Notice of Correction 6/17/2011: The unit of measure for Bazett's QTc interval has been corrected to milliseconds *on page 795 (last sentence) and page 796 (first line).*

An 8-Week, Double-Blind, Randomized, Placebo-Controlled Study of Olanzapine Long-Acting Injection in Acutely Ill Patients With Schizophrenia

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Objective: To examine the efficacy and tolerability of a new injectable formulation of olanzapine, olanzapine long-acting injection (LAI), relative to placebo for treatment of acutely ill patients with schizophrenia.

Method: Patients with DSM-IV or DSM-IV-TR schizophrenia in this 8-week, double-blind study were randomly assigned to receive 210 mg/2 weeks, 300 mg/2 weeks, or 405 mg/4 weeks of olanzapine LAI or placebo/2 weeks. No oral antipsychotic supplementation was permitted. The primary efficacy measure was mean baseline-to–end point change in Positive and Negative Syndrome Scale (PANSS) total score. The study was conducted from June 2004 to April 2005.

Results: Mean baseline-to–end point decreases in PANSS total scores were significantly greater for all olanzapine LAI regimens relative to placebo (all p values < .001). The 300 mg/2 weeks and 405 mg/4 weeks olanzapine LAI groups separated from placebo on the PANSS total at 3 days after starting treatment, and all olanzapine LAI groups separated from placebo by 7 days. Rates of clinical improvement (end point Clinical Global Impressions-Improvement scale score ≤ 3) were significantly higher for all olanzapine LAI groups relative to placebo ($p < .001$). Incidences of sedation and increased appetite were significantly higher for 300 mg/2 weeks olanzapine LAI relative to placebo ($p < .05$). Mean weight gain (3.2–4.8 vs. 0.3 kg, $p < .001$) and incidence of weight gain ≥ 7% of baseline (23.6–35.4% vs. 12.4%, $p \leq .046$) were significantly greater for olanzapine LAI relative to placebo. Significant differences between all olanzapine LAI groups and placebo were observed regarding mean baseline-to–end point changes in fasting total cholesterol (5.5–10.4 vs. –7.0 mg/dL; $p \leq .015$) and between the 210 mg/2 weeks and 405 mg/4 weeks groups (26.3–30.3 vs. –9.4 mg/dL; $p \leq .016$), but not the 300 mg/2 weeks group (17.6 mg/dL; $p = .055$), and placebo for fasting triglycerides.

Conclusions: In this 8-week study, olanzapine LAI administered at 2- or 4-week injection intervals was significantly more efficacious than placebo for the treatment of acutely ill patients with schizophrenia despite no use of supplemental oral antipsychotics. Consistent with changes previously observed with oral olanzapine, clinically significant weight gain and changes in some lipid parameters were observed in patients treated with olanzapine LAI.

Trial Registration: clinicaltrials.gov Identifier: NCT00088478

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Nonadherence or partial adherence to medications among acutely ill patients with schizophrenia greatly diminishes the chances of treatment success. Unfortunately, nonadherence is very common, and most non-biological estimates (e.g., clinician judgment, patient self-report) typically inflate adherence rates.[1,2] According to recent estimates, approximately 40% of psychotic patients are poorly adherent to medications at any given time.[3]

Long-acting (depot) antipsychotics may reduce nonadherence by allowing for rapid identification of missed injections.[4] Additionally, a long-lasting injection offers greater convenience, because it can be administered every few weeks, as opposed to a patient's having to take daily medication. Until recently, the only depot formulations

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available were first-generation "typical" depot antipsychotics, and although they have been reported to improve adherence,[5–7] their use has been associated with debilitating motor disturbances[8] and cognitive, affective, metabolic,[9] and neurohormonal adverse events. Despite the current availability of both an atypical[10] and a variety of typical depot antipsychotics, nonadherence continues to be a very important clinical issue.[2,4,11–13]

Olanzapine long-acting injection (LAI), a salt of pamoic acid and olanzapine, is a formulation that is suspended in an aqueous vehicle for deep gluteal intramuscular injection. The doses of olanzapine LAI were selected based on pharmacokinetic and safety data from Phase 1 studies. (Detailed analyses of these data will be presented in a separate article.) These studies showed that the distribution of olanzapine plasma concentrations after doses of 210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks were within the 10th and 90th percentiles of the range of plasma olanzapine concentrations associated with once-daily oral olanzapine doses of 5 mg (10th percentile) to 20 mg (90th percentile). The dose strengths of olanzapine LAI are best described by the amount of olanzapine provided in each injection, and approximate daily doses can be calculated by dividing by the number of days in the prescribed injection interval. Thus, an olanzapine LAI dose of 210 mg/2 weeks provides approximately 15 mg/day of olanzapine, 300 mg/2 weeks approximately 20 mg/day, and 405 mg/4 weeks approximately 15 mg/day.

The objectives of this 8-week, double-blind clinical trial were to investigate the acute efficacy, onset of effect, and tolerability of 3 doses and 2 dosing regimens of olanzapine LAI (210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) relative to placebo for the treatment of acutely ill patients with schizophrenia. As part of the study design, patients were switched from previous treatment directly to olanzapine LAI without supplementation or cross titration with oral antipsychotic medication. Olanzapine LAI has not yet been approved for clinical use. This study was part of a larger clinical registration program by Eli Lilly and Company, which also assessed the use of olanzapine LAI for maintenance treatment in schizophrenia.

METHOD

Patient Population

Participants were male or female patients 18 to 75 years of age with a diagnosis of schizophrenia (DSM-IV or DSM-IV-TR). At study entry, patients were required to have a Positive and Negative Syndrome Scale (PANSS)–derived Brief Psychiatric Rating Scale (BPRS) score ≥ 30 (0–6 scale), which reflects a moderate-to-high level of symptom severity. For patients treated previously with a depot antipsychotic, the last injection must have been received at least 2 weeks or 1 injection interval, whichever was longer, before double-blind treatment. Patients were excluded if they had previously experienced clinically significant adverse events during treatment with oral olanzapine that would preclude the use of the long-acting depot formulation. Additional exclusion criteria included significant suicidal or homicidal risk; pregnancy or breast-feeding; acute, serious, or unstable medical conditions; or substance dependency (except nicotine or caffeine) within the past 30 days. The study protocol was approved by local ethical review boards, and all patients (and authorized representative where required by local law) signed written, informed consent documents after the details of the study and possible treatment-emergent adverse events were fully described.

Study Design

This 8-week, double-blind, multicenter study (study code: F1D-MC-HGJZ) was conducted from June 2004 to April 2005 at 43 study sites in the United States, Russia, and Croatia (clinical trials.gov Identifier NCT00088478). The study consisted of a 2- to 7-day washout/screening period followed by an 8-week, double-blind treatment period. After the brief washout period, eligible patients were allocated in a 1:1:1:1 ratio to 210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks olanzapine LAI or placebo. The study design included blinding of both dosing interval and treatment assignment. Thus, patients who were randomly assigned to 405 mg/4 weeks olanzapine LAI received a placebo injection at the 2-week interval between their active study drug injections, and patients randomly assigned to placebo received placebo injections every 2 weeks. Patients could be outpatients or inpatients before study entry. All patients were then hospitalized upon study entry and were required to be inpatients during the washout period and for the first 2 weeks after random assignment. Patients were assessed daily using the Clinical Global Impressions scale (CGI) during the first 2 weeks after random assignment. Assessments with the PANSS were performed at baseline, on day 3, on day 7, and weekly thereafter. Patients could remain inpatients for the full duration of the study. After 2 weeks, patients could either receive a day pass or be discharged from the hospital if all hospital discharge criteria were met. Patients were deemed clinically appropriate for discharge if they showed clinical improvement over at least 3 days, were not at risk for suicidal or homicidal behavior, and could be discharged into a suitable supervised environment.

Concomitant Medications

Medications with primarily central nervous system activity (including antidepressants and mood stabilizers) other than study drug were not permitted during the double-blind period, except where specified in the study protocol. The use of multiple benzodiazepines/sedative hypnotics as sleep aids was permitted (≤ 2 mg/day lora-

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zepam equivalents each). All clinical ratings were performed during daytime hours. The use of anticholinergic medications for treatment-emergent extrapyramidal symptoms was permitted (≤ 6 mg/day biperiden equivalents), but prophylactic use was prohibited.

Measures of Efficacy and Safety

The primary efficacy measure was mean baseline-to–end point change (last observation carried forward [LOCF]) in PANSS total score after 8 weeks of treatment. Secondary efficacy measures included mean baseline-to–end point changes in scores on the PANSS positive, negative, and general psychopathology subscales, PANSS-derived BPRS, and CGI-Severity of Illness scale (CGI-S). Clinical improvement was defined as an end point score on the CGI-Improvement scale (CGI-I) of ≤ 3. Response was defined as a ≥ 40% improvement in PANSS total score.

Treatment-emergent adverse events (unsolicited) were recorded using the Medical Dictionary for Regulatory Activities. Analyses of all laboratory samples were performed under strict control by 1 company (Covance, Princeton, N.J.). Treatment-emergent categorical changes in lipid parameters were defined using National Cholesterol Education Program Adult Treatment Panel III[14] criteria and changes in glucose were defined using American Diabetes Association[15] criteria. Extrapyramidal symptoms were assessed using the following scales: the Barnes Akathisia Scale (akathisia),[16] the Simpson-Angus Scale (parkinsonism),[17] and the Abnormal Involuntary Movement Scale (dyskinesia).[18]

Statistical Methods

Data were analyzed on an intent-to-treat basis. Baseline frequencies were compared using the χ^2 test. Baseline means were compared by analysis of variance (ANOVA) with independent factors for treatment and investigator. For analysis of LOCF mean change, patients with baseline and at least 1 postbaseline measurement were included in the analysis. Comparisons between olanzapine LAI and placebo on the primary efficacy measure, LOCF change from baseline to end point in PANSS total score, were carried out in a sequential manner to control for type I error: (1) 300 mg/2 weeks versus placebo (the highest dose allowable); (2) 405 mg/4 weeks versus placebo; and (3) 210 mg/2 weeks versus placebo. Thus, the 210 mg/2 weeks versus placebo comparison could be declared statistically significant only if all 3 comparisons were significant. The rationale for this sequence of comparisons was that the 300 mg/2 weeks dose might be the most efficacious but that the 405 mg/4 weeks dose might be desirable from a patient perspective if it provided similar efficacy to the 2-week dosing regimens. Subgroup analyses of the PANSS total score were performed by age (< 40 and ≥ 40 years), sex, ethnic origin (white or nonwhite), and geographic region (United States or Eastern Europe). Analysis of the PANSS total score was also performed using a mixed-effects model repeated-measures (MMRM) method with a compound-symmetric covariance matrix to model within-patient error. Independent factors included in the model were treatment, investigator, visit, and treatment-by-visit interaction. Treatment differences for each visit were tested using a single df contrast, based on least squares means from the model. Inference from the MMRM analyses was based on the restricted maximum likelihood solution and on approximated F tests and t tests using df's estimated by the Kenward-Roger method.

Comparisons of response (defined a priori as ≥ 40% decrease from baseline PANSS total score) rates between each olanzapine LAI group and the placebo group were assessed by Fisher exact test. The PANSS scores were adjusted to a 0 to 6 scale so that a complete lack of symptoms would correspond to a score of 0.[19] Rates of clinical improvement were compared between the olanzapine LAI and placebo groups using Fisher exact test. Analyses of mean LOCF changes from baseline to end point on secondary efficacy scales used ANOVA models that included terms for treatment and investigator study site. Baseline-to–end point (LOCF) changes in continuous safety measures were analyzed using ANOVA models with terms for treatment and investigator. Additionally, an analysis using the MMRM model described previously was performed on changes in weight. Analyses of proportions used the Fisher exact test. A 2-sided α level of .05 was used for all tests of hypotheses. All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, N.C.).

RESULTS

Baseline Characteristics and Disposition

Patient flow through the study is shown in Figure 1. Patients were recruited from research sites in the United States (N = 315), Russia (N = 61), and Croatia (N = 28). No statistically significant differences were observed in the percentage of patients assigned to each treatment within each country (p = .996). All patients carried a diagnosis of schizophrenia according to DSM-IV or DSM-IV-TR criteria with an acute exacerbation (defined by a BPRS score ≥ 30 [0–6 scale]). Recent adherence to medication was not assessed, but 71% of patients reported ≥ 2 previous episodes or exacerbations of schizophrenia in the previous 24 months, which may reflect difficulty with adherence.[20,21] Eighty-three percent of patients remained inpatients throughout their participation in the study. Rates of study discontinuation did not differ significantly among treatment groups (28%–43%; p = .167). No statistically significant differences were observed among treatment groups at baseline with respect to patient demographics or severity of illness (Table 1). The mean baseline PANSS total score across all treatment groups was 101, and the

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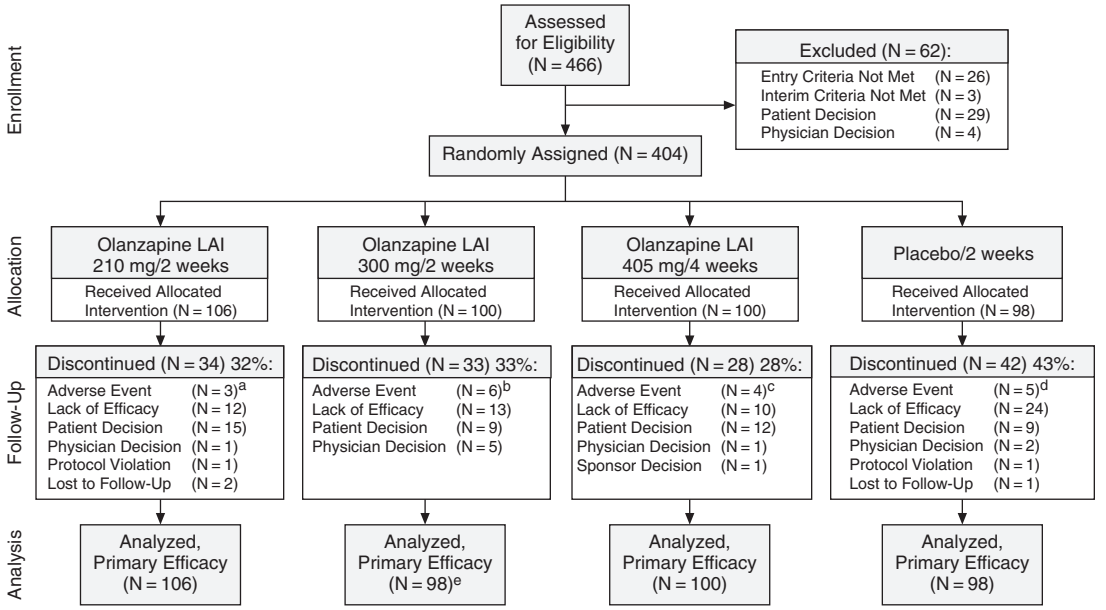
Figure 1. Summary of Patient Disposition



[a]Psychotic disorder, N = 1; blood glucose increased, N = 1; and cholecystitis, N = 1.
[b]Hepatic enzyme increased, N = 2; sedation, N = 1; agitation, N = 1; depressed level of consciousness, N = 1; and respiratory acidosis, N = 1.
[c]Psychotic disorder, N = 2; sedation, N = 1; and alanine aminotransferase increased, N = 1.
[d]Psychotic disorder, N = 1; atrial fibrillation, N = 1; convulsion, N = 1; hip fracture, N = 1; schizophrenia, N = 1.
[e]One randomly assigned patient discontinued before receiving any injection (no baseline or postbaseline data), and 1 patient discontinued after receiving the injection but before having any postbaseline PANSS evaluations.
Abbreviations: LAI = long-acting injection, PANSS = Positive and Negative Syndrome Scale.

Table 1. Baseline Demographic and Clinical Characteristics and Concomitant Medications of 404 Subjects With DSM-IV or DSM-IV-TR Schizophrenia Treated With Olanzapine Long-Acting Injection (LAI)

	Olanzapine LAI Group			
Characteristic	210 mg/2 wk (N = 106)	300 mg/2 wk (N = 100)	405 mg/4 wk (N = 100)	Placebo Group (N = 98)
Sex, male, N (%)	79 (74.5)	72 (72.0)	73 (73.0)	61 (62.2)
Ethnic origin, white, N (%)	61 (57.5)	58 (58.0)	54 (54.0)	53 (54.1)
Previous use of ≥ 1 antipsychotic, N (%)	102 (96.2)	95 (95.0)	94 (94.0)	89 (90.8)
Previous antipsychotic, N (%)				
Risperidone	43 (40.6)	42 (42.0)	39 (39.0)	35 (35.7)
Olanzapine	47 (44.3)	36 (36.0)	38 (38.0)	32 (32.7)
Haloperidol	27 (25.5)	26 (26.0)	26 (26.0)	25 (25.5)
Country, N (%)				
United States (N = 315)	82 (26.0)	79 (25.1)	78 (24.8)	76 (24.1)
Russia (N = 61)	17 (27.9)	14 (23.0)	16 (26.2)	14 (23.0)
Croatia (N = 28)	7 (25.0)	7 (25.0)	6 (21.4)	8 (28.6)
≥ 2 episodes or exacerbations of schizophrenia in the past 24 mo, N (%)	78 (73.6)	76 (76.0)	68 (68.0)	64 (65.3)
Age, mean (SD), y	39.8 (10.8)	41.5 (11.1)	39.5 (11.4)	42.6 (11.2)
Age at onset of illness, mean (SD), y	23.5 (7.9)	23.5 (7.8)[a]	22.8 (8.5)	23.8 (8.7)
Length of current episode, mean (SD), d	146.0 (406.8)	213.0 (591.7)	186.5 (678.6)	318.5 (831.3)
Weight, mean (SD), kg	87.0 (21.5)	85.5 (20.8)[a]	87.3 (22.1)	82.2 (19.1)
Body mass index, mean (SD), kg/m^2	28.7 (6.0)[b]	28.9 (7.6)[a]	29.4 (7.5)	28.3 (6.5)
Concomitant benzodiazepine use				
N (%)	78 (73.6)	76 (76.0)	69 (69.0)	77 (78.6)
Mean daily dose, lorazepam equivalents, mg	6.2	4.7	5.4	7.7
Median daily dose, lorazepam equivalents, mg	1.2	1.2	0.6	1.3
Concomitant anticholinergic use				
N (%)	13 (12.3)	5 (5.0)	12 (12.0)	8 (8.2)
Mean daily dose, biperiden equivalents, mg	1.3	0.6	0.7	1.7
Median daily dose, biperiden equivalents, mg	0.3	0.8	0.6	1.4

[a]N = 99.
[b]N = 105.

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Table 2. Mean Baseline-to–End Point (LOCF) Changes on the Efficacy Scales After 8 Weeks of Treatment

Measurement and Treatment Group	N	Baseline Score, Mean (SD)	Change, Mean (SD)	p Value vs Placebo[a]	t	df
PANSS total						
Olanzapine LAI 210 mg/2 wk	106	99.6 (15.8)	–22.5 (21.8)	< .001	5.39	357
Olanzapine LAI 300 mg/2 wk	98	102.6 (15.6)	–26.3 (24.9)	< .001	6.46	357
Olanzapine LAI 405 mg/4 wk	100	101.3 (14.4)	–22.6 (22.1)	< .001	5.16	357
Placebo	98	100.6 (16.7)	–8.5 (23.0)	…		
PANSS positive subscale						
Olanzapine LAI 210 mg/2 wk	106	25.2 (5.0)	–6.3 (6.8)	< .001	5.15	357
Olanzapine LAI 300 mg/2 wk	98	25.8 (4.8)	–7.4 (7.8)	< .001	6.01	357
Olanzapine LAI 405 mg/4 wk	100	25.7 (5.0)	–7.2 (6.9)	< .001	5.73	357
Placebo	98	25.4 (5.3)	–2.0 (7.6)	…		
PANSS negative subscale						
Olanzapine LAI 210 mg/2 wk	106	24.7 (5.2)	–4.8 (5.6)	< .001	4.13	357
Olanzapine LAI 300 mg/2 wk	98	26.0 (5.3)	–6.3 (6.2)	< .001	6.03	357
Olanzapine LAI 405 mg/4 wk	100	25.4 (5.1)	–4.6 (5.4)	< .001	3.64	357
Placebo	98	25.1 (5.6)	–2.1 (5.8)	…		
PANSS general psychopathology subscale						
Olanzapine LAI 210 mg/2 wk	106	49.6 (9.0)	–11.4 (11.5)	< .001	5.00	357
Olanzapine LAI 300 mg/2 wk	98	50.7 (8.4)	–12.6 (12.8)	< .001	5.59	357
Olanzapine LAI 405 mg/4 wk	100	50.2 (8.1)	–10.8 (11.4)	< .001	4.45	357
Placebo	98	50.1 (8.9)	–4.4 (12.0)	…		
BPRS total						
Olanzapine LAI 210 mg/2 wk	106	40.5 (9.2)	–14.1 (13.7)	< .001	5.15	357
Olanzapine LAI 300 mg/2 wk	98	41.4 (8.3)	–16.4 (14.3)	< .001	6.19	357
Olanzapine LAI 405 mg/4 wk	100	41.1 (8.3)	–14.5 (13.9)	< .001	5.08	357
Placebo	98	40.4 (9.7)	–6.0 (13.6)	…		
CGI-S						
Olanzapine LAI 210 mg/2 wk	105	4.7 (0.7)	–0.6 (1.1)	.003	4.80	356
Olanzapine LAI 300 mg/2 wk	99	4.8 (0.7)	–0.6 (1.2)	.001	5.30	356
Olanzapine LAI 405 mg/4 wk	99	4.9 (0.8)	–0.6 (1.1)	< .001	4.63	356
Placebo	98	4.7 (0.7)	–0.3 (1.1)	…		

[a]Type III sum of squares (ANOVA = therapy + investigator): PANSS total and subscales, BPRS total, and CGI-S; least squares mean from the ANOVA using the mean square for error.
Abbreviations: ANOVA = analysis of variance, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, LAI = long-acting injection, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.
Symbol: … = not applicable.

mean BPRS total score was 41 (0–6 scale). No significant differences were observed between countries on mean (SD) baseline PANSS total score (United States, 101.1 [16.2]; Russia, 101.1 [14.4]; Croatia, 99.5 [10.3]). Before study entry, 94% of patients had received previous antipsychotic medications, the most common being risperidone (39.4%), olanzapine (37.9%), and haloperidol (25.7%); and 76 patients (18.8%) had received a depot antipsychotic (risperidone long-acting injection, N = 15; fluphenazine decanoate, N = 21; haloperidol decanoate, N = 31; zuclopenthixol decanoate, N = 9).

Concomitant Medications

Benzodiazepine use was reported by 300 patients (74%) with no statistically significant differences between treatment groups in rates of use (p = .471) or mean daily dose (p = .562). No significant between-group differences were observed in the incidence of anticholinergic use (p = .220) or mean daily dose (p = .086; Table 1).

Efficacy

In the primary efficacy analysis, mean baseline-to–end point decreases in PANSS total scores were significantly greater for all 3 olanzapine LAI groups relative to placebo (all p values < .001; Table 2). At 8 weeks, PANSS total scores decreased a mean of 26.3 points in the 300 mg/2 weeks, 22.6 in the 405 mg/4 weeks, and 22.5 in the 210 mg/2 weeks olanzapine LAI treatment groups compared with 8.5 points in the placebo treatment group. No statistically significant differences were observed among the olanzapine LAI treatment groups at end point. Mean PANSS total scores in the 300 mg/2 weeks and 405 mg/4 weeks olanzapine LAI groups separated significantly from the placebo group by day 3 (week 0.4, Figure 2), with all 3 olanzapine LAI groups separating from day 7 to end point. These findings were also supported by an MMRM analysis that showed that the 3 olanzapine LAI groups separated from placebo at day 7 through the end of the study.

The following treatment-by-subgroup interactions regarding baseline-to–end point changes in PANSS total scores were not statistically significant: age, sex, ethnic origin, investigator, and country. However, the treatment-by–previous depot exposure interaction was statistically significant. While the mean decreases in PANSS total scores were significantly greater for all 3 olanzapine LAI

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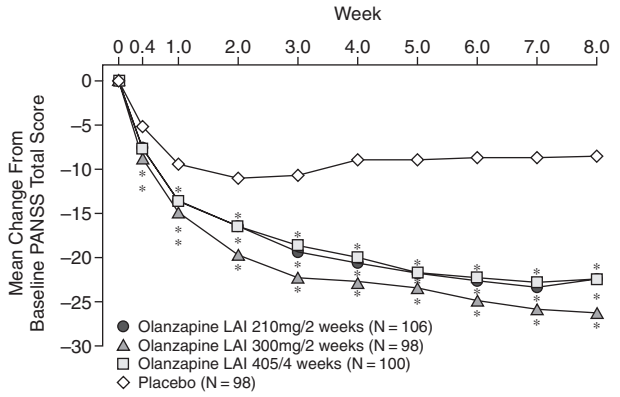
Figure 2. Weekly Mean Changes in PANSS Total Score of Patients With Schizophrenia Treated With Olanzapine Long-Acting Injection or Placebo (N = 404)



*p < .05 type III sum of squares (analysis of variance).
Abbreviations: LAI = long-acting injection, PANSS = Positive and Negative Syndrome Scale.

groups relative to placebo (all p values < .001) for both depot-naive patients and nonnaive patients, the significant interaction (p = .0411) indicated that the treatment effect was stronger in the depot-naive patients (all depot-naive effect sizes ≥ 0.9 and all nonnaive effect sizes ≥ 0.5).

On the secondary efficacy measures, all 3 olanzapine LAI groups showed significantly greater mean baseline-to–end point decreases in PANSS positive, negative, and general psychopathology symptom subscales (all p values < .001), PANSS-derived BPRS total (all p values < .001), and CGI-S (all p values < .05) scores relative to placebo (Table 2). By the fourth day of double-blind treatment, 51%, 52%, and 50% of patients in the 210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks olanzapine LAI groups, respectively, achieved clinical improvement from baseline (CGI-I score ≤ 3) compared with 26% for placebo (all p values < .001). The incidence of response was significantly higher for all 3 olanzapine LAI dosages (300 mg/2 weeks, 48.0% [p < .001]; 405 mg/4 weeks, 40.0% [p = .003]; and 210 mg/2 weeks, 47.2% [p < .001]) relative to placebo (20.4%).

Safety

Adverse events. A summary of the most frequently reported adverse events and serious adverse events is presented in Table 3. Sedation and increased appetite were reported significantly more frequently in the 300 mg/2 weeks group than the placebo group. Of the 25 sedation reports in the olanzapine LAI groups, 13 occurred in the first day after injection, and none were severe (moderate, N = 11; mild, N = 14). Injection site reactions, which were mild to moderate in severity, occurred in 11 patients (3.6%) treated with olanzapine LAI versus none for placebo (p = .073), and no patients discontinued because of injection site reactions.

No deaths occurred during this study. Overall, 19 patients (4.7%) experienced serious adverse events (210 mg/2 weeks, N = 6; 300 mg/2 weeks, N = 5; 405 mg/4 weeks, N = 3; placebo, N = 5) (Table 3).

Laboratory measures, vital signs, weight, and extrapyramidal symptoms. A summary of mean baseline-to–end point changes in safety measures is provided in Table 4.

Laboratory measures. Mean baseline-to–end point changes in fasting glucose did not differ significantly between treatment groups. Significant group differences were observed for mean baseline-to–end point changes in fasting total cholesterol (210 mg/2 weeks, 8.2 mg/dL, p = .004; 300 mg/2 weeks, 5.5 mg/dL, p = .015; 405 mg/4 weeks, 10.4 mg/dL, p < .001 vs. placebo, –7.0 mg/dL) and fasting triglycerides (210 mg/2 weeks, 26.3 mg/dL, p = .016; 405 mg/4 weeks, 30.3 mg/dL, p = .016 for the olanzapine LAI groups vs. placebo, –9.4 mg/dL). A significantly greater percentage of patients in the 210 mg/2 weeks (12.8%, p = .029) and 300 mg/2 weeks (14.3%, p = .016) olanzapine LAI groups experienced changes from normal to high levels of triglycerides relative to placebo (3.4%). An increase in aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) for olanzapine LAI 300 mg/2 weeks–treated patients was significantly greater than the change observed in placebo-treated patients (4.1 U/L vs. –3.9 U/L, p = .023). No other significant group differences were observed for baseline-to–end point or categorical changes in analytes related to liver function, AST/SGOT, or alanine aminotransferase/serum glutamic pyruvic transaminase.

Weight. Mean baseline-to–end point (LOCF) weight gain was significantly greater for the olanzapine LAI groups relative to placebo (all p values ≤ .001) (Table 4). Additional analyses using MMRM methodology showed significantly greater weight increases for the olanzapine LAI groups relative to placebo (210 mg/2 weeks, 4.8 kg; 300 mg/2 weeks, 4.8 kg; 405 mg/4 weeks, 3.2 kg; all p values < .001 vs. placebo, 0.3 kg). Furthermore, weight gain in the 210 mg/2 weeks and 300 mg/2 weeks groups was significantly greater relative to the 405 mg/4 weeks group. The incidence of weight gain ≥ 7% of baseline was significantly higher in the olanzapine LAI groups (210 mg/2 weeks, 23.6%, p = .046; 300 mg/2 weeks, 35.4%, p < .001; 405 mg/4 weeks, 27.0%, p = .012) relative to placebo (12.4%).

Electrocardiogram. No significant group differences were observed in mean baseline-to–end point changes on any of the electrocardiogram measures. In total, 1 patient in the 300 mg/2 weeks group experienced a QTc interval (Bazett's) ≥ 500 milliseconds during treatment. Six patients experienced a QTc interval (Bazett's) increase

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Table 3. Treatment-Emergent Adverse Events That Occurred in ≥ 5% of Patients in Any Treatment Group and Serious Adverse Events

	Olanzapine LAI Group			
Adverse Event	210 mg/2 wk (N = 106), N (%)	300 mg/2 wk (N = 100), N (%)	405 mg/4 wk (N = 100), N (%)	Placebo Group[a] (N = 98), N (%)
Headache	16 (15.1)	17 (17.0)	11 (11.0)	8 (8.2)
Insomnia	12 (11.3)	11 (11.0)	10 (10.0)	14 (14.3)
Sedation	7 (6.6)	10 (10.0)*	8 (8.0)	2 (2.0)
Constipation	7 (6.6)	6 (6.0)	6 (6.0)	12 (12.2)
Agitation	6 (5.7)	5 (5.0)	8 (8.0)	11 (11.2)
Weight gain	6 (5.7)	7 (7.0)	5 (5.0)	5 (5.1)
Cough	5 (4.7)	9 (9.0)	3 (3.0)	5 (5.1)
Diarrhea	7 (6.6)	5 (5.0)	2 (2.0)	4 (4.1)
Anxiety	3 (2.8)	2 (2.0)	5 (5.0)	6 (6.1)
Back pain	3 (2.8)	5 (5.0)	4 (4.0)	4 (4.1)
Dyspepsia	4 (3.8)	3 (3.0)	3 (3.0)	5 (5.1)
Nausea	5 (4.7)	4 (4.0)	5 (5.0)	2 (2.0)
Somnolence	1 (0.9)	3 (3.0)	6 (6.0)	5 (5.1)
Dry mouth	6 (5.7)	4 (4.0)	2 (2.0)	1 (1.0)
Paranoia	3 (2.8)	1 (1.0)*	2 (2.0)	7 (7.1)
Psychotic disorder	2 (1.9)	1 (1.0)	4 (4.0)	6 (6.1)
Delusion	2 (1.9)	2 (2.0)	2 (2.0)	6 (6.1)
Nasopharyngitis	6 (5.7)	1 (1.0)	3 (3.0)	2 (2.0)
Increased appetite	4 (3.8)	6 (6.0)*	1 (1.0)	0 (0.0)
Vomiting	1 (0.9)	2 (2.0)	6 (6.0)	2 (2.0)
Serious Adverse Event	N	N	N	N
Psychotic disorder	2	…	2	…
Schizophrenia	1	…	…	1
Agitation	…	…	1	…
Anxiety	…	1	…	…
Asthenia	…	…	…	1
Atrial fibrillation	…	…	…	1
Blood glucose increase	1	…	…	…
Chest pain	…	…	…	1
Cholecystitis	1	…	…	…
Convulsion	…	…	…	1
Depressed level of consciousness	…	1	…	…
Hip fracture	…	…	…	1
Pneumonia	…	1	…	…
Respiratory acidosis	…	1	…	…
Schizophrenia, paranoid type	…	1	…	…
Social problem	1	…	…	…

[a]One patient experienced 2 serious adverse events.
*p < .05 vs. placebo (Fisher exact test).
Abbreviation: LAI = long-acting injection.
Symbol: … = not applicable.

from baseline ≥ 60 milliseconds (210 mg/2 weeks, N = 3; 300 mg/2 weeks, N = 2; 405 mg/4 weeks, N = 1; placebo, N = 0).

Treatment-emergent extrapyramidal symptoms. Extrapyramidal symptoms were low at baseline for all treatment groups, and none of the group differences in baseline-to–end point changes on the Simpson-Angus or Barnes Akathisia scales or AIMS were clinically meaningful (Table 4).

DISCUSSION

In this 8-week, randomized, double-blind study, olanzapine LAI was significantly more efficacious than placebo for the treatment of acutely ill patients with schizophrenia. Decreases in PANSS total scores at end point were 22.5 to 26.3 points for the olanzapine LAI groups versus 8.5 points for the placebo group. Significant separation between all olanzapine LAI groups and placebo occurred within the first week and was sustained for the remainder of the study. Notably, patients in this study were markedly ill at baseline (PANSS total scores ~100) and had been ill a relatively long time (~17 years), and almost all had previously taken antipsychotics. These results suggest superior efficacy for olanzapine LAI relative to placebo and a notably early drug effect.

With respect to baseline illness severity, as well as magnitude and timing of symptom improvement, the present findings are consistent with those from previous studies of oral olanzapine in acutely ill patients with schizophrenia.[22–24] Mean baseline PANSS (mean = 101)

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Table 4. Mean (SD) Baseline-to–End Point Changes in Laboratory Values, Vital Signs, Weight, and Extrapyramidal Symptoms[a]

	Olanzapine LAI Group							
	210 mg/2 wk		300 mg/2 wk		405 mg/4 wk		Placebo Group	
Measure	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
Glucose, mg/dL[b]	96.5 (24.7)	3.9 (27.6)	100.0 (31.6)	–0.2 (29.9)	97.5 (24.4)	4.1 (32.3)	95.9 (31.0)	1.6 (19.6)
Cholesterol, mg/dL[b]	190.6 (46.5)	8.2 (37.0)[c]	194.5 (42.5)	5.5 (35.4)[c]	202.7 (44.8)	10.4 (35.3)[c]	199.5 (40.3)	–7.0 (34.6)
LDL cholesterol, mg/dL[b]	114.5 (41.3)	6.7 (33.1)	118.4 (35.2)	4.4 (28.3)	120.8 (32.8)	7.0 (31.0)	122.2 (35.8)	–2.7 (32.0)
HDL cholesterol, mg/dL[b]	45.5 (12.8)	–2.1 (10.2)	44.0 (10.6)	–1.5 (9.5)	44.9 (12.7)	–0.3 (9.4)	46.2 (10.9)	–2.0 (10.9)
Triglycerides, mg/dL	157.4 (126.9)	26.3 (96.7)[c]	165.8 (116.1)	17.6 (112.9)	176.1 (115.7)	30.3 (115.4)[c]	155.2 (81.9)	–9.4 (77.8)
AST/SGOT, U/L	29.2 (20.5)	–1.1 (24.5)	24.7 (16.2)	4.1 (17.9)[c]	25.1 (15.9)	1.6 (16.1)	28.3 (34.4)	–3.9 (35.3)
ALT/SGPT, U/L	33.6 (28.2)	5.4 (50.1)	30.9 (28.4)	7.9 (36.0)	33.1 (35.4)	3.1 (34.4)	29.4 (20.5)	–0.6 (26.8)
Extrapyramidal symptoms measure								
Simpson-Angus Scale total score	1.1 (2.0)	–0.4 (1.8)	0.8 (1.6)	–0.3 (1.3)	1.3 (2.1)	–0.7 (2.1)	0.7 (1.3)	–0.1 (1.5)
Barnes Akathisia Scale total score	0.4 (0.7)	–0.2 (0.7)	0.3 (0.6)	–0.0 (0.6)	0.4 (0.7)	–0.2 (0.8)	0.3 (0.6)	0.0 (0.6)
AIMS total score	1.0 (2.6)	–0.2 (1.7)[c]	1.1 (2.7)	–0.3 (1.3)[c]	1.1 (2.0)	–0.6 (1.5)[c]	0.9 (2.0)	0.3 (2.7)
Weight, kg	86.9 (21.5)	3.8 (8.1)[c]	85.4 (20.8)	3.9 (4.9)[c]	87.3 (22.1)	2.8 (4.1)[c]	81.9 (18.9)	0.3 (4.4)
Incidence of weight gain ≥ 7% of baseline, N (%)	…	25 (23.6)[d]	…	35 (35.4)[d]	…	27 (27.0)[d]	…	12 (12.4)

[a]Values are mean (SD) except where noted.
[b]Glucose and lipids values were obtained under fasting conditions (≥ 8 hours prior to venipuncture in which the only oral consumption was water).
[c]$p < .05$ vs. placebo (type III sum of squares ANOVA controlling for treatment and investigator).
[d]$p < .05$ vs. placebo (Fisher exact test).
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase, ANOVA = analysis of variance, AST/SGOT = aspartate aminotransferase/serum glutamic-oxaloacetic transaminase, HDL = high-density lipoprotein, LAI = long-acting injection, LDL = low-density lipoprotein.
Symbol: … = not applicable.

and BPRS (mean = 41) total scores confirm that the patient population was acutely ill at study entry. In an analysis of correlations between symptom rating scales, a PANSS total score of approximately 100 corresponded to a CGI severity rating of "markedly ill."[25] In a double-blind, placebo-controlled trial of oral olanzapine (dose range: 2.5–17.5 mg/day) in patients with schizophrenia,[23] mean baseline-to–LOCF end point changes in BPRS total scores were comparable to those observed in the present study (oral olanzapine, range: –6.7 to –15.2; olanzapine LAI, range: –14.1 to –16.4). BPRS total scores at baseline were also similar, indicating that the studies examined patient populations with comparable illness severities. Although the symptoms of schizophrenia may not have resolved completely in the present study (olanzapine LAI end point BPRS total scores, range: 25.0–26.6), the magnitude of treatment effects may have been limited by the 8-week duration. The duration of the study was constrained by concern for the safety of acutely ill patients treated with placebo. To ensure that patients could continue to receive treatment after leaving the study, they were given the option of entering an open-label, flexible dose study that evaluated the long-term safety of olanzapine LAI. It should also be noted that the duration of the current episode prior to study entry (range: 146–318.5 days) and the large variability around this measure suggest that a portion of the patient population may have been partially treatment responsive, especially since 94% of patients had received previous antipsychotic medications, and illness severity scores were nevertheless quite high.[23]

The significant treatment-by–depot history interaction indicated that, while treatment with olanzapine LAI produced significantly greater decreases in symptom severity relative to placebo in both depot-experienced and depot-naive groups, the treatment effect was larger for depot-naive patients. It is also likely that, for patients who received regular depot injections prior to entry into the study, medication adherence was not a contributing factor to their acute status. This finding may reflect the clinical observation that patients who receive treatment with depot antipsychotics are likely to have had a longer course of illness and may thus represent a population that is more difficult to treat.

The greater efficacy of olanzapine LAI relative to placebo observed within 1 week of treatment is notable given that no oral antipsychotic supplementation was permitted. This may be explained by the chemical properties of the pamoate salt of olanzapine, which allow for release of active compound in the first hours after injection. (Pharmacokinetic data to be presented in detail in a separate publication.) The early and sustained efficacy of treatment with olanzapine LAI suggests that transitioning from previous oral medications can be relatively straightforward, because the calculation and timing of supplemental oral doses may not be necessary. Furthermore, the present data suggest that the 2-week and 4-week dosing regimens of olanzapine LAI were similarly efficacious. This finding may be relevant to patients for whom and services in which, for various reasons, injections every 4 weeks are more suitable. For the physician, the choice of dosing

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intervals provides a greater degree of dynamic prescribing control.

The incidence of concomitant benzodiazepine use in this study was high (74%) but similar to those reported in previous oral olanzapine studies.[22–24] The adjunctive use of benzodiazepines with atypical antipsychotics has been recommended in current clinical guidelines for the treatment of acutely psychotic patients[26] and has been observed in clinical practice. Although the use of benzodiazepines in this study may account for some of the changes in symptom severity, the differential outcomes in efficacy cannot be attributed to their use, because no significant group differences were observed with respect to rates of use or mean daily dose.

One concern with using an intramuscularly injected depot antipsychotic is that patients with schizophrenia may be reluctant to have an injection because of the perception that it might be painful. Although no formal ratings of injection site pain were undertaken, few injection-site reactions were reported, and those reported were considered mild to moderate in severity. It should be noted that injection site adverse events were only reported when patients complained of symptoms and there was no systematic collection of injection site events; thus, their frequency may have been underestimated. Nevertheless, no patient dropped out of the study because of an injection site adverse event.

Patients treated with olanzapine LAI experienced significant weight gain (mean = 4.3 kg), and the magnitude was consistent with that observed previously with oral olanzapine (mean = 2–4 kg).[22,23] Significantly more patients in the olanzapine LAI treatment groups gained ≥ 7% of their baseline weight relative to placebo. The degree of weight gain during this short 8-week trial was consistent with that seen with oral olanzapine, thereby raising similar benefit/risk decisions that clinicians face when using oral olanzapine. For these patients, mitigation strategies[27–29] and other options should be considered, depending on the efficacy and tolerability of alternative treatments.

Significant differences in some metabolic parameters were observed between the olanzapine LAI and placebo treatment groups. There were no significant differences in mean change in fasting glucose, but longer studies are needed, since changes in glucose homeostasis may take longer than 8 weeks to become apparent. Significantly greater mean changes in fasting total cholesterol and fasting triglycerides were reported in patients treated with olanzapine LAI compared to patients treated with placebo. Thus, as with oral olanzapine, patients treated with olanzapine LAI should be monitored regularly for hyperglycemia and diabetes.[30,31]

The short study length presents a limitation in terms of understanding the role of olanzapine LAI in the broader management of schizophrenia. The 8-week duration was chosen to minimize exposure of acutely ill patients to placebo while permitting a sufficient time window to evaluate the efficacy and tolerability of this novel formulation of olanzapine. Further studies will be required to evaluate long-term outcomes in acutely ill patients treated with olanzapine LAI. Additionally, long-term studies are necessary to evaluate the role of olanzapine LAI for maintenance treatment in patients who are not currently experiencing acute exacerbation.

In conclusion, olanzapine LAI was significantly more efficacious than placebo in acutely ill patients with schizophrenia during 8 weeks of treatment. Importantly, the early efficacy of olanzapine LAI without oral supplementation observed in this study was similar to that observed with oral olanzapine. The benefits of olanzapine LAI for the treatment of acutely ill patients with schizophrenia should be considered within the context of the known safety profile of olanzapine and the potential risks of intramuscular injection. Consistent with changes seen with oral olanzapine, patients treated with olanzapine LAI experienced significant increases in cholesterol, triglycerides, and weight. Informed discussions between patients and their physicians are warranted when considering this treatment among the available options. Longer term studies will be necessary to further characterize the relative benefits and risks of treatment with this long-acting formulation of olanzapine, especially with respect to relapse prevention through improvements in adherence.

Drug names: biperiden (Akineton), haloperidol decanoate (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal).

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