence $\geq 10\%$) treatment-emergent categorical changes observed in olanzapine-treated patients.

Table HGEH.14. Treatment-Emergent Abnormal High or Low Laboratory Analytes at Any Time – Open-Label Phase

Name of Lab Test	Direction	N	n	(%)
ALT/SGPT	High	94	16	17.0%
AST/SGOT	High	104	10	9.6%
BILIRUBIN, TOTAL	High	108	4	3.7%
CHOLESTEROL	High	83	1	1.2%
EOSINOPHILS	High	83	1	1.2%

GLUCOSE, NON-FASTING	High	82	2	2.4%
NEUTROPHILS, SEGMENTED	Low	86	1	1.2%
UA-PROTEIN	ABNM	83	10	12.0%
UA-WBC	ABNM	75	3	4.0%

Abbreviations: ABNM = abnormal; ALT/SGPT = alanine transaminase; AST/SGOT = aspartate transaminase; N = total number of patients with baseline and postbaseline measures; n = total number of patients with abnormal measure; UA = urine analysis; WBC = white blood cell count.

Vital Signs and Weight:

In both phases of the study, a potentially clinically significant change in orthostatic blood pressure was ≥ 30 mm Hg decrease in systolic blood pressure. A potentially clinically significant weight increase was $\geq 10\%$. A potentially clinically significant change in corrected QT (QTc) interval was a value ≥ 430 msec at any time during the extension phase, given that it was below this threshold at baseline.

Statistically significant differences between treatment groups were seen in mean weight change from baseline to endpoint ($p < .001$) in the acute phase of the study. The mean weight change for olanzapine-treated patients was 1.65 kg, while the mean weight change for placebo-treated patients was -0.44 kg.

Table HGEH.15 shows the proportions of patients with potentially clinically significant changes in vital signs or weight at any time during the acute phase of the study. There were no statistically significant differences between treatment groups.

Table HGEH.15. Potentially Clinically Significant Change in Vital Signs and Weight – Acute Phase

Vital	Direction	Placebo			Olz			Fisher's Exact p-Value
		N	n	(%)	N	n	(%)	
Orthostatic Sys BP	Decrease	63	2	3.2%	68	3	4.4%	1.00
Weight (kg)	Gain	60	0	0.0%	69	0	0.0%	
	Loss	60	0	0.0%	69	0	0.0%	
ECG QT corrected	High	42	3	7.1%	48	8	16.7%	.209

Abbreviations: Olz = olanzapine.

During the open-label phase, olanzapine-treated patients experienced a statistically significant within-group increase from baseline to endpoint in weight (5.81 kg, $p < .001$).

Table HGEH.16 shows the proportions of patients with potentially clinically significant changes in vital signs or weight at any time during the open-label phase of the study. The most frequently observed potentially clinically significant change in olanzapine-treated patients was an increase in the QTc interval (10.3%). Given that 10.3% (7 of 68) of the patients in the olanzapine-treated group showed a potentially clinically significant change in the QTc interval from < 430 msec to ≥ 430 msec, these 7 patients were reviewed in detail, and the incidence of QTc prolongation at baseline was considered. Of these 7 patients, only 1 (1.5% of the total 68) experienced a QTc increase to ≥ 450 msec. None of these patients experienced an increase in absolute QT interval to ≥ 450 msec.

Table HGEH.16. Incidence of Potentially Clinically Significant Change in Vital Signs and Weight – Open-Label Phase

Vital	Direction	Therapy	N	n	(%)
Orthostatic Sys BP	Decrease	Olz	107	1	0.9%
Weight (kg)	Gain	Olz	109	3	2.8%
	Loss	Olz	109	1	0.9%
ECG QT corrected	High	Olz	68	7	10.3%

Abbreviations: Olz = olanzapine.

Other Safety Findings:

No patients died during the acute phase of the study. No olanzapine-treated patients experienced a serious adverse event, while 5 placebo-treated patients experienced a total of 14 serious adverse events. In addition, no olanzapine-treated patient discontinued due to an adverse event, while 2 placebo-treated patients discontinued because of an adverse event.

No olanzapine-treated patient died during the open-label phase of the study. However, 1 death occurred 1 day after the patient completed the open-label phase of Study FID-MC-HGEH. The death appeared unrelated to olanzapine. No patients experienced an adverse event that was serious, unexpected, and possibly causally related to study drug during or within 30 days of discontinuation from the trial.

Summary of Results:

The primary efficacy measure in the acute phase was the LOCF comparison of mean change from baseline to endpoint in YMRS total score. In this analysis, the improvement in the olanzapine treatment group was significantly greater than in the placebo treatment group (Olz, -10.26; Pla, -4.88; $p=.019$). The antimanic effects of olanzapine were further demonstrated in the acute phase by the fact that the olanzapine-treated patients had a significantly greater mean decrease from baseline in CGI-BP Severity of mania scores compared with the placebo-treated patients ($p=.019$). The significantly greater reduction in PANSS total scores ($p=.019$) in the olanzapine treatment group demonstrated olanzapine's efficacy in improving psychotic symptoms in manic patients.

The primary objective of the open-label phase was to assess the efficacy of open-label olanzapine (5, 10, 15, or 20 mg/day) in the long-term treatment of patients with bipolar I disorder in improving clinical symptomatology. The primary efficacy analysis was the mean change in YMRS total score from baseline to endpoint, LOCF. The YMRS total scores statistically significantly decreased from baseline to endpoint. In addition, 60.6% of patients were classified as responders at endpoint of the open-label phase. The remission criterion for mania was met in 97 of 109 (89.0%) patients at some point during open-label therapy. The majority of these remissions occurred within the first 25 days of open-label therapy. The relapse criterion for mania was met in 22 of 94 (23.4%) patients. The relapse criterion for depression was met in 17 of 95 (17.9%) patients at some point during open-label therapy.

The antimanic effect of olanzapine was further demonstrated during the open-label phase by the fact that the CGI-BP Severity of mania scores had a statistically significant mean change from baseline to endpoint. Also, the CGI-BP Severity of overall bipolar illness scores statistically significantly decreased from baseline to endpoint. The results of the PANSS analysis provide evidence of olanzapine's improvement of psychotic symptoms in manic patients. PANSS total, positive, and negative scores had a statistically significant mean change from baseline to endpoint. In addition, the HAM-D-21 total scores were statistically significantly reduced from baseline.

During the open-label phase, olanzapine-treated patients experienced a statistically significant within-group increase from baseline to endpoint in weight (5.81 kg). The most frequently observed potentially clinically significant change in olanzapine-treated patients was an increase in the QTc interval (10.3%), but comparison with previously observed rates in the placebo-controlled portion of the study suggests that the rates are comparable in incidence with those observed in the bipolar population at baseline. No olanzapine-treated patients discontinued because of an adverse event associated with electrocardiograms.