

Summary ID #1032

Clinical Study Summary: Study F1D-MC-HGEU

Title of Study: Olanzapine Versus Placebo in the Treatment of Psychosis and Behavioral Disturbances Associated with Alzheimer's Disease	
Investigator(s): This multicenter study included 29 principal investigators.	
Study Center(s): This study was conducted at 28 study center(s).	
Length of Study: 18 months Date first patient enrolled: 30 December 1996 Date last patient completed acute phase: 02 June 1998 Date last patient completed open-label extension: 06 October 1998	Phase of Development: 3
<p>Objectives, Acute Phase: The primary objective of this study was to assess the efficacy of 5, 10, or 15 mg/day of olanzapine compared with placebo in the treatment of psychiatric symptoms (including psychosis) and behavioral disturbances associated with moderate to severe dementia in patients who met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible or probable Alzheimer's disease. Reductions of mean score from baseline to endpoint on the sum of the agitation, delusions, and hallucinations items of the Neuropsychiatric Inventory Nursing Home version (NPI/NH) after 6 weeks of therapy was the primary efficacy measure.</p> <p>Secondary objectives included assessing the safety of treatment and the effects of treatment on occupational disruptiveness, cognitive function, attention/concentration, changes in severity of global psychopathology, severity of Alzheimer's disease and behavioral disturbances, mood, and quality of life.</p> <p>Objectives, Open-Label Extension: The primary objective of the extension phase of this trial was to assess the long-term safety and efficacy of open-label olanzapine (flexible dose) over up to 18 weeks of additional treatment.</p>	
<p>Study Design: This protocol was designed as a multicenter, randomized, double-blind, placebo-controlled study of approximately 200 nursing home patients, aged 40 years and older, who were exhibiting clinically significant psychiatric symptoms (including psychosis) and behavioral disturbances associated with Alzheimer's disease. After a 3- to 14-day placebo lead-in period, patients who met the criteria for enrollment were assigned by random allocation to 1 of 4 treatment groups in the 6-week, double-blind, acute therapy period of the study (Study Period II): olanzapine 5 mg/day, olanzapine 10 mg/day, olanzapine 15 mg/day, or placebo. Patients randomized to the 10- and 15-mg/day treatment groups began treatment with 5 mg/day and were titrated to the target dose by increasing the dose in 5-mg/day increments every 7 days. Randomization was performed to allow equal distribution of patients among the four treatment groups.</p> <p>Patients who completed Study Period II (through Visit 8) had the opportunity to continue into Study Period III and receive open-label olanzapine 5, 10, or 15 mg/day for up to 18 weeks.</p>	

Number of Patients:**Acute Phase:**

Planned: 200 (50 in each of four treatment groups)

Olz5.0: 56 randomized; 45 completed

Olz10.0: 50 randomized; 36 completed

Olz15.0: 53 randomized; 36 completed

Placebo: 47 randomized; 35 completed

Overall: 206 randomized; 152 completed.

Note: During data analysis, one patient from the placebo treatment group was erroneously assessed as part of the Olz15.0 treatment group. As a result of this error, the acute phase data tables in this summary contain 54, rather than 53, patients in the Olz15.0 treatment group and 46, rather than 47, patients in the placebo treatment group. Subsequent calculations based on the number of patients in each treatment group are slightly off but do not change any statistically significant conclusions.

Open-Label Extension:

137 entered, 85 completed.

Diagnosis and Main Criteria for Inclusion: Patients were male and female nursing home patients at least 40 years of age with possible or probable Alzheimer's disease, as defined by NINCDS-ADRDA criteria. Patients needed to have a total score ≥ 3 on any of the agitation, delusions, or hallucinations items of the NPI/NH at both Visits 1 and 2. Patients were excluded if they fulfilled DSM-IV diagnostic criteria for delirium or if they had any other diagnosis of a serious neurologic condition other than Alzheimer's disease. Patients with a score >24 on the Mini-Mental State Examination (MMSE) at Visits 1 and 2 were also excluded, as were bedridden patients.

Additionally, in order to meet randomization criteria at Visit 2, patients were excluded if they showed placebo response, as determined by a $\geq 50\%$ decrease from Visit 1 to Visit 2 in the sum of the agitation, delusions, and hallucinations items of the NPI/NH.

Patients who completed the 6 week acute phase of the study (Study Period II) were eligible to enter the open-label extension.

Test Product, Dose, and Mode of Administration: Olanzapine 5, 10, or 15 mg/day, given orally once per day.

Duration of Treatment: 6 weeks of double-blind treatment with olanzapine (5, 10, or 15 mg/day) or placebo.

Reference Therapy, Dose, and Mode of Administration: Placebo given orally once per day

Variables

Efficacy: Reductions of mean score from baseline to endpoint on the sum of the agitation, delusions, and hallucinations items of the NPI/NH served as the primary efficacy criterion. Secondary assessments included mean change from baseline to endpoint in the individual items, the total score, and the total occupational disruptiveness of the NPI/NH; cognitive function assessment using the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and the MMSE; assessment of attention/concentration using the Cancellation Test, a supplement to the ADAS-Cog; changes in severity of global psychopathology using the Brief Psychiatric Rating Scale (BPRS) total and subscale scores; assessment of both the severity of Alzheimer's disease and behavioral disturbances using the Clinical Global Impression Scales; and mood assessment (using the Montgomery - Asberg Depression Rating Scale [MADRS]). For patients who were randomized to receive olanzapine in the acute phase of the study, baseline was defined as the measurement at Visit 2 (visit at which randomization occurred) for the extension-phase analyses. For patients who were randomized to receive placebo in the acute phase of the study, baseline for the open-label period was defined as the measurement at Visit 8 (the last assessment prior to starting open-label olanzapine treatment).

Safety: Safety evaluations were based on records of treatment-emergent adverse events (TEAEs), change in vital signs and laboratory analytes, and severity of extrapyramidal symptoms (EPS). Measures for EPS included the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS). A hepatitis screen and thyroid function test were performed at Visit 1 and as clinically indicated throughout the study. At Visit 1, a medical history, physical examination, and an electrocardiogram (ECG) were performed. The physical examination and ECG were also performed at study completion.

For all patients, the baseline for safety analyses during the open-label extension was defined as the measurement at Visit 8 (the last assessment prior to starting open-label olanzapine treatment).

Health Outcomes: Quality of life was assessed for mean change from baseline to endpoint using the Medical Outcomes Study 36-Item Short Form Health Survey (SF36).

Evaluation Methods:

Analysis of variance was used to evaluate continuous data, and the model generally included the terms for treatment, investigator, and treatment-by-investigator interaction. Fisher's exact test was used to evaluate categorical data.

Patient data were analyzed on an intent-to-treat basis. For analysis of last observation carried forward (LOCF) mean change from baseline to endpoint, patients with a baseline and at least one postbaseline measurement were included in the analysis.

Summary: (continued on following pages)

Note: During data analysis, one patient from the placebo treatment group was erroneously assessed as part of the Olz15.0 treatment group. As a result of this error, the acute phase data tables in this summary contain 54, rather than 53, patients in the Olz15.0 treatment group and 46, rather than 47, patients in the placebo treatment group. Subsequent calculations based on the number of patients in each treatment group are slightly off but do not change any statistically significant conclusions.

Summary and Conclusions

Patient Disposition

Acute Phase

A total of 288 patients entered the washout and placebo lead-in period of this study (Study Period I). Of these patients, 206 were randomized in the double-blind acute therapy phase (Visit 2, Study Period II). More than half (152) of those patients completed the acute phase. There were no statistically significant differences in the proportion of patients completing the acute phase of the study between the olanzapine treatment groups and the placebo treatment group.

Open-Label Extension

A total of 137 patients qualified for and entered the open-label extension (Study Period III). Of these patients, more than half (85 patients) completed the open-label extension.

Patient and Illness Characteristics

Acute Phase

Tables HGEU.1 and HGEU.2 present patient and illness characteristics for the acute phase of the study. Patients had a mean age of 82.8 years, 92.7% were Caucasian, and 61.2% were female. The treatment groups were comparable at baseline with respect to gender, origin, and age. The average time since nursing home admission to entry into the study was 1.6 years (581.41 days), and there were no significant differences in this time among treatment groups. The average time since onset of first definite symptom to entry into the study was 4.8 years (1762.83 days). While this characteristic varied among treatment groups, the placebo group was not significantly different from any of the olanzapine groups. The average time since date of diagnosis to entry into the study was 2.2 years (803.92 days). This characteristic also varied among treatment groups, but the placebo group was not significantly different from any of the olanzapine groups.

**Table HGEU.1. Patient Characteristics
F1D-MC-HGEU, Acute Phase**

Variable	Placebo (N=46)	Olz5.0 (N=56)	Olz10.0 (N=50)	Olz15.0 (N=54)	Total (N=206)	p-Value
Sex: No. (%)						
No. Patients	46	56	50	54	206	.808*
Male	17 (37.0)	23 (41.1)	17 (34.0)	23 (42.6)	80 (38.8)	
Female	29 (63.0)	33 (58.9)	33 (66.0)	31 (57.4)	126 (61.2)	
Origin: No. (%)						
No. Patients	46	56	50	54	206	.524*
Caucasian	44 (95.7)	49 (87.5)	48 (96.0)	50 (92.6)	191 (92.7)	
African Descent	2 (4.3)	5 (8.9)	2 (4.0)	4 (7.4)	13 (6.3)	
Hispanic	0	2 (3.6)	0	0	2 (1.0)	
Age:yrs.						
No. Patients	46	56	50	54	206	.347**
Mean	81.35	82.93	83.57	83.06	82.77	
Median	81.20	83.25	85.05	84.45	83.60	
Standard Dev.	6.78	6.47	6.52	6.65	6.60	
Minimum	61.70	67.80	65.50	67.70	61.70	
Maximum	94.60	94.30	97.70	94.30	97.70	

Abbreviations: Dev. = deviation; N = number of patients; No. = number; Olz5.0 = olanzapine 5 mg/day;
Olz10.0 = olanzapine 10 mg/day; Olz15.0 = olanzapine 15 mg/day; yrs = years.

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

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

**Table HGEU.2. Illness Characteristics
F1D-MC-HGEU, Acute Phase**

Variable	Placebo (N=46)	Olz5.0 (N=56)	Olz10.0 (N=50)	Olz15.0 (N=54)	Total (N=206)	p-Value
Time since Nursing Home Admission to Visit 1						
No. Patients	46	56	50	54	206	.611**
Mean	599.13	554.55	572.18	602.72	581.41	
Median	456.50	452.50	332.50	382.50	416.50	
Standard Dev.	561.02	456.51	581.44	621.46	553.23	
Minimum	31.00	13.00	9.00	14.00	9.00	
Maximum	2296.00	1974.00	2956.00	3189.00	3189.00	
Time since Onset of First Def Symptom to Visit 1						
No. Patients	45	54	48	52	199	.015**
Mean	1689.51	1579.89	1904.27	1885.71	1762.83	
Median	1519.00	1417.50	1404.50	1604.00	1502.00	
Standard Dev.	1050.84	1287.84	1819.25	1369.88	1406.23	
Minimum	198.00	203.00	64.00	176.00	64.00	
Maximum	4091.00	7067.00	9274.00	6859.00	9274.00	
Time since Date of Diagnosis to Visit 1						
No. Patients	45	53	49	54	201	.017**
Mean	816.62	596.06	972.10	844.74	803.92	
Median	585.00	452.00	654.00	585.00	567.00	
Standard Dev.	784.23	563.80	1029.37	861.41	829.31	
Minimum	1.00	1.00	1.00	1.00	1.00	
Maximum	3205.00	2109.00	5612.00	3936.00	5612.00	

Abbreviations: Dev. = deviation; N = number of patients; No. = number; Olz5.0 = olanzapine 5 mg/day;
Olz10.0 = olanzapine 10 mg/day; Olz15.0 = olanzapine 15 mg/day; yrs = years.

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

Open-Label Extension

Table HGEU.3 presents the patient characteristics for patients in the open-label extension phase of the study (Study Period III). Patients had a mean age of 83.1 years; 93.4% were Caucasian, and 62.8% were female.

**Table HGEU.3. Patient Characteristics
F1D-MC-HGEU, Open-Label Phase**

Variable	Olz (N=137)
Sex: No. (%)	
No. Patients	137
Male	51 (37.2)
Female	86 (62.8)
Origin: No. (%)	
No. Patients	137
Caucasian	128 (93.4)
African Descent	8 (5.8)
Hispanic	1 (0.7)
Age:yrs.	
No. Patients	137
Mean	83.13
Median	84.00
Standard Dev.	6.57
Minimum	65.50
Maximum	97.70

Abbreviations: Dev. = deviation; N = number of patients; No. = number; Olz = olanzapine.

Efficacy Results

Acute Phase

The primary efficacy analysis for the acute phase of the study was the LOCF change in the sum of the agitation, delusions, and hallucinations items of the NPI/NH scale (NPI/NH core total) from baseline to endpoint. Table HGEU.4 presents results from the primary efficacy analysis. For this primary analysis, there was a significant treatment effect. Both the olanzapine 5 mg/day and the olanzapine 10 mg/day treatment groups experienced a statistically significantly greater mean improvement in NPI/NH core total score than the placebo treatment group ($p<.001$ and $p=.006$, respectively).

Table HGEU.4. Primary Efficacy Scores
Mean change from baseline to endpoint
F1D-MC-HGEU, Acute Phase

				Change to		-----Baseline-----		-----Endpoint-----		- p-Values -	
Variables	Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy	Pair-	(Int*1)	wse*2
CORETOT		Placebo	44	14.43	8.56	-3.30	10.02	.002			
		Olz5.0	55	14.44	7.36	-7.62	7.74	(.239)	<.001		
		Olz10.0	49	14.10	7.41	-6.12	8.17		.006		
		Olz15.0	52	14.42	7.68	-5.21	8.04		.231		

Abbreviations: CORETOT = Core NPI/NH Total; n = number of patients; SD = standard deviation;
 Olz5.0 = olanzapine 5 mg/day; Olz10.0 = olanzapine 10 mg/day; Olz15.0 = olanzapine 15 mg/day.

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
 model=inv., treatment, and interaction.

*2 Least-squares mean option in PROC GLM from the ANOVA using the mean square for
 error.

Secondary efficacy analyses during the acute phase included comparisons of the treatment groups with regards to LOCF mean change from baseline to endpoint on the NPI/NH individual items, NPI/NH total score, NPI/NH two-item total for hallucinations and delusions, and NPI/NH occupational disruptiveness for agitation, delusions and hallucinations (NPI/NH core distress); the BPRS (total, positive, negative, anxiety-depression scores); CGI Severity of Alzheimer's disease; CGI Severity of psychosis and behavior; MMSE total; ADAS-Cog total; Cancellation Test; MADRS total; and the subscales/summary scores of the SF-36. Table HGEU.5 presents results from the secondary analyses. The olanzapine 5 mg/day treatment group had a statistically significantly greater mean improvement in the NPI/NH total ($p=.005$), NPI/NH two-item total ($p=.001$), NPI/NH delusions ($p=.013$), NPI/NH hallucinations ($p=.007$), NPI/NH agitation ($p=.014$), NPI/NH anxiety ($p=.009$), NPI/NH core distress ($p=.008$), BPRS total ($p=.002$), BPRS positive ($p=.043$), BPRS anxiety-depression ($p=.024$), and the MMSE total ($p=.001$) compared with the placebo treatment group. No other efficacy scores had statistically significant treatment differences between olanzapine 5 mg/day and placebo.

In addition to the NPI/NH core total, the olanzapine 10 mg/day treatment group had a statistically significant improvement in the NPI/NH two-item total ($p=.037$), NPI/NH hallucinations ($p=.049$), NPI/NH agitation ($p=.018$), BPRS total ($p=.034$), and BPRS anxiety-depression ($p=.012$) compared with the placebo treatment group. The olanzapine 15 mg/day treatment group had a statistically significant improvement in the BPRS total ($p=.050$) and a statistically significant worsening in the NPI/NH apathy/indifference ($p=.049$) compared with the placebo treatment group. No other efficacy scores had statistically significant differences between either the olanzapine 10 mg/day or olanzapine 15 mg/day treatment groups and the placebo treatment group.

Table HGEU.5. Secondary Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Acute Phase

			Change to				p-Values	
			-----Baseline-----		-----Endpoint-----		--	
Variables	Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy Pair-
								(Int*1) wse*2
NPIPPO		Placebo	44	43.63	24.22	-9.51	27.13	.005
		Olz5.0	55	43.66	22.97	-18.72	21.32	(.117) .005
		Olz10.0	49	40.69	20.84	-14.00	21.71	.088
		Olz15.0	52	41.56	22.16	-10.45	26.41	.833
AB_TOT		Placebo	44	7.07	7.11	-1.34	7.16	.012
		Olz5.0	55	6.16	6.31	-3.60	5.64	(.079) .001
		Olz10.0	49	5.76	5.68	-2.20	5.82	.037
		Olz15.0	52	6.46	6.58	-2.10	5.52	.189
A_TOT		Placebo	44	4.77	4.61	-1.45	4.22	.059
		Olz5.0	55	4.51	4.34	-2.87	3.85	(.677) .013
		Olz10.0	49	4.43	4.36	-2.02	4.22	.149
		Olz15.0	53	4.11	4.07	-1.40	3.48	.605
B_TOT		Placebo	44	2.30	3.66	0.11	4.14	.053
		Olz5.0	55	1.65	3.16	-0.73	3.21	(.005) .007
		Olz10.0	49	1.33	2.99	-0.18	3.05	.049
		Olz15.0	52	2.33	3.81	-0.73	2.88	.096
C_TOT		Placebo	44	7.36	3.43	-1.95	4.58	.021
		Olz5.0	55	8.38	3.20	-4.13	3.66	(.925) .014
		Olz10.0	49	8.35	3.03	-3.92	4.18	.018
		Olz15.0	53	7.92	3.37	-3.15	4.04	.597
D_TOT		Placebo	44	2.61	3.43	-1.00	3.24	.204
		Olz5.0	55	2.75	3.65	-1.96	3.65	(.467) .299
		Olz10.0	49	2.12	3.12	-0.61	3.05	.975
		Olz15.0	52	2.19	2.97	-0.23	3.75	.303

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Table HGEU.5. Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Acute Phase (Continued)

Variables Analyzed	Therapy	n	Change to				p-Values	
			-----Baseline-----		-----Endpoint-----		Therapy (Int*1)	Pair-wse*2
			Mean	SD	Mean	SD		
E_TOT	Placebo	44	4.05	4.11	-0.57	4.51	.033	
	Olz5.0	55	4.89	4.32	-1.98	4.34	(.532)	.009
	Olz10.0	49	4.78	4.45	-1.53	3.48		.272
	Olz15.0	53	3.68	4.15	-0.66	3.30		.793
F_TOT	Placebo	44	0.61	1.86	-0.11	1.65	.260	
	Olz5.0	55	0.56	1.94	-0.38	1.91	(.037)	.091
	Olz10.0	49	0.41	1.29	0.08	1.98		.925
	Olz15.0	52	0.81	1.89	-0.35	2.35		.833
G_TOT	Placebo	44	3.39	4.44	-0.89	3.85	.044	
	Olz5.0	55	2.49	3.76	-0.49	3.67	(.184)	.517
	Olz10.0	49	2.31	3.59	-0.18	2.77		.979
	Olz15.0	52	2.90	3.62	0.60	4.37		.049
H_TOT	Placebo	44	3.41	3.72	-0.43	3.78	.679	
	Olz5.0	55	3.24	4.18	-1.45	4.00	(.286)	.297
	Olz10.0	49	2.90	3.93	-1.02	3.29		.279
	Olz15.0	53	3.72	3.90	-1.47	3.59		.404
I_TOT	Placebo	44	6.55	4.22	-1.52	4.52	.198	
	Olz5.0	55	6.82	4.37	-2.95	4.66	(.508)	.117
	Olz10.0	49	5.61	3.80	-2.33	4.71		.295
	Olz15.0	53	6.15	4.13	-1.89	4.77		.807
J_TOT	Placebo	44	4.91	4.47	-1.20	3.38	.512	
	Olz5.0	55	4.40	4.68	-1.25	4.07	(.387)	.976
	Olz10.0	49	4.45	4.42	-1.59	4.31		.841
	Olz15.0	53	4.06	4.02	-1.25	4.21		.256
K_TOT	Placebo	43	2.21	3.27	-0.56	2.46	.949	
	Olz5.0	55	2.29	3.39	-0.56	3.45	(.295)	.884
	Olz10.0	49	2.10	3.31	-0.45	3.46		.772
	Olz15.0	52	2.33	3.47	-0.67	4.37		.809
L_TOT	Placebo	44	1.39	3.41	0.18	3.65	.732	
	Olz5.0	55	1.47	3.14	0.35	3.75	(.967)	.536
	Olz10.0	49	1.92	3.26	-0.24	2.26		.362
	Olz15.0	52	1.21	2.57	0.56	3.95		.998
BPRSTOT	Placebo	32	25.38	8.30	-0.47	9.94	.020	
	Olz5.0	40	30.88	11.70	-6.80	8.59	(.196)	.002
	Olz10.0	37	25.97	11.04	-5.57	10.04		.034
	Olz15.0	40	30.18	10.83	-4.68	11.49		.050

Table HGEU.5. Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Acute Phase (Continued)

				Change to		p-Values		
		-----Baseline-----		-----Endpoint-----				
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy Pair- (Int*1) wse*2	Model
Analyzed								
BPRSPOS	Placebo	34	7.59	3.20	-0.18	4.24	.198	RDUC2
	Olz5.0	40	8.48	4.56	-2.03	3.49	(.007)	
	Olz10.0	37	7.35	3.87	-1.38	3.50		
	Olz15.0	42	8.19	4.89	-1.60	5.25		
BPRSNEG	Placebo	41	4.93	4.24	-0.44	1.72	.197	RDUC2
	Olz5.0	51	4.53	3.92	-0.61	3.26	(.690)	
	Olz10.0	45	3.67	4.38	0.49	2.44		
	Olz15.0	45	5.40	3.91	-0.33	3.23		
BPRSAD	Placebo	34	3.65	3.17	0.32	3.47	.058	RDUC2
	Olz5.0	42	4.95	3.01	-1.29	2.98	(.431)	
	Olz10.0	39	4.18	2.96	-1.46	2.49		
	Olz15.0	40	4.25	3.33	-0.80	2.86		
CS_ALZH	Placebo	46	4.87	0.75	-0.11	0.60	.938	FULL2
	Olz5.0	56	4.84	0.95	-0.11	0.49	(.967)	
	Olz10.0	49	4.69	0.80	-0.02	0.56		
	Olz15.0	54	4.98	0.90	-0.04	0.58		
CS_PSYCH	Placebo	46	4.57	0.91	-0.70	1.23	.712	FULL2
	Olz5.0	56	4.59	0.85	-0.91	1.39	(.763)	
	Olz10.0	49	4.31	0.85	-0.92	1.13		
	Olz15.0	54	4.70	0.94	-0.93	1.33		
MADRSTOT	Placebo	38	11.18	9.21	0.08	5.84	.778	RDUC2
	Olz5.0	45	10.56	8.02	-0.58	8.17	(.865)	
	Olz10.0	40	8.78	6.78	0.00	4.27		
	Olz15.0	42	10.93	8.54	1.17	6.82		
ADASPRO	Placebo	41	55.40	13.81	0.07	11.48	.603	FULL2
	Olz5.0	47	51.85	14.33	0.36	7.22	(<.001)	
	Olz10.0	46	55.98	12.92	1.50	7.37		
	Olz15.0	48	56.71	13.84	1.67	5.57		
MMSEPRO	Placebo	43	7.91	7.15	-1.02	4.53	.014	FULL2
	Olz5.0	52	7.31	6.53	0.81	3.94	(<.001)	
	Olz10.0	47	6.62	6.71	-0.49	3.28		
	Olz15.0	49	6.45	6.65	-0.88	3.21		
CTESTSCR	Placebo	42	-0.64	6.69	1.12	7.58	.221	RDUC2
	Olz5.0	56	0.48	5.45	0.68	3.93	(.939)	
	Olz10.0	50	0.90	7.17	-1.58	6.84		
	Olz15.0	50	0.22	6.25	-0.30	5.17		

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Table HGEU.5. Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Acute Phase (Concluded)

			Change to				p-Values		
			-----Baseline-----		-----Endpoint-----				
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy	Pair-	Model
Analyzed							(Int*1)	wse*2	
COREDIST	Placebo	44	5.20	3.32	-1.34	3.40	.064		FULL2
	Olz5.0	55	5.07	3.25	-2.65	3.24	(.256)	.008	
	Olz10.0	49	4.98	2.86	-2.14	2.68		.276	
	Olz15.0	52	5.79	3.39	-2.42	3.45		.135	

Abbreviations: A_TOT = Delusions: Total; AB_TOT = Delusions and Hallucinations Total;

ADASPRO = ADAS Total; B_TOT = Hallucinations: Total; BPRSAD = BPRS Anxiety Depression;

BPRSNEG = BPRS Negative; BPRSPOS = BPRS Positive; BPRSTOT = BPRS Total;

C_TOT = Agitation/Aggression: Total; COREDIST = Core Distress Total; CS_ALZH = CGI Severity of Alzheimer's Disease; CS_PSYCH = CGI Severity of Psych. and Behav. Dist.; CTESTSCR = CTEST Score; D_TOT = Depression/Dysphoria: Total; E_TOT = Anxiety: Total; F_TOT = Euphoria/Elation: Total; G_TOT = Apathy/Indifference: Total; H_TOT = Disinhibition: Total; I_TOT =

Irritability/Lability: Total; J_TOT = Aberrant Motor Behavior: Total; K_TOT = Night Time Behavior: Total; L_TOT = Appetite/Eating Change: Total; MADRSTOT = Totals for Questions 1 – 10;

MMSEPRO = MMSE Total; n = number of patients; NPIPRO = NPI Total; Olz5.0 = olanzapine 5 mg/day, Olz10.0 = olanzapine 10 mg/day, Olz15.0 = olanzapine 15 mg/day; SD = standard deviation.

*1 Type III Sums of Squares from an analysis of variance (ANOVA); PROC GLM model=inv., treatment, and interaction.

*2 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Open-Label Extension

Table HGEU.6 presents primary efficacy results for the open-label extension phase of the study. The primary efficacy analysis was the LOCF comparison of mean change from baseline to endpoint (NPI/NH). In this analysis, the improvement in the NPI/NH core total was statistically significant ($p < .001$).

Table HGEU.6. Primary Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Open-Label Phase

					Change to		p-Value	
					-----Baseline-----			-----Endpoint-----
Variables								
Analyzed	Therapy	n	Mean	SD	Mean	SD		Within Group
CORETOT	Olz	120	13.73	7.67	-7.55	8.53		<.001

Abbreviations: CORETOT = Core NPI/NH Total; n = number of patients; Olz = olanzapine.

Within treatment group mean change is tested with Student's t-test

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Safety Results

Patient Exposure

Acute Phase

The safety of three doses of olanzapine (5, 10, and 15 mg/day) versus placebo was evaluated in 206 randomized patients. The total exposures to olanzapine and placebo were 5,816 patient-days and 1,675 patient-days, respectively.

The patients who met the inclusion/exclusion criteria for Study Period II at Visit 2 were randomized to 1 of the 4 treatment groups as follows: olanzapine 5 mg/day, 56 patients; olanzapine 10 mg/day, 50 patients; olanzapine 15 mg/day, 54 patients; and placebo, 46 patients. Patients assigned to the olanzapine 10 mg/day and olanzapine 15 mg/day treatment groups were titrated to the target dose by increasing the dose in 5-mg increments approximately every 7 days. Of the 160 patients definitively exposed to olanzapine therapy, 117 (73.1%) had a therapy duration of greater than 35 days.

Open-Label Extension

All 137 patients, regardless of their treatment group in the double-blind acute period, began open-label therapy at Visit 8 with 5 mg/day, with adjustments within the allowed dose range of 5 to 15 mg/day.

The safety of a flexible dose of olanzapine (dosage range of 5, 10, or 15 mg/day) was also evaluated. The total exposure to olanzapine was 13,299 patient-days. The most common modal dose was 5 mg/day, taken by 91 (66.4%) of 137 patients.

Treatment-Emergent Adverse Events (TEAEs)

Acute Phase

Treatment-emergent adverse events (TEAEs) are events that originally occurred or worsened during the acute phase. Table HGEU.7 summarizes TEAEs that occurred with a frequency $\geq 10\%$ or showed a statistically significant difference between treatment groups, reported by olanzapine-treated patients or placebo-treated patients. They are listed by decreasing frequency for the olanzapine 15 mg/day treatment group.

The TEAE somnolence occurred statistically significantly more frequently in the olanzapine treatment groups than in the placebo treatment group. The highest incidence (35.2%) of somnolence occurred in the olanzapine 15 mg/day treatment group. When grouped by classification term, 2 patients (3.6%) in the olanzapine 5 mg/day treatment group and 7 patients (13.0%) in the olanzapine 15 mg/day treatment group experienced severe somnolence. There were no reports of severe somnolence in the olanzapine 10 mg/day treatment group.

The TEAE abnormal gait occurred statistically significantly more frequently in the olanzapine 5 mg/day and olanzapine 15 mg/day treatment groups than in the placebo treatment group. The highest incidence (19.6%) of abnormal gait was reported in the olanzapine 5 mg/day treatment group. When grouped by classification 2 patients (3.6%) in the olanzapine 5 mg/day treatment group, 1 patient (2.0%) in the olanzapine 10 mg/day treatment group, and 2 patients (3.7%) in the olanzapine 15 mg/day treatment group experienced severe abnormal gait.

The adverse events (AEs) somnolence and accidental injury were reported as related to study drug by the investigator statistically significantly more frequently in the olanzapine 15 mg/day treatment group than the placebo treatment group. No other AE was reported as related to study drug at a rate statistically significantly different among the placebo group and any of the olanzapine groups.

**Table HGEU.7. Treatment-Emergent Adverse Events
By Decreasing Frequency: Olanzapine 15 mg/day
F1D-MC-HGEU, Acute Phase**

Event Classification	Placebo(1)			Olz5.0(2)			Olz10.0(3)			Olz15.0(4)			Overall p-Value	----- pairwise ----- p-Value		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)		1 vs 2	1 vs 3	1 vs 4
ACCIDENTAL INJURY	46	11	23.9%	56	14	25.0%	50	12	24.0%	54	21	38.9%	.264	1.000	1.000	.134
SOMNOLENCE	46	3	6.5%	56	14	25.0%	50	13	26.0%	54	19	35.2%	.005	.016	.013	.001
PAIN	46	5	10.9%	56	6	10.7%	50	6	12.0%	54	13	24.1%	.183	1.000	1.000	.118
ABNORMAL GAIT	46	1	2.2%	56	11	19.6%	50	7	14.0%	54	9	16.7%	.033	.011	.061	.019
ANOREXIA	46	4	8.7%	56	1	1.8%	50	2	4.0%	54	8	14.8%	.055	.172	.422	.539
ECCHYMOSIS	46	6	13.0%	56	5	8.9%	50	6	12.0%	54	8	14.8%	.812	.538	1.000	1.000
FEVER	46	1	2.2%	56	5	8.9%	50	7	14.0%	54	7	13.0%	.155	.219	.061	.066
AGITATION	46	4	8.7%	56	5	8.9%	50	7	14.0%	54	6	11.1%	.841	1.000	.528	.750
WEIGHT LOSS	46	3	6.5%	56	0	0.0%	50	2	4.0%	54	6	11.1%	.045	.088	.668	.501
COUGH INCREASED	46	2	4.3%	56	7	12.5%	50	5	10.0%	54	5	9.3%	.555	.179	.438	.447
PERIPHERAL EDEMA	46	3	6.5%	56	2	3.6%	50	6	12.0%	54	5	9.3%	.406	.656	.490	.723
CONFUSION	46	2	4.3%	56	2	3.6%	50	5	10.0%	54	3	5.6%	.568	1.000	.438	1.000
URINARY INCONTINENCE	46	1	2.2%	56	2	3.6%	50	5	10.0%	54	2	3.7%	.349	1.000	.206	1.000
NERVOUSNESS	46	2	4.3%	56	4	7.1%	50	6	12.0%	54	1	1.9%	.191	.688	.271	.593
AKATHISIA	46	2	4.3%	56	0	0.0%	50	0	0.0%	54	0	0.0%	.049	.201	.227	.209
THINKING ABNORMAL	46	0	0.0%	56	3	5.4%	50	4	8.0%	54	0	0.0%	.043	.250	.118	

Abbreviations: N = total number of patients in treatment group; n = total number of patients reporting TEAE; Olz5.0 = olanzapine 5 mg/day, Olz10.0 = olanzapine 10 mg/day, Olz15.0 = olanzapine 15 mg/day; vs = versus.
p-value obtained from the Fisher's exact test

Open-Label Extension

Overall, 128 of the 137 patients experienced one or more TEAEs. According to investigators' rating, the most severe level TEAE experienced was mild for 24.1% of patients, moderate for 46% of patients, and severe for 24.1% of patients. The most frequently reported TEAEs were accidental injury (25.5%), somnolence (25.5%), rash (21.9%), fever (17.5%), abnormal gait (15.3%), and weight loss (15.3%). Table HGEU.8 presents TEAEs that occurred with a frequency $\geq 10\%$ during the open-label extension.

**Table HGEU.8. Treatment-Emergent Adverse Events by Decreasing Frequency
F1D-MC-HGEU, Open-Label Phase**

Event Classification	Olz(1)		
	N	n	(%)
ACCIDENTAL INJURY	137	35	25.5%
SOMNOLENCE	137	35	25.5%
RASH	137	30	21.9%
FEVER	137	24	17.5%
ABNORMAL GAIT	137	21	15.3%
WEIGHT LOSS	137	21	15.3%
RHINITIS	137	20	14.6%
COUGH INCREASED	137	19	13.9%
DIARRHEA	137	19	13.9%
ECCHYMOSIS	137	19	13.9%
URINARY TRACT INFECTION	137	17	12.4%
CONSTIPATION	137	15	10.9%
INFECTION	137	15	10.9%
PAIN	137	15	10.9%
PERIPHERAL EDEMA	137	15	10.9%
SKIN ULCER	137	15	10.9%
CONFUSION	137	14	10.2%

Abbreviations: N = total number of patients; n = number of reports.

Discontinuations Due to Adverse Events (AEs)

Acute Phase

Overall, 19 patients (11.9 %) from the olanzapine treatment groups discontinued from the study due to an AE, while 2 (4.3%) patients from the placebo treatment group discontinued due to an AE. When broken down by treatment group, 6 patients (10.7%) from the olanzapine 5 mg/day treatment group, 4 patients (8.0%) from the olanzapine 10 mg/day treatment group, and 9 patients (16.7%) from the olanzapine 15 mg/day treatment group discontinued due to an AE. No statistically significant differences were noted between the olanzapine treatment groups and the placebo treatment group in reasons for discontinuation.

Open-Label Extension

Thirty-one patients overall were discontinued from the open-label extension phase due to the following AEs: abnormal gait, accidental injury, apnea, ataxia, atrial fibrillation,

cellulitis, colitis, congestive heart failure, convulsion, creatine phosphokinase increased, death (due to cardiopulmonary arrest), delirium, dystonia, extrapyramidal syndrome, heart arrest, hematemesis, leukopenia, pneumonia, sepsis, somnolence, and stupor. At the time of study discontinuation, 24 of these patients were taking olanzapine 5 mg/day, 6 patients were taking olanzapine 10 mg/day, and 1 patient was taking olanzapine 15 mg/day.

Deaths and Other Serious Adverse Events (SAEs)

Acute Phase

The rate of deaths and other SAEs was not statistically significantly different between the treatment groups.

Fourteen deaths were reported to the sponsor through 08 July 1998. These 14 reports include 8 patients who had received olanzapine treatment (three of whom died more than 30 days after the last dose of olanzapine) and 6 patients who never received study drug. Careful individual review of the eight deaths in patients who had received olanzapine suggested that it was unlikely that olanzapine was an etiologic contributor, and alternative etiologies were apparent, based on the history. The 14 reports of death reflect causes commonly identified in an elderly population with Alzheimer's disease and living in a long-term care setting. The causes of death for the group of patients that never received study drug and the causes of death for the group of patients treated with olanzapine are not dissimilar.

Serious adverse events (SAEs) were associated with the following five outcomes: death, disability, hospitalization, life-threatening, and other serious outcome as identified by the reporting investigator. Hospitalization was the most frequently-occurring SAE outcome, but the rate of hospitalization was not significantly different among the treatment groups. In the olanzapine 10 mg/day treatment group, hospitalization and life-threatening were the two most frequently reported serious outcomes. Table HGEU.9 summarizes serious outcomes by treatment group. There were no statistically significant treatment group differences in the rates of any of these five outcomes associated with SAEs, except for life-threatening ($p = .024$). However, none of the individual pairwise comparisons of treatment groups was statistically significant.

Table HGEU.9. Number of Patients Experiencing a Serious Adverse Event Summarized by Serious Outcome F1D-MC-HGEU, Acute Phase

Serious Outcome:	NR	Treatment Randomized				p-Value ^b
		Placebo	Olz5.0	Olz10.0	Olz15.0	
Death ^a	4	0	1	1	3	.406
Disability	0	0	0	0	1	.728
Hospitalization	6	2	5	3	7	.450
Life-Threatening	1	0	0	3	0	.024
Other	0	0	0	1	1	.724

Abbreviations: NR = not randomized; Olz5.0 = olanzapine 5 mg/day, Olz10.0 = olanzapine 10 mg/day, Olz15.0 = olanzapine 15 mg/day.

^a Three patients (018-1803 [(not randomized)], 003-323 [Olz5.0], and 003-330 [Olz15.0]), were not included as deaths. These deaths did not occur within 30 days of ending participation in the trial.

^b p-Values comparing randomized groups using Fisher's exact test.

Open-Label Extension

A total of 24 patients experienced 46 SAEs during the open-label phase of the trial. Of these, eight deaths were reported to the sponsor. Of the eight reports, two deaths occurred while the patient was still receiving olanzapine therapy, and six occurred within 30 days after the last dose of olanzapine. For the 2 patients who died while receiving olanzapine, causes of death were cardiac arrest and cardiopulmonary arrest. Of the 6 patients who died within 30 days of receiving the last dose of olanzapine, causes were congestive heart failure, infectious pneumonia, respiratory failure, respiratory failure secondary to infectious pneumonia, and deep-vein thrombosis. Table HGEU.10 presents SAEs by decreasing frequency for the open-label extension.

**Table HGEU.10. Serious Adverse Events by Decreasing Frequency
F1D-MC-HGEU, Open-Label Phase**

Serious Adverse Events	Olz (N=137)	
	n	%
Pneumonia	6	4.4
Delirium	3	2.2
Accidental Injury	2	1.5
Apnea	2	1.5
Cellulitis	2	1.5
Stupor	2	1.5
Tachycardia	2	1.5
Abdominal Pain	1	0.7
Agitation	1	0.7
Allergic Reaction	1	0.7
Arthralgia	1	0.7
Bronchitis	1	0.7
Chest Pain	1	0.7
Colitis	1	0.7
Congestive Heart Failure	1	0.7
Convulsion	1	0.7
Creatine Phosphokinase Increased	1	0.7
Death ^a	1	0.7
Dehydration	1	0.7
Edema	1	0.7
Eye Disorder	1	0.7
Eye Hemorrhage	1	0.7
Heart Arrest	1	0.7
Hematemesis	1	0.7
Myasthenia	1	0.7
Myopathy	1	0.7
Pain	1	0.7
Peptic Ulcer	1	0.7
Rash	1	0.7
Respiratory Disorder	1	0.7
Sepsis	1	0.7
Somnolence	1	0.7
Vomiting	1	0.7
Weight Gain	1	0.7
Total	46	

Abbreviations: Olz = olanzapine; N = total number of patients; n = total number of events.

^a There were a total of eight deaths in the open-label phase of the trial. For 1 patient, no autopsy was performed. Possible causes of death were reported to be sepsis, cardiovascular demise, or pulmonary embolism.

Laboratory Values

Acute Phase

Table HGEU.11 summarizes the analysis of treatment-emergent abnormal, high, or low laboratory values at any time during the acute phase. The only statistically significant difference between the placebo group and any of the olanzapine treatment groups occurred in the urine analyte white blood cell (WBC). Patients in the olanzapine 15 mg/day treatment group had a significantly ($p=.050$) greater incidence of abnormal urinary WBC values than the placebo treatment group (5 of 8 or 62.5% versus 1 of 9 or 11.1%). It should be noted that only 71 out of the 206 patients had a baseline and postbaseline urinalysis.

**Table HGEU.11. Treatment-Emergent Abnormal, High, or Low Laboratory Values at Anytime
F1D-MC-HGEU, Acute Phase**

Name of Lab Test	Direction	No. Therapy	N	n	(%)	----- p-Values -----			
						----- Pairwise -----			
						Overall	vs.(2)	vs.(3)	vs.(4)
ALT/SGPT	High	1) Placebo	44	1	2.3%	.405	1.00	.473	.463
		2) Olz5.0	54	2	3.7%				
		3) Olz10.0	49	0	0.0%				
		4) Olz15.0	51	0	0.0%				
	Low	1) Placebo	44	0	0.0%			.496	.496
		2) Olz5.0	53	0	0.0%				
		3) Olz10.0	49	0	0.0%				
		4) Olz15.0	51	0	0.0%				
AST/SGOT	High	1) Placebo	44	2	4.5%	.258	1.00	.221	.212
		2) Olz5.0	54	2	3.7%				
		3) Olz10.0	49	0	0.0%				
		4) Olz15.0	51	0	0.0%				
	Low	1) Placebo	44	0	0.0%				
		2) Olz5.0	53	0	0.0%				
		3) Olz10.0	49	0	0.0%				
		4) Olz15.0	51	0	0.0%				
BILIRUBIN, TOTAL	High	1) Placebo	44	0	0.0%	1.00	1.00	1.00	1.00
		2) Olz5.0	54	1	1.9%				
		3) Olz10.0	50	0	0.0%				
		4) Olz15.0	51	0	0.0%				
	Low	1) Placebo	44	0	0.0%				
		2) Olz5.0	54	0	0.0%				
		3) Olz10.0	50	0	0.0%				
		4) Olz15.0	51	0	0.0%				
CHOLESTEROL	High	1) Placebo	44	0	0.0%				
		2) Olz5.0	54	0	0.0%				
		3) Olz10.0	50	0	0.0%				
		4) Olz15.0	51	0	0.0%				
	Low	1) Placebo	39	3	7.7%	.569	.312	.659	1.00
		2) Olz5.0	51	1	2.0%				
		3) Olz10.0	45	2	4.4%				
		4) Olz15.0	47	3	6.4%				

(continued)

**Table HGEU.11. Treatment-Emergent Abnormal, High, or Low Laboratory Values at Anytime
F1D-MC-HGEU, Acute Phase (Concluded)**

Name of Lab Test	Direction	No. Therapy	N	n	(%)	----- p-Values -----			
						Overall	----- Pairwise -----		
							vs.(2)	vs.(3)	vs.(4)
GLUCOSE, NON-FASTING	High	1) Placebo	44	0	0.0%				
		2) Olz5.0	54	0	0.0%				
		3) Olz10.0	49	0	0.0%				
		4) Olz15.0	50	0	0.0%				
	Low	1) Placebo	39	6	15.4%	.565	.320	.536	.292
		2) Olz5.0	51	4	7.8%			.734	1.00
		3) Olz10.0	47	5	10.6%				.714
		4) Olz15.0	45	3	6.7%				
UA-WBC	ABNM	1) Placebo	9	1	11.1%	.015	1.00	.338	.050
		2) Olz5.0	16	1	6.3%			.133	.007
		3) Olz10.0	12	4	33.3%				.362
		4) Olz15.0	8	5	62.5%				

Abbreviations: ABNM = abnormal; ALT/SGPT = alanine transaminase/serum glutamic-pyruvic transaminase; AST/SGOT = aspartate transaminase/serum glutamic-oxaloacetic transaminase; N = number of patients; n = number of events; Olz5.0 = olanzapine 5 mg/day, Olz10.0 = olanzapine 10 mg/day, Olz15.0 = olanzapine 15 mg/day; UA-WBC = urinalysis-white blood cell.

Open-Label Extension

Statistically significant changes in mean change from baseline to endpoint were observed in 10 of the 38 laboratory analytes explored. There were small decreases in RBC and related decreases in hematocrit, hemoglobin, MCH, and MCV. There was also an elevation of AST and ALT, as has been observed in younger, nondemented patients. Additionally, a statistically significant increase in cholesterol was observed (Table HGEU.12).

Table HGEU.12. Laboratory Analytes
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Open-Label Phase

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Value
				Mean	SD	Mean	SD	
HCT	l	Olz	132	0.40	0.04	-0.01	0.04	<.001
HGB	mmL/L-Fe	Olz	132	7.94	0.88	-0.24	0.60	<.001
RBC	TI/L	Olz	132	4.26	0.49	-0.07	0.34	0.015
MCH	fmoL(Fe)	Olz	132	1.87	0.11	-0.03	0.09	<.001
WBC	GI/L	Olz	132	7.12	2.15	-0.02	2.30	0.923
POLYS	GI/L	Olz	132	4.75	1.93	0.02	2.07	0.915
MCV	fL	Olz	132	93.27	5.99	-1.83	5.15	<.001
AST	U/L	Olz	132	20.09	7.39	1.48	7.05	0.017
ALT	U/L	Olz	132	15.95	8.09	2.05	12.56	0.063
BUN	mmol/L	Olz	133	7.86	2.51	0.66	2.95	0.011
ALBUM	g/L	Olz	132	36.20	4.05	-1.58	3.78	<.001
NFGLU	mmol/L	Olz	132	6.39	2.04	-0.19	1.96	0.268
UR AC	umol/L	Olz	133	294.36	78.60	19.45	76.75	0.004
CHOL	mmol/L	Olz	133	4.93	1.05	-0.15	0.58	0.003
T.BILI	umol/L	Olz	132	8.46	2.97	-0.35	3.06	0.191

Abbreviations: HCT = hematocrit; HGB = hemoglobin; RBC = erythrocyte count; MCH = mean cell hemoglobin; WBC = leukocyte count; POLYS = neutrophils, segmented; MCV = mean cell volume; AST = AST/SGOT aspartate transaminase/serum glutamic-oxaloacetic transaminase; ALT = ALT/SGPT alanine transaminase/serum glutamic-pyruvic transaminase; BUN = urea nitrogen; ALBUM = albumin; NFGLU = glucose, non-fasting; UR AC = uric acid; CHOL = cholesterol; T.BILI = bilirubin, total.

Within treatment group mean change is tested with Student's t-test

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Vital Signs and Weight

Acute Phase

Table HGEU.13 shows the proportions of patients with potentially clinically significant changes in vital signs or weight at any time while on therapy. There were no statistically significant differences between placebo-treated patients and olanzapine-treated patients. The most frequent potentially clinically significant change observed in olanzapine-treated patients was decreased orthostatic systolic blood pressure meeting the definition of orthostatic hypotension (≥ 30 mm Hg decrease in systolic blood pressure supine to sitting) within the olanzapine 10 mg/day treatment group (13.3%). The most frequently occurring potentially clinically significant changes observed in placebo-treated patients were decreased orthostatic systolic blood pressure (7.0%) and low supine diastolic blood pressure (7.3%).

**Table HGEU.13. Potentially Clinically Significant Change in Vital Signs and Weight
F1D-MC-HGEU, Acute Phase**

Vital	Direction	No. Therapy	N	n	(%)	----- p-Values -----			
						Overall	----- Pairwise -----		
							vs.(2)	vs.(3)	vs.(4)
Orthostatic Sys BP	Decrease	1) Placebo	43	3	7.0%	.192	.329	.485	1.00
		2) Olz5.0	51	1	2.0%				
		3) Olz10.0	45	6	13.3%				
		4) Olz15.0	43	3	7.0%				
Weight (kg)	Gain	1) Placebo	45	1	2.2%	.546	1.00	1.00	.459
		2) Olz5.0	54	1	1.9%				
		3) Olz10.0	50	2	4.0%				
		4) Olz15.0	53	0	0.0%				
	Loss	1) Placebo	45	0	0.0%	.263	.499	1.00	.122
		2) Olz5.0	54	2	3.7%				
		3) Olz10.0	50	1	2.0%				
		4) Olz15.0	53	4	7.5%				

Frequencies analyzed using two-tailed Fisher's Exact Test

Open-Label Extension

Table HGEU.14 displays mean change from baseline to endpoint for vital signs and weight during the open-label extension. No statistically significant changes were observed for any of the vital sign or weight measurements.

**Table HGEU.14. All Vital Measurements
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Open-Label Phase**

		-----Baseline-----		Change to -----Endpoint-----		p-Value	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Within Group
WEIGHTKG	Olz	136	61.22	12.67	0.24	4.32	0.512
DIABP_SI	Olz	136	70.42	10.93	-0.61	11.72	0.545
PULSE_SI	Olz	135	76.85	10.38	-1.73	10.89	0.068
TEMPCPO	Olz	136	36.58	0.47	-0.00	0.64	0.979
SYSBP_OR	Olz	130	1.81	10.82	-0.99	12.44	0.365
PULSE_OR	Olz	129	2.57	6.36	-0.95	8.75	0.222
SYSBP_SU	Olz	130	129.63	16.98	-3.11	21.88	0.108
DIABP_SU	Olz	130	70.62	10.38	-0.71	11.03	0.466
PULSE_SU	Olz	129	74.87	9.29	-1.06	11.69	0.304
SYSBP_SI	Olz	136	128.12	16.20	-2.07	20.22	0.234

Abbreviations: DIABP_SI = Diastolic Blood Pressure – Sitting; DIABP_SU = Diastolic Blood Pressure – Supine; Olz = olanzapine; PULSE_OR = Pulse – Ortho; PULSE_SI = Pulse-Sitting; PULSE_SU = Pulse – Supine; SYSBP_OR = Systolic Blood Pressure – Ortho; SYSBP_SI = Systolic Blood Pressure – Sitting; SYSBP_SU = Systolic Blood Pressure – Supine; TEMPCPO = Temp in Centigrade Standardized to PO; WEIGHTKG = Weight in kg.

Within treatment group mean change is tested with Student's t-test

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Electrocardiogram (ECG)

Acute Phase

In the analysis of mean change from baseline to endpoint for ECG heart rate and interval times (PR, QRS, QT, and corrected QT), there were no statistically significant differences between any of the olanzapine and placebo treatment groups. In the analysis of potentially clinically significant changes in ECG interval times and heart rate, there also were no statistically significant differences among treatment groups. In addition, there

were no statistically significant differences in the pairwise comparisons of the placebo group to any of the olanzapine groups for any of the ECG abnormality categories.

Open-Label Extension

There were no statistically significant changes from baseline to endpoint for ECG heart rate and interval times (PR, QRS, QT, and corrected QT) during the open-label extension.

Extrapyramidal Symptoms (EPS)

Acute Phase

Table HGEU.15 contains a summary of the proportion of patients with abnormal Simpson-Angus and Barnes Akathisia global scores at endpoint. Simpson-Angus total scores >3 are considered outside the normal range. Treatment-emergent Parkinsonism was defined as a score of ≤ 3 at baseline to a score of >3 at any postbaseline visit. The numbers and percentages of patients with treatment-emergent Parkinsonism were 3 of 23 (13.0%) olanzapine 5 mg/day-treated patients, 3 of 17 (17.6%) olanzapine 10 mg/day-treated patients, 4 of 17 (23.5%) olanzapine 15 mg/day-treated patients, and 4 of 17 (23.5%) placebo-treated patients. There was no statistically significant difference in these percentages ($p=.815$). Barnes Akathisia global scores of ≥ 2 are indicative of akathisia. Treatment-emergent akathisia was defined as a score of <2 at baseline to a score of ≥ 2 at any postbaseline visit. The numbers and percentages of patients with reported treatment-emergent akathisia were 3 of 50 (6.0%) olanzapine 5 mg/day-treated patients, 1 of 47 (2.1%) olanzapine 10 mg/day-treated patients, 2 of 48 (4.2%) Olz15.0olanzapine 15 mg/day-treated patients, and 3 of 43 (7.0%) placebo-treated patients. There was no statistically significant difference in these percentages ($p=.767$). There were no statistically significant differences in between treatment groups in the categorical analysis of treatment-emergent Parkinsonism or treatment-emergent akathisia.

**Table HGEU.15. Simpson-Angus and Barnes Akathisia Total Score
Proportion of Patients with Abnormal Score at Anytime
F1D-MC-HGEU, Acute Phase**

	No. Therapy	N	n	(%)	p-Value			
					Overall	vs. (2)	vs. (3)	vs. (4)
Simpson-Angus Total Score	1) Placebo	17	4	(23.5)	0.815	0.432	1.00	1.00
	2) Olz5.0	23	3	(13.0)			1.00	0.432
	3) Olz10.0	17	3	(17.6)				1.00
	4) Olz15.0	17	4	(23.5)				
Barnes Akathisia Global Score	1) Placebo	43	3	(7.0)	0.767	1.00	0.345	0.664
	2) Olz5.0	50	3	(6.0)			0.618	1.00
	3) Olz10.0	47	1	(2.1)				1.00
	4) Olz15.0	48	2	(4.2)				

p-Value obtained by using Fisher's Exact Test

Open-Label Extension

Table HGEU.16 presents the mean change from baseline to endpoint in the Barnes, Simpson-Angus, and AIMS total scores. No statistically significant changes were noted.

**Table HGEU.16. Extrapyramidal Symptoms Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGEU, Open-Label Phase**

		-----Baseline-----		Change to -----Endpoint-----		p-Value	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Within Group
SATOT	Olz	108	5.19	6.54	0.45	3.43	0.172
AIMS1T7	Olz	135	1.67	3.43	-0.21	1.93	0.199
BRNS04	Olz	133	0.34	0.86	-0.22	0.80	0.002

Abbreviations: AIMS1T7 = AIMS Total Score; BRNS04 = Barnes Global Score; SATOT = Simpson-Angus Total Score.

Within treatment group mean change is tested with Student's t-test

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Conclusions

The primary efficacy acute phase analysis was the comparison of mean change from baseline to last observation carried forward endpoint in NPI core total. In this analysis, the improvement in both the Olz5.0 and Olz10.0 treatment groups was significantly greater than in the placebo treatment group (Olz5.0: -7.62 vs. Placebo: -3.30, $p < .001$; Olz10.0: -6.12 vs. Placebo: -3.30, $p = .006$).

There were no treatment group differences in clinically significant changes in vital signs, weight, laboratory analytes, ECGs, or extrapyramidal symptoms during the acute phase.

The primary efficacy open-label phase analysis was the mean change from baseline to LOCF endpoint (NPI/NH). In this analysis, the with-in group improvement in the NPI/NH core total was statistically significant ($p < .001$).