

ORIGINAL RESEARCH

OPEN ACCESS

Full open access to this and thousands of other papers at <http://www.la-press.com>.

Long-Term Safety and Tolerability of Open-Label Olanzapine Long-Acting Injection in the Treatment of Schizophrenia: 190-Week Interim Results

David P. McDonnell, Scott W. Andersen, Holland C. Detke, Fangyi Zhao and Susan B. Watson

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA.

Corresponding author email: mcdonneldp@lilly.com

Abstract: The primary objective of this ongoing study is to examine the long-term safety and tolerability of olanzapine long-acting injection (LAI). Current results are from a 190-week interim analysis. Patients were 18–75 years of age with schizophrenia (N = 909) or schizoaffective disorder (N = 22) previously enrolled in 1 of 3 randomized clinical trials of olanzapine LAI. In this open-label extension study, all patients received flexibly-dosed olanzapine LAI every 2–4 weeks. At time of analysis, rate of study discontinuation was 46.3%. The 18-month discontinuation rate was 34.2%. Adverse events in $\geq 5\%$ of patients were increased weight, insomnia, anxiety, somnolence, headache, and nasopharyngitis. There were 26 occurrences of post-injection delirium/sedation syndrome which all fully resolved within 72 hours. Mean weight change was +1.81 kg, with 32.1% of patients experiencing $\geq 7\%$ weight gain. Mean Clinical Global Impressions-Severity scores remained stable throughout (2.9 at baseline to 2.8 at endpoint). Pharmacokinetic analyses indicated consistent olanzapine plasma concentrations over time, with no evidence of long-term accumulation. Safety profile was consistent with that of oral olanzapine, with the exception of findings specific to intramuscular injection. During the study period, there were 16 (1.7%) occurrences of treatment-emergent diabetes and 1 occurrence of treatment-emergent diabetic ketoacidosis. Percentages of patients with EPS scale-defined treatment-emergent akathisia, parkinsonism, and dyskinesia were 3.3%, 6.6%, and 3.0%, respectively.

Keywords: schizophrenia, olanzapine, long-acting, injection, long-term safety, tolerability

Clinical Medicine Insights: Psychiatry 2011:3 37–47

doi: [10.4137/CMPsy.S6659](https://doi.org/10.4137/CMPsy.S6659)

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.



Introduction

Recently introduced long-acting formulations of second-generation antipsychotics offer the advantages of atypical agents, such as a lower risk of extrapyramidal symptoms (EPS), while also offering the prospect of greater adherence due to its less frequent dosing schedule. The use of antipsychotics in depot form has been limited in the United States (approximately 15% of patients with schizophrenia on maintenance treatment),^{1,2} but the use of depots may increase as new atypical depot formulations are becoming available. Because depot antipsychotics are intended for long-term use, there is a critical need for long-term safety data. However, few studies of depot antipsychotics have examined use beyond 1 year of treatment.

Safety results for long-acting risperidone, the first long-acting second generation antipsychotic introduced to the market, have been reported in a 12-month open-label study (N = 615)³ and a long-term open-label extension study (N = 371) of at least 12 months in duration.⁴ The most commonly reported adverse events in these studies were psychosis, headache, insomnia, agitation, and anxiety. Rates of extrapyramidal adverse events were 25% for Fleischhacker et al and 33% and 22% for the 2 study cohorts in Lindenmayer et al. Reported 12-month discontinuation rates were 35% for Fleischhacker et al and 45% and 48% for Lindenmayer et al. A more recent subgroup analysis⁵ of a larger study of risperidone long-acting injection⁶ followed 529 patients out to 18 months and showed an 18-month discontinuation rate of 55.7% based on Kaplan-Meier estimates.

Two previous studies have presented data on the acute efficacy and safety of olanzapine long-acting injection (LAI) in schizophrenia. In an 8-week, randomized, placebo-controlled study of olanzapine LAI in schizophrenia,⁷ patients were randomly assigned to 1 of 3 dosing groups or to placebo. Supplementation with oral antipsychotics was not permitted. Mean decreases in baseline-to-endpoint Positive and Negative Syndrome Scale (PANSS) total score were significantly greater for all olanzapine LAI groups versus placebo. The acute tolerability profile for olanzapine LAI appeared consistent with that for oral olanzapine, with the exception of injection-related adverse events, and the results did not suggest any differences in efficacy between the 2-week and 4-week dosing regimens.

In a maintenance study of olanzapine LAI,⁸ patients with schizophrenia who were stabilized on open-label oral olanzapine for 4 to 8 weeks were randomly assigned to 1 of 4 olanzapine LAI dosing groups (1 of which was considered subtherapeutic) or to oral olanzapine for 24 weeks of double-blind treatment. At 24 weeks, relapse rates ranged from 5% to 16% for the 3 therapeutic dose groups, and the 4-week and pooled 2-week dosing regimens demonstrated noninferiority to oral olanzapine as well as to each other. There were no clinically significant differences between olanzapine LAI and oral olanzapine with respect to laboratory measures, vital signs, electrocardiography, or EPS. Two olanzapine LAI-treated patients in this study experienced post-injection delirium/sedation syndrome following possible inadvertent intravascular injection, resulting in symptoms consistent with olanzapine overdose.⁹

Although these studies have helped to establish the efficacy and safety of olanzapine long-acting injection in the acute and maintenance treatment of schizophrenia, longer-term data are helpful when evaluating a depot medication intended for chronic use. The present trial is an open-label extension designed with the primary objective of studying the long-term safety and tolerability of olanzapine LAI in patients with schizophrenia or schizoaffective disorder. This paper reports results from an interim analysis with up to 3.6 years (190 weeks) of data from patients with schizophrenia or schizoaffective disorder treated with olanzapine LAI.

Methods

Study design

All procedures were conducted in compliance with the Declaration of Helsinki and any standards applicable to individual institutional review boards. Data for this analysis were collected from 30-Aug-2004 (first patient enrolled) to 30-Apr-2008, which was the interim analysis cutoff date for all analyses. The study was conducted at 128 sites in 25 countries.

Previous (feeder) study designs

Patients participated in 1 of 3 feeder studies prior to entering the present open-label study. The first was an 8-week randomized, double-blind, controlled study of olanzapine LAI (N = 306) versus placebo (N = 98) in the treatment of acutely ill patients with schizophrenia.⁷



The second study was a maintenance of effect study in which patients with schizophrenia were stabilized on oral olanzapine for 4 to 8 weeks and then randomly assigned to oral olanzapine (N = 322) or olanzapine LAI (N = 743) for 24 weeks of double-blind treatment.⁸ The third study was a Phase I pharmacokinetic study (olanzapine LAI, N = 134),¹⁰ which also included patients with schizoaffective disorder.

Current study design

Patients could enter this open-label extension trial immediately following any of the 3 feeder studies. No more than 10 days were to elapse between the feeder and the extension. All patients received an injection of olanzapine LAI 210 mg at the first open-label visit. Beginning at Visit 3 (2 weeks), patients received a flexible dose (45 to 405 mg) of olanzapine LAI at flexible dosing intervals of 2 to 4 weeks. Patients who received an individual dose of >300 mg were required to wait 4 weeks to receive their next injection (see Table 1 for

Table 1. Permissible dosages and dosing intervals for olanzapine long-acting injection.

Permissible dosages (mg)			Injection volume (mL)
2-week interval	3-week interval	4-week interval	
45	45	45	0.3
60	60	60	0.4
75	75	75	0.5
90	90	90	0.6
105	105	105	0.7
120	120	120	0.8
135	135	135	0.9
150	150	150	1.0
165	165	165	1.1
180	180	180	1.2
195	195	195	1.3
210	210	210	1.4
225	225	225	1.5
240	240	240	1.6
255	255	255	1.7
270	270	270	1.8
285	280	280	1.9
300	300	300	2.0
–	–	315	2.1
–	–	330	2.2
–	–	345	2.3
–	–	360	2.4
–	–	375	2.5
–	–	390	2.6
–	–	405	2.7

permissible dosages and dosing intervals). Any individual dose could not exceed 405 mg, with the cumulative total allowed in a 4-week period limited to no more than 600 mg, except when switching from a 2- or 3-week dosing interval to a 4-week dosing interval. The investigator assessed the patients' clinical status and adjusted the dose of olanzapine LAI according to clinical judgment. Concomitant antipsychotic medication was limited to supplemental oral olanzapine, at a dose up to 20 mg/day, at the clinical discretion of the investigator. Other concomitant psychotropic medications, including antidepressants and mood stabilizers, were generally allowed. Disallowed medications included anorexics, antiarrhythmics, anticonvulsants (unless used as mood stabilizers), antiretrovirals, psychostimulants, and systemic/oral steroids. A complete list of all allowed and disallowed medications is available upon request. Patients were seen weekly from Visit 3 to Visit 9 and at each injection visit thereafter (see Measures for specific assessment schedule). Final enrollment completed with 931 patients in the study. At the time of this interim analysis, study participation ranged from 19 to 43 months.

Patients

Patients were 18 to 75 years of age, had a diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV or DSM-IV-Text Revision), and had previously completed 1 of 3 controlled studies of olanzapine LAI. 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. All patients signed a written informed consent after receiving a complete description of the study and prior to participating.

Measures

Safety and tolerability

Measures of safety and tolerability included incidence of unsolicited treatment-emergent adverse events, mean changes in vital signs, treatment-emergent categorical changes in glucose and lipid measures, and mean changes and treatment-emergent categorical changes in weight and QTc.

The screening assessment, which was conducted at the first open-label visit, included a standard



history and physical, psychiatric examination, laboratory profile, and electrocardiogram (ECG). Vital signs were measured at every injection visit, and otherwise were measured at Weeks 1, 4, and 8; at each quarterly or 6-month visit; and at the discontinuation visit. Laboratory assessments were conducted at the first open-label visit; at Weeks 1, 4, and 8; at each quarterly or 6-month visit; and at the discontinuation visit. Fasting status was required at each 6-month visit and at the discontinuation visit. Lipids results represent a combination of fasting and non-fasting visits but glucose was analyzed separately based on actual fasting status. An ECG was conducted at Week 1, at each 6-month visit, and at the discontinuation visit. Spontaneously reported adverse events were recorded at each visit. EPS were assessed at the first open-label visit, at each 6-month visit, and at the discontinuation visit using the Simpson-Angus Scale,¹¹ the Barnes Akathisia Scale,¹² and the Abnormal Involuntary Movement Scale (AIMS).¹³

In addition to the safety/tolerability assessments mentioned above, beginning in August 2006, all ongoing patients were required to be observed for a minimum of 3 hours following each olanzapine LAI injection in order to assess for signs of post-injection delirium/sedation syndrome and to manage any such signs or symptoms that appeared. As part of this change in study procedures, mental status assessments were conducted on all patients immediately prior to an olanzapine LAI injection and at 1, 2, and 3 hours post injection.

Efficacy

Efficacy was measured using mean changes on the PANSS¹⁴ total, positive, and negative scores and on the Clinical Global Impressions Severity of Illness scale (CGI-S).¹⁵ The PANSS was administered at the first open-label visit, at each 6-month visit, and at the discontinuation visit. The CGI-S was administered at each visit. Measures of effectiveness were rates of and time to discontinuation due to any reason, due to adverse event, and due to lack of efficacy.

Pharmacokinetic methods

Blood samples for the assessment of olanzapine plasma concentrations were collected at quarterly study visits and at the patient's last visit. Plasma samples were measured by a validated high performance

liquid chromatography/electrochemical detection (HPLC/ECD) method at BAS Analytics, Inc., West Lafayette, Indiana, US. Plasma olanzapine concentration data were analyzed graphically and descriptively. Given its open-label nature, patients in this study were on a range of dosages and permitted by protocol to change dosage at the clinician's discretion. To facilitate interpretation of pharmacokinetic data and to compare results across the range of doses studied, steady-state olanzapine concentrations were normalized by dividing an individual's measured olanzapine concentration at each visit by the total dose of olanzapine administered over the dosing regimen.

Statistical methods

Analyses were based on all the patients who received at least 1 depot injection. Except for adverse event analyses, patients were included in an analysis only if they had a baseline and at least 1 postbaseline measure. Baseline was defined as the observation at the patient's first open-label visit. All hypotheses were tested at a 2-tailed significance level of 0.05. Mean change analyses of continuous data used a last-observation-carried-forward (LOCF) approach and were evaluated using 1-sample t-tests with a null hypothesis of mean change = 0. Incidences and rates were calculated for categorical data. Unless otherwise indicated, percentages for adverse events and reasons for discontinuation used all patients as a denominator. Time-to-event analyses were conducted using Kaplan-Meier survival analysis.

Results

Patient characteristics

A total of 931 patients were enrolled in this open-label trial. Most patients were male, with a mean age of 39 years. Mean baseline scores for the PANSS total score (54.5, SD = 17.7) and for the CGI-S (2.9, SD = 0.9) indicated borderline to mild illness severity, which was consistent with the patients' having been stabilized on medication prior to study entry. Table 2 summarizes baseline demographics and characteristics for all patients.

Patient disposition and dosing information

The all-cause discontinuation rate was 27.3% at 12 months of study participation and 34.2% at 18 months of study

**Table 2.** Baseline patient demographic and illness characteristics.

Variable	Olanzapine LAI N = 931
Age (yrs), mean (SD)	39.3 (11.7)
Male, n (%)	621 (66.7)
Origin, n (%)	
African	102 (11.0)
Caucasian	629 (67.6)
East Asian	39 (4.2)
Hispanic	140 (15.0)
Native American	2 (0.2)
West Asian	19 (2.0)
Weight in kg, mean (SD)	80.2 (17.3)
Age of onset of schizophrenia, mean (SD)	25.3 (8.6)
≥2 episodes in last 24 mos, n (%)	387 (42.6)
Diagnosis of schizophrenia, n (%)	909 (97.6)
Diagnosis of schizoaffective disorder, n (%)	22 (2.4)
CGI-S, mean (SD)	2.9 (0.9)

Abbreviations: CGI-S, Clinical Global Impressions Severity of Illness; LAI, long-acting injection; mos, months; N/n, number; SD, standard deviation; yrs, years.

participation. When not adjusting for length of time in the trial, the discontinuation rate was 46.3% of all enrolled patients at the time of the interim analysis. Table 3 shows primary reasons for discontinuation at 12 and 18 months of study participation, and for the entire study period (ie, up to the data cut-off date).

Based on injections with a quantifiable injection interval (n = 28,750), the mean prescribed dose across all olanzapine LAI injections was the equivalent of 15.5 mg/day. Dosing ranged from a minimum of 45 mg approximately every 4 weeks (1.6 mg/day) to a maximum of 405 mg approximately every

2 weeks (28.9 mg/day; use of a dose of 405 mg/2 weeks was a protocol violation). The most frequently used dosages (≥1% of total injections) were 300mg/2weeks (29.5% of injections), 405 mg/4 weeks (17.4%), 210mg/2weeks (10.3%), 300mg/4weeks (6.7%), 210 mg/4 weeks (5.6%), 300 mg/3 weeks (5.3%), 210 mg/3 weeks (2.9%), 150 mg/2 weeks (1.8%), and 150 mg/4 weeks (1.5%). Oral olanzapine supplementation was used at some time by 24.9% of patients and was sporadic, for a cumulative average of 133 days during the study at a mean dose of 2.6 mg/day oral olanzapine. Rate of concomitant benzodiazepine use was 21.1% for an average of 205 days at a mean dose of 4.9 mg/day (in lorazepam equivalents) (SD = 14.0). Rate of concomitant anticholinergic use was 4.9% for an average of 326 days at a mean dose of 3.0 mg/day (in biperiden equivalents) (SD = 1.5).

Olanzapine plasma concentrations

Steady-state olanzapine plasma concentrations remained consistent over time, with no evidence of continuing accumulation over the course of 3.5 years of treatment (Fig. 3). Median dose-normalized olanzapine plasma concentrations were 2.26 (ng/mL)/(mg/day) with a range of 0.87 (ng/mL)/(mg/day) (10th percentile) to 4.73 (ng/mL)/(mg/day) (90th percentile), consistent with concentrations previously reported for olanzapine LAI⁸ and oral olanzapine.¹⁶

Safety and tolerability

All patients who entered the study (N = 931) were evaluated for safety. There were 1,676 patient-years of exposure to olanzapine LAI during the study

Table 3. Patient discontinuation at 12 and 18 months of study participation and at the data cutoff date.

Reason for discontinuation	At 12 months (N = 931)		At 18 months (N = 931)		At data cutoff (N = 931)	
	n	%	n	%	n	%
Continuing study	677	72.7	613	65.8	500	53.7
Patient decision/withdrew consent	128	13.7	157	16.9	218	23.4
Adverse event	37	4.0	50	5.4	62	6.7
Lost to follow-up	37	4.0	45	4.8	53	5.7
Physician decision	18	1.9	25	2.7	30	3.2
Lack of efficacy	20	2.1	22	2.4	25	2.7
Protocol violation	9	1.0	10	1.1	11	1.2
Sponsor decision	3	0.3	6	0.6	27	2.9
Death	2	0.2	3	0.3	5	0.5



period and a total of 30,480 injections of olanzapine LAI were administered.

Adverse events

The 5 most commonly reported treatment-emergent adverse events were increased weight, insomnia, anxiety, somnolence, and headache. Table 4 summarizes the treatment-emergent adverse events reported by $\geq 2.0\%$ of the patients, in order of frequency. Adverse events reported as the reason for discontinuation in 2 or more patients were schizophrenia (n = 12), weight increased (n = 7), psychotic disorder (n = 6), somnolence (n = 4), suicidal ideation (n = 3), blood glucose increased (n = 2), diabetes mellitus (n = 2), hypertension (n = 2), suicide attempt (n = 2), and tardive dyskinesia (n = 2). Serious adverse events (SAEs; defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: 1) life-threatening, 2) death, 3) hospitalization/prolongation of hospitalization, 4) congenital anomaly, 5) persistent or significant

disability/incapacity, or 6) required intervention to prevent permanent impairment/damage) were experienced by 140 (15.0%) patients. SAEs reported by 2 or more patients were schizophrenia (n = 29), psychotic disorder (n = 19), sedation (n = 8), suicidal ideation (n = 7), agitation (n = 6), paranoia (n = 6), somnolence (n = 6), anxiety (n = 5), confusional state (n = 5), aggression (n = 4), depression (n = 4), dizziness (n = 3), hypertension (n = 3), overdose (n = 3), suicide attempt (n = 3), appendicitis (n = 2), breast cancer (n = 2), cellulitis (n = 2), delirium (n = 2), diabetes mellitus (n = 2), auditory hallucination (n = 2), myocardial infarction (n = 2), and pneumonia (n = 2). There were 5 patient deaths during the study period. Causes of death were acute heart failure with associated toxic/alcoholic heart damage, cardiomyopathy (n = 1), severe leptospirosis (n = 1), essential hypertension, probable hypertensive stroke (n = 1), pneumonia (n = 1), and hypertrophic cardiomyopathy (n = 1). None of these deaths was considered related to study drug or study procedures in the opinion of the investigator.

Injection-site adverse events were reported by 34 patients (3.7%, see Table 5). The only event with incidence greater than 1% was injection site pain (1.5%). Other events included irritation, reaction, induration, nodule, swelling, mass, discoloration, and hemorrhage. There were 26 occurrences of post-injection delirium/sedation syndrome⁹ in 25 patients during the study period. These patients experienced temporary symptoms of delirium and/or excessive sedation following possible inadvertent intravascular

Table 4. Treatment-emergent adverse events occurring in $\geq 2.0\%$ of patients receiving olanzapine long-acting injection.

Event	Olanzapine LAI	
	n	%
Any event	621	66.7
Weight increased	116	12.5
Insomnia	80	8.6
Anxiety	79	8.5
Somnolence	77	8.3
Headache	61	6.6
Nasopharyngitis	58	6.2
Dizziness	46	4.9
Depression	45	4.8
Sedation	45	4.8
Weight decreased	35	3.8
Schizophrenia	34	3.7
Fatigue	33	3.5
Diarrhea	30	3.2
Psychotic disorder	30	3.2
Agitation	29	3.1
Back pain	27	2.9
Hypertriglyceridemia	26	2.8
Influenza	26	2.8
Hypertension	24	2.6
Increased appetite	24	2.6
Constipation	21	2.3
Nausea	19	2.0

Abbreviation: LAI, long-acting injection.

Table 5. Injection site reactions occurring in ≥ 2 patients receiving olanzapine long-acting injection.

Adverse event	Olanzapine LAI N = 931	
	n	%
Patients with any injection site reaction event	34	3.7
Injection site pain	14	1.5
Injection site irritation	6	0.6
Injection site reaction	4	0.4
Skin induration	3	0.3
Injection site hemorrhage	2	0.2
Injection site induration	2	0.2
Injection site nodule	2	0.2
Injection site swelling	2	0.2

Abbreviation: LAI, long-acting injection.



injection of a portion of the dose. Clinical presentation varied but was consistent with symptoms reported in cases of oral olanzapine overdose and could include any of the following: sedation, dizziness, confusion, disorientation, slurred speech, altered gait, agitation, EPS, hypertension, convulsions, or unconsciousness. Onset of symptoms ranged from immediately to 300 minutes post injection, with a median onset time of 25 minutes post injection. All 25 patients fully recovered within 3 to 72 hours. Incidence of post-injection syndrome per injection for this interim analysis was 0.09% of injections. In 19 of the 26 cases, patients chose to continue treatment with olanzapine LAI following the post-injection syndrome event.

Vital signs and weight

There were small but statistically significant mean increases in blood pressure (≤ 3 mm Hg standing and supine systolic, standing and supine diastolic), pulse rate (approx. 2 bpm, standing and supine), and temperature (0.04 °C). These changes in vital signs were not judged to be clinically meaningful. Mean weight gain from baseline to endpoint was 1.81 kg (SD = 6.57) over an average of 642 days. During the study period, 295 patients (32.1%) experienced an increase of $\geq 7\%$ of baseline body weight, whereas 157 patients (17.1%) experienced a decrease of $\geq 7\%$ of baseline body weight.

Laboratory analytes

Mean change in fasting glucose (mg/dL) was +3.24 (SD = 21.80) from a baseline of 97.30 (SD = 22.52). Mean changes in cholesterol measures (mg/dL) were

as follows: total cholesterol +2.32 (SD = 35.91) from a baseline of 198.07 (SD = 42.47); HDL cholesterol +1.16 (SD = 10.04) from a baseline of 43.63 (SD = 12.36); and LDL cholesterol +0.39 (SD = 31.27) from a baseline of 121.62 (SD = 37.07). Mean change in triglycerides (mg/dL) was +5.31 (SD = 130.09) from a baseline of 169.91 (SD = 109.73). Mean change in prolactin ($\mu\text{g/L}$) was +3.44 (SD = 25.17) from a baseline of 16.93 (SD = 18.33). Treatment-emergent significant changes in glucose and lipid measures, from normal to borderline and normal to high/very high are shown in Table 6. There were 16 (1.7%) occurrences of reported treatment-emergent diabetes mellitus. One patient reported treatment-emergent ketoacidosis.

Electrocardiography

ECG analyses showed that there was a statistically significant increase in the QTc interval, Bazett: +1.2 msec (SD = 17.4), $P = 0.041$; however, Fridericia: +0.6 msec (SD = 15.6), $P = 0.285$ was not significant. Percentage of patients with baseline to endpoint changes ≥ 60 msec was 0.1% (Bazett) and 0.3% (Fridericia). One patient had QTc ≥ 500 msec based on Bazett; none had QTc ≥ 500 msec based on Fridericia.

Extrapyramidal symptoms

On scales measuring EPS, mean change from baseline on the Barnes Akathisia Scale was +0.00 (SD = 0.47, $P = 0.774$) from baseline of 0.12 (SD = 0.42). The percentage of patients with scale-defined treatment-emergent akathisia (Barnes global score of ≥ 2 at

Table 6. Percentages of patients with categorical glucose and lipids values at any time.

Analyte	Category	N	n	%
Glucose (fasting) ²¹	Normal to high (baseline <100 mg/dL and ≥ 126 at any time)	871	48	5.5
Total cholesterol ²²	Normal to borderline (baseline <200 mg/dL and ≥ 200 to <240 at any time)	517	160	30.9
	Normal to high (baseline <200 mg/dL and ≥ 240 mg/dL at any time)	517	27	5.2
LDL cholesterol ²²	Normal to borderline (baseline <100 mg/dL and ≥ 100 to <160 at any time)	260	131	50.4
	Normal to high (baseline <100 mg/dL to ≥ 160 at any time)	260	8	3.1
HDL cholesterol ²²	Normal to borderline (baseline ≥ 40 mg/dL and <40 at any time)	519	128	24.7
Triglycerides	Normal to borderline (baseline <150 mg/dL and ≥ 150 and <200 at any time)	488	107	21.9
	Normal to high (baseline <150 mg/dL and ≥ 200 to <500 at any time)	488	70	14.3
	Normal to very high (baseline <150 mg/dL and ≥ 500 at any time)	488	1	0.2

Notes: Ns represent number of patients with normal baseline and at least 1 post-baseline measurement. Lipids results represent a combination of fasting and non-fasting visits but glucose was analyzed separately based on actual fasting status.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.



any postbaseline visit and baseline Barnes global score <2) was 3.3%. Mean change on the Simpson–Angus scale was -0.11 (SD = 1.57, $P = 0.036$) from a baseline of 0.75 (SD = 1.62). Percentage of patients with scale-defined treatment-emergent parkinsonism (total Simpson–Angus score of >3 at any postbaseline visit and a baseline total score ≤ 3) was 6.6%. Mean change on the AIMS was -0.06 (SD = 1.52, $P = 0.256$) from a baseline of 0.49 (SD = 1.40). Percentage of patients with scale-defined treatment-emergent dyskinesia (a score of ≥ 3 on any 1 of the AIMS items 1 through 7, or a score of 2 or more on any 2 of these items at any post-baseline visit, without either at baseline) was 3.0%.

Efficacy and effectiveness

Baseline-to-endpoint mean change was -0.26 (SD = 14.5) on the PANSS total score, -0.05 (SD = 4.3) on the PANSS positive score, and -0.13 (SD = 4.5) on the PANSS negative score. Mean baseline CGI-S total score was 2.92 (SD = 0.9), borderline to mildly ill, and this level of severity was maintained throughout the study period (see Fig. 1). There was an overall LOCF baseline-to-endpoint CGI-S mean change of -0.15 (SD = 0.9).

During the study period, 222 patients (23.8%) were hospitalized, with the majority of hospital days

attributed to psychiatric (11.13 days per patient year) rather than to general medical (1.34 days per patient year) or ICU care (0.07 days per patient year).

Times to discontinuation due to any reason, due to adverse event, and due to lack of efficacy are depicted in Figure 2. Median time to all-cause discontinuation was 1,044 days (95% C.I.: 945, 1,204).

Discussion

In this interim analysis of an open-label extension trial of olanzapine LAI in patients with schizophrenia and a small number of patients with schizoaffective disorder, the types of adverse events reported were generally consistent with the known safety profile of olanzapine,¹⁷ with the exception of those specific to an injection. The profile of injection site-related adverse events appeared to be generally consistent with that seen with other products that involve the use of an intramuscular injection. Patients gained an average of 1.8 kg, with almost one third of patients experiencing clinically significant weight gain. Some patients experienced worsening in glucose and lipids measures (categorical increases in glucose, total cholesterol, LDL cholesterol, and triglycerides and decreases in HDL cholesterol), consistent with the safety profile for oral olanzapine. Pharmacokinetic

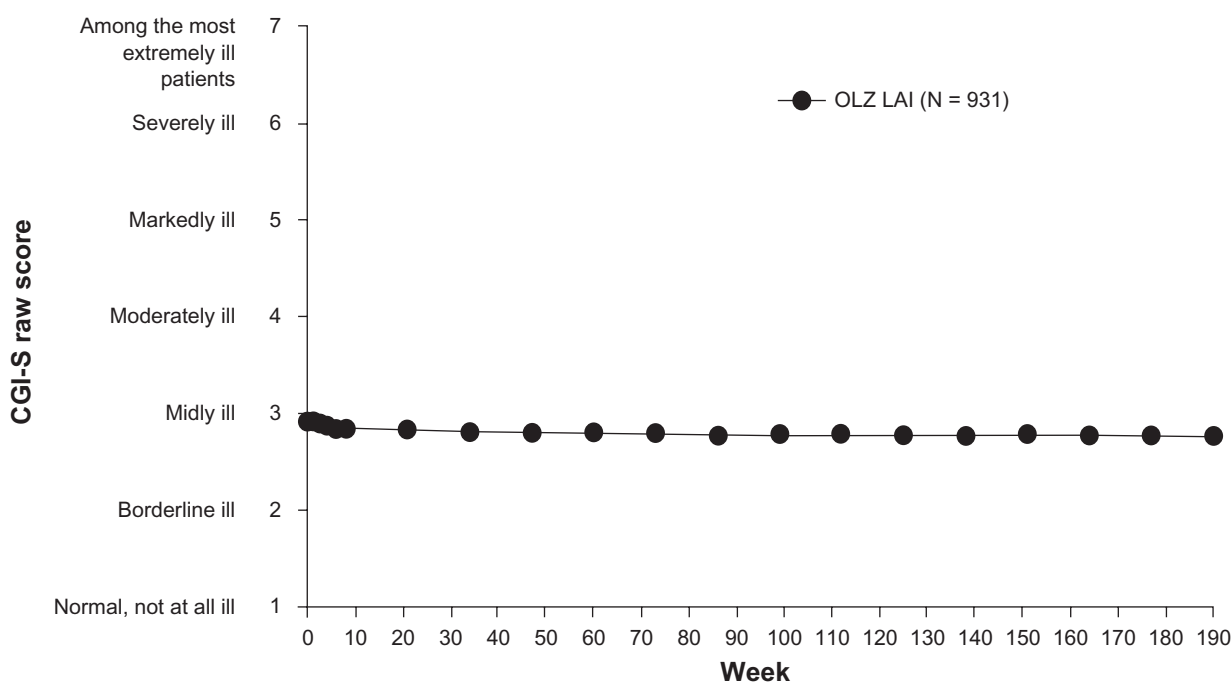


Figure 1. The CGI-S visit-wise mean score by week for all 931 patients enrolled in the olanzapine LAI open-label extension study (mean baseline = 2.9, mean endpoint = 2.8, $P < 0.001$).

Abbreviations: CGI-S, Clinical Global Impressions Severity of Illness scale; OLZ LAI, olanzapine long-acting injection.

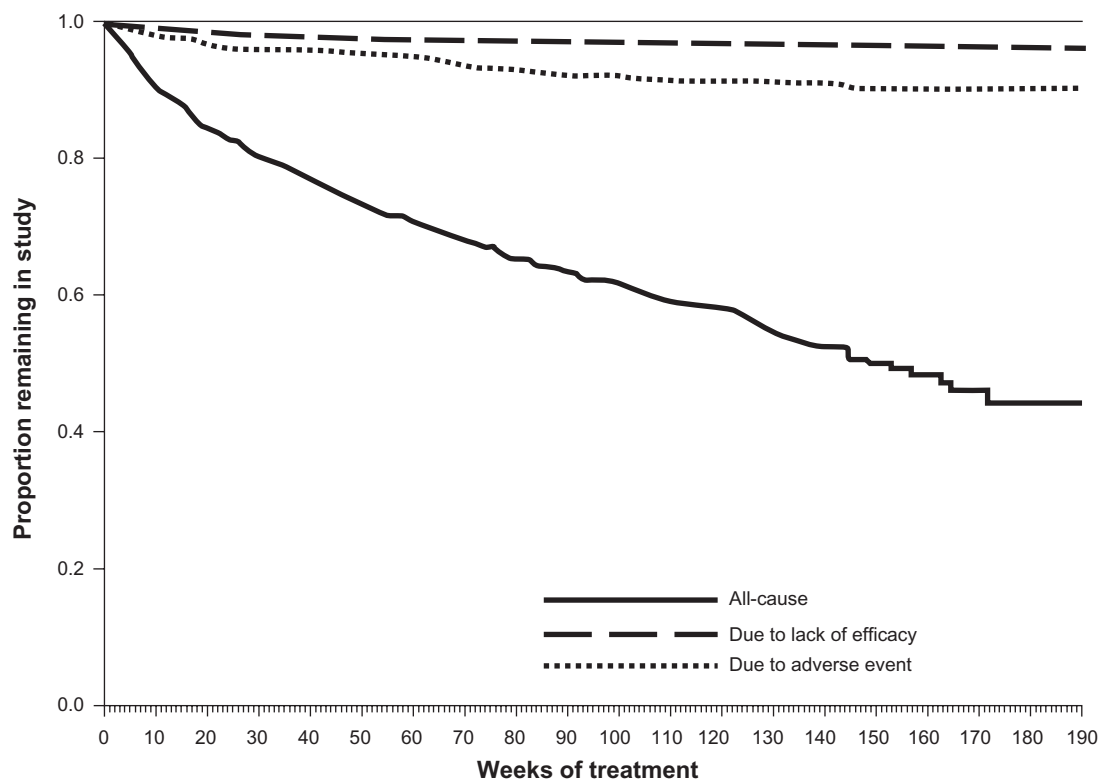


Figure 2. Kaplan-Meier survival curves showing time to all-cause discontinuation, time to discontinuation due to lack of efficacy, and time to discontinuation due to adverse event during the 190-week interim analysis for the 931 patients enrolled in the olanzapine LAI open-label extension study. Median time to all-cause discontinuation was 1,044 days (95% C.I.: 945, 1,204).

analyses revealed no indication of long-term systemic accumulation of olanzapine, even after 3.5 years of treatment.

Post-injection delirium/sedation syndrome, which is believed to be related to inadvertent intravascular injection of a portion of the dose resulting in olanzapine overdose,¹⁸ occurred in 0.09% of injections. All patients with post-injection delirium/sedation syndrome in this study period fully recovered without lingering or permanent sequelae. Most patients who experienced post-injection syndrome during the study (73%) chose to continue treatment with olanzapine LAI following the event. As a result of the possibility of these events, which could occur in any patient at any given injection, the study protocol was subsequently amended in August 2006 to require that patients remain at the investigator's site for 3 hours post injection. The purpose of this post-injection observation period was to ensure that the patient was free of any symptoms of olanzapine overdose prior to leaving the clinic and also to ensure that the patient was in a safe environment in the event that a post-injection syndrome event occurred.

Efficacy results evaluated maintenance of treatment effect, as the majority of patients entered the open-label extension after having been stabilized on treatment in their respective feeder studies. Patients receiving olanzapine LAI for up to 190 weeks showed improvement or no significant change from baseline to endpoint in PANSS and CGI-S scores, thus demonstrating positive clinical stability. The olanzapine LAI 18-month discontinuation rate of 34.2% was low relative to those reported for oral antipsychotic medications (eg, 74% across all antipsychotics in the CATIE trial¹⁹).

Strengths of this study include the duration and ecological validity of the design. The current analysis includes patients with over 3 years of treatment with olanzapine LAI, representing the longest depot treatment study of an atypical antipsychotic to date. In addition, the study was designed to closely replicate real-world prescribing practices (eg, permitting oral supplementation,²⁰ use of antidepressants and mood stabilizers, flexible dosing, flexible dosing intervals, and concomitant medications). These factors enhance the generalizability of the results to clinical practice.

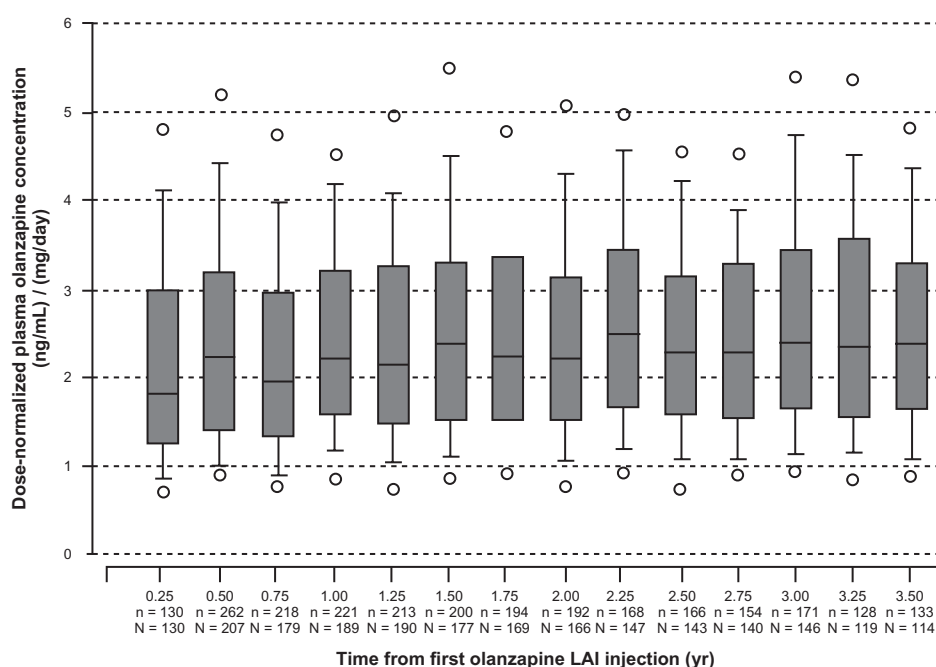


Figure 3. Box-and-whisker plot of olanzapine plasma concentration distributions for all doses (normalized by equivalent mg/day) through up to 3.5 years of olanzapine LAI dosing. The middle line in each box plot represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points outside the whiskers represent the 5th and 95th percentiles.

Abbreviations: n, number of observations; N, number of patients.

Limitations of this study include the open-label design and lack of comparators, making it difficult to draw firm conclusions regarding efficacy. In addition, this report is an interim analysis, and final study results are not yet available. The fact that oral antipsychotics and other medications were allowed throughout the study theoretically could have limited the detection of any potential safety signals unique to the injectable formulation. However, as stated above, these factors also increase the generalizability to actual clinical settings in which patients with schizophrenia are treated with multiple pharmacological regimens. Finally, it should be noted that the introduction of the post-injection observation period in August 2006 could have been responsible for some of the patient discontinuations, although it is not possible to determine the exact number.

In summary, these results represent some of the longest-term safety and tolerability findings yet conducted with a long-acting injectable antipsychotic and suggest good maintenance of effect and positive tolerability, as demonstrated by the low discontinuation rate over 3 years of treatment. Safety findings were consistent with the known profile observed with oral olanzapine therapy, with the exception of adverse events specific to use of an intramuscular injection. Incidence

of injection site-related adverse events was low, but a number of patients did experience post-injection delirium/sedation syndrome. As a result, all patients were required to be observed at a healthcare facility for a minimum of 3 hours post injection. Patient continuation rates supported a positive benefit/risk profile of olanzapine LAI in the long term. Although health care providers should weigh the potential benefits and potential risks of treatment for each individual patient, olanzapine LAI may represent an important treatment option for patients with schizophrenia who struggle with adherence to oral antipsychotic medication.

Acknowledgements

The authors wish to acknowledge Prajakti Kothare Ph.D. and Tonya Quinlan B.A. for pharmacokinetics consultation and analysis.

Portions of These Data were Presented at the Following Meetings

Schizophrenia International Research Society (SIRS) 1st Annual Meeting, June 2008, Venice, Italy, Collegium Internationale Neuro-Psychopharmacologicum (CINP) XXVI Congress, July 2008, Munich, Germany. Clinicaltrials.gov Identifier: NCT00088465



Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. All authors are employees and/or shareholders of Eli Lilly and Company. The peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Valenstein M, Copeland LA, Owen R, et al. Adherence assessments and the use of depot antipsychotics in patients with schizophrenia. *J Clin Psychiatry*. 2001;62:545–51.
2. Rothbard AB, Kuno E, Foley K. Trends in the rate and type of antipsychotic medications prescribed to persons with schizophrenia. *Schizophr Bull*. 2003;29:531–40.
3. Fleischhacker WW, Eerdeken M, Karcher K, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry*. 2003;64:1250–7.
4. Lindenmayer JP, Khan A, Eerdeken M, et al. Long-term safety and tolerability of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol*. 2007;17: 138–44.
5. Llorca PM, Sacchetti E, Lloyd K, et al. Long-term remission in schizophrenia and related psychoses with long-acting risperidone: results obtained in an open-label study with an observation period of 18 months. *Int J Clin Pharmacol Ther*. 2008;46:14–22.
6. Moller HJ, Llorca PM, Sacchetti E, et al. Efficacy and safety of direct transition to risperidone long-acting injectable in patients treated with various antipsychotic therapies. *Int Clin Psychopharmacol*. 2005;20:121–30.
7. Lauriello J, Lambert T, Andersen S, et al. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *J Clin Psychiatry*. 2008;69:790–9.
8. Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry*. 2010;167:181–9.
9. Detke HC, McDonnell DP, Brunner E, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. *BMC Psychiatry*. 2010;10:43.
10. Eli Lilly and Company. Clinical study summary: study F1D-EW-LOBS, pharmacokinetic characterization of intramuscular olanzapine depot as a function of particle size distribution. PhRMA Clinical Study Results Database. Available at: http://www.clinicalstudyresults.org/documents/company-study_6254_0.pdf. Accessed October 6, 2010.
11. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand*. 1970;45 Suppl 212:11–9.
12. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–6.
13. National Institute of Mental Health: Abnormal Involuntary Movement Scale (AIMS). In ECDEU Assessment Manual for Psychopharmacology, Revised. Edited by Edited by Guy W. Rockville, MD: US National Institute of Health; 1976:534–7.
14. Kay SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) User's Manual*. North Tonawanda, NY: Multi-Health Systems, Inc.; 2000.
15. National Institute of Mental Health: Clinical Global Impressions (CGI). In ECDEU assessment manual for psychopharmacology, revised. Edited by Guy W. Rockville, MD: US National Institute of Health; 1976:217–22.
16. Citrome L, Stauffer VL, Chen L, et al. Olanzapine plasma concentrations after treatment with 10, 20, and 40 mg/d in patients with schizophrenia: an analysis of correlations with efficacy, weight gain, and prolactin concentration. *J Clin Psychopharmacol*. 2009;29:278–83.
17. Kantrowitz JT, Citrome L. Olanzapine: review of safety 2008. *Expert Opin Drug Saf*. 2008;7:761–9.
18. McDonnell DP, Detke HC, Kothare P, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II. investigations of mechanism. *BMC Psychiatry*. 2010;10:45.
19. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353: 1209–23.
20. Ascher-Svanum H, Peng X, Montgomery W, et al. Assessing the infrequent oral supplementation of olanzapine long-acting injection in the treatment of schizophrenia. *Eur Psychiatry*. 2010.
21. American Diabetes Association. Standards of medical care in diabetes, 2010. *Diabetes Care*. 2010;33(Suppl 1):S11–61.
22. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–97.

Publish with Libertas Academica and every scientist working in your field can read your article

"I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely."

"The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I've never had such complete communication with a journal."

"LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought."

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

<http://www.la-press.com>