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Long-term safety and efficacy of olanzapine long-acting injection in patients with schizophrenia or schizoaffective disorder: a 6-year, multinational, single-arm, open-label study

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The objective of this study was to assess the long-term safety and efficacy of olanzapine long-acting injection (LAI). A 6-year, single-arm, open-label extension study of olanzapine LAI was conducted at 127 sites in 25 countries. Patients were 18–76 years of age, were diagnosed with schizophrenia or schizoaffective disorder ($N=931$), and had been previously enrolled in one of three clinical trials of olanzapine LAI. Patients received flexibly dosed (45-405 mg) olanzapine LAI every 2–4 weeks. The mean duration of exposure was ~3 years. A total of 393 (42.2%) patients completed the study. The mean weight change was +2.1 kg ($P<0.001$), with 40.6% of patients experiencing 7% or higher weight gain. Treatment-emergent categorical changes occurred in fasting glucose, total cholesterol, and triglyceride levels. Pharmacokinetic analyses revealed no systemic accumulation of olanzapine after long-term treatment. There were 36 occurrences of post-injection delirium/sedation syndrome, all resolving within 72 h. The mean Positive and Negative Syndrome Scale total and subscale scores did not change significantly over the course of the study, indicating clinical stability. Olanzapine LAI appeared effective as a long-term maintenance treatment, with a safety profile generally consistent with the known profile of oral olanzapine, except for injection-related events (including post-injection delirium/sedation syndrome). *Int Clin Psychopharmacol* **29:322–331 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Long-acting injectable antipsychotics are an important treatment option for patients with schizophrenia who have difficulty adhering to oral regimens, as long-acting formulations ensure that the patient has received treatment, and it is immediately known when the patient does not return for treatment (Kane, 2006; Leucht *et al.*, 2011). Guidelines for the long-term treatment of schizophrenia (Hasan *et al.*, 2013) recommend these formulations as the treatment of choice when the 'avoidance of covert nonadherence with antipsychotic drugs is a clinical priority' and even recommend that, in certain cases, 'patients should be actively motivated and educated' about using long-acting formulations. However, the majority of studies evaluating the safety and efficacy of these medications are typically 1 year or less in duration (Leucht *et al.*, 2011; Kishimoto *et al.*, 2014). Although there are some clinical trials on long-acting injectable antipsychotics that are 2 years in duration (Hogarty *et al.*, 1979; Macfadden *et al.*, 2010; Detke *et al.*, 2014; Lambert *et al.*, 2011; Rosenheck *et al.*, 2011), few studies have examined these medications for longer durations. As schizophrenia is often a lifelong disorder, and as long-acting injectable treatments in schizophrenia are intended for long-term use, there is need for longer term data.

Olanzapine long-acting injection (LAI) is a pamoate monohydrate salt of olanzapine that is administered by deep intramuscular gluteal injection. Two double-blind, pivotal clinical trials of 8 and 24 weeks duration demonstrated the efficacy and safety of olanzapine LAI in the acute and maintenance treatment of schizophrenia (Lauriello *et al.*, 2008; Kane *et al.*, 2010). In the 8-week study, olanzapine LAI administered at 2-week or 4-week injection intervals was significantly more efficacious than placebo for the treatment of acutely ill patients with schizophrenia despite not using supplemental oral antipsychotics (Lauriello *et al.*, 2008). During the 24-week study, the therapeutic 4-week regimen and pooled 2-week regimen had efficacies similar to that of oral olanzapine, as well as to each other (Kane *et al.*, 2010). The safety and tolerability profile of olanzapine LAI was similar to that of oral olanzapine, except for the adverse events (AEs) related to the injection (Lauriello *et al.*, 2008; Kane *et al.*, 2010).

The present paper presents final results from a 6-year, open-label clinical trial of olanzapine LAI in the

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treatment of patients with schizophrenia or schizoaffective disorder. The study evaluated the long-term safety, tolerability, and effectiveness of olanzapine LAI.

Methods

Subjects and design

This was a multinational, multicenter, single-arm, open-label phase 3 study of olanzapine LAI in patients with schizophrenia or schizoaffective disorder. The patient enrollment for this study began in August 2004, and the last patient completed the study in December 2010. The study was conducted at 127 sites in 25 countries. Patients could enter the current study immediately following any of the three feeder studies (studies: F1D-MC-HGJZ, F1D-MC-HGKA, or F1D-EW-LOBS). Study F1D-MC-HGJZ (Lauriello *et al.*, 2008) 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. Study F1D-MC-HGKA (Kane *et al.*, 2010) was a maintenance study in which patients with schizophrenia were stabilized on oral olanzapine for 4–8 weeks and then randomized to 24 weeks of double-blind treatment with olanzapine LAI ($N = 743$) or oral olanzapine ($N = 322$). Study F1D-EW-LOBS was a 46-day pharmacokinetic study of olanzapine LAI ($N = 134$) in patients with schizophrenia or schizoaffective disorder.

Patients were either male or female, were between 18 and 76 years of age, met diagnostic criteria for schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. – text revision (DSM-IV-TR; American Psychiatric Association, 2000), and had previously completed (within 10 days) one of the three allowed olanzapine LAI studies. Exclusion criteria included a history of one or more seizures without a clear and resolved etiology; significant suicidal or homicidal risk; positive pregnancy test or breastfeeding; acute, serious, or unstable medical conditions; or DSM-IV-TR substance (except nicotine and caffeine) dependence within the past 30 days.

It should be noted that although the total duration of the study was 6 years and 4 months, the allowed duration of the study varied by country. Patients were permitted to continue treatment in the study until such time as the product was commercially available in their country or until 31 December 2010, whichever came first. In some countries, olanzapine LAI was commercially available as early as 2009, and thus some patients had a shorter possible duration in the study. Patients who discontinued the study because the product had become commercially available in their country did not always report that reason for discontinuation correctly. Instead, on occasion the reason for discontinuation was reported as early discontinuation (e.g. because of patient decision or sponsor decision). This may have led to an inflated discontinuation rate, and thus a post-hoc analysis was carried out to assess the differences in overall discontinuation rates if these events were captured as study completions.

All patients signed an informed consent form before any changes were made to their medical treatment plan for the purpose of study participation and before any study procedures were performed. Ethical review boards approved the conduct of the study, which was developed in accordance with good clinical practice guidelines and the ethical principles in the Declaration of Helsinki.

Procedures

Dosing

All patients received 210 mg olanzapine LAI at the first open-label visit. Because olanzapine LAI can be dosed by volume (150 mg/ml), patients were permitted to receive any dose between 45 and 405 mg of olanzapine LAI in 15 mg (0.1 ml) increments. Doses were permitted to be administered at 2-, 3-, or 4-week intervals. Dosing after the first visit was determined on the basis of the investigators' clinical judgment. Patients were permitted to receive up to 20 mg/day supplemental oral olanzapine. The maximum total dose of olanzapine LAI permitted was 600 mg over 4 weeks.

Efficacy

Efficacy was analyzed in terms of mean change in the Positive and Negative Syndrome Scale (PANSS) scores over time (assessed every 6 months and at the discontinuation visit; Kay *et al.*, 1987). The Clinical Global Impression-Severity of Illness (CGI-S) scale was administered at each visit to assess the mean change from baseline over time (Guy, 1976).

Health outcomes/quality of life

The Patient Satisfaction with Medication Questionnaire was specifically developed to assess the level of patient satisfaction with antipsychotics (Kalali, 1999). The Patient Satisfaction with Medication Questionnaire-Modified (hereafter simply referred to as PSMQ) includes three questions concerning the following topics: satisfaction with current depot medication, preference comparing current depot medication versus previous oral medications, and impact of side effects comparing current depot medication versus previous oral medications. Each of the questions requested a Likert-type response score from 1 to 5. The PSMQ was administered every 6 months and at the discontinuation visit and is summarized by item.

Hospitalizations were summarized over the course of the study. The aggregate number of days spent in the hospital per patient-year of exposure to treatment was computed. The summary included the mean number of hospital days, the proportion of patients with hospitalizations, and the mean length of stay per hospital admission.

Pharmacokinetic methods

Blood samples for the assessment of olanzapine plasma concentrations were planned to be collected from approximately the first 350 patients who participated in the study. These pharmacokinetic samples were collected every 3 months for the duration of the patient's participation in the study and were collected immediately before administration of olanzapine LAI at that visit (thus reflecting trough olanzapine concentration). In total, pharmacokinetic blood samples were collected from 377 patients, and 3844 plasma olanzapine concentrations were analyzed. Plasma samples were analyzed using a validated high-performance liquid chromatography/electrochemical detection method at BAS Analytics Inc. (West Lafayette, Indiana, USA). Plasma olanzapine concentration data were analyzed graphically and descriptively.

To facilitate interpretation of pharmacokinetic data and to compare results across the range of doses studied, steady-state olanzapine concentrations were dose-normalized by dividing an individual's measured olanzapine concentration at each visit by the total dose of olanzapine administered over the dosing regimens.

Safety

Safety and tolerability variables included the incidence of all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to study discontinuation; mean changes in vital signs and weight; mean changes and treatment-emergent abnormal, high, and low values in glucose, lipid, and other laboratory measures; and treatment-emergent categorical changes in weight and ECG measurements.

At the first open-label visit, the screening assessments included standard history taking, physical and psychiatric examination, obtaining a laboratory profile, and ECG. Vital signs were measured at weeks 1, 4, and 8; at each quarterly or 6-month visit; at the discontinuation visit; and at any visit at which olanzapine LAI was administered. Laboratory assessments were performed at weeks 1, 4, and 8; at each quarterly or 6-month visit; and at the discontinuation visit. Patients were required to be fasting for a minimum of 8 h before collection of blood specimens for laboratory tests at 6-month visits and the summary visit. ECG was performed at the first open-label visit, at each 6-month visit, and at the discontinuation visit. Extrapyramidal symptoms (EPS) were assessed with the Simpson–Angus Scale (SAS), the Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS) at the first open-label visit, at each 6-month visit, and at the discontinuation visit. Analyses were carried out to evaluate the proportion of patients with treatment-emergent parkinsonism (SAS total score > 3 at any visit), akathisia (BAS global score ≥ 2 at any visit), and abnormal dyskinetic movements (score ≥ 3 for any of the AIMS items from 1 to 7 or score ≥ 2 for any two of these items; Simpson and Angus, 1970; Barnes, 1989).

As a result of the possibility of the occurrence of post-injection delirium/sedation syndrome (PDSS) events after administration of olanzapine LAI, this study was amended ~ 2 years after its initiation, requiring patients to be observed at the healthcare facility for 3 h after administration of olanzapine LAI and to be accompanied to their destination after leaving the facility (Detke *et al.*, 2010).

Statistics

All patients who received at least one dose of olanzapine LAI were included in the primary safety analyses for this report. For efficacy analyses, patients were included only if they had a baseline and postbaseline measure. Baseline was defined as the last observation before receiving the injection either at the first open-label visit or at the last observation from the feeder study, and the endpoint measure was defined as the last measure in the study. The total scores were considered as missing if any of the individual items were missing. For the analysis of continuous measures, missing data were handled using last-observation-carried-forward (LOCF) change from baseline-to-endpoint analyses. The statistical significance of within-group changes from baseline was assessed using paired *t*-statistics. Analyses with categorical factors (e.g. sex, race) used between-group *P*-values from analysis of variance models. Time to discontinuation was evaluated by Kaplan–Meier survival analysis. All null hypotheses were assessed with a two-sided significance level of 0.05. Results of statistical tests were taken as informative and not confirmatory.

Results

Patients

Table 1 shows patient demographics and baseline characteristics. Of the 931 patients who participated in this long-term study, the majority was male (66.7%), White (67.6%), and diagnosed with schizophrenia (97.6%); the mean age was 39.3 years. The olanzapine LAI mean daily dose, expressed as milligrams of olanzapine per day, was 14.2 mg/day (SD = 4.2), and the modal daily dose was 14.3 mg/day (SD = 4.8). Frequency of injection dosages (mg) and injection intervals (in $\geq 1\%$ of patients) for olanzapine LAI are shown in Table 2 and indicate that the 300 mg/2 weeks dosing regimen was the most commonly used. A total of 294 (31.6%) patients received supplemental oral olanzapine at some time during their participation in the study for a mean of 15.8% of the days that they were treated with olanzapine LAI. The mean dose administered on those days was 10 mg. Benzodiazepines were used in 37.4% of patients, and anticholinergics were used in 10.3% of patients at some time during the study.

Table 1 Patient demographics and baseline characteristics in patients receiving olanzapine long-acting injection

	Olanzapine LAI group ($N=931$)
Age [mean (SD)]	39.3 (11.7)
Sex (male) [*n* (%)]	621 (66.7)
Race [*n* (%)]	
White	629 (67.6)
Hispanic	140 (15.0)
African	102 (11.0)
East Asian	39 (4.2)
West Asian	19 (2.0)
Native American	2 (0.2)
Patient diagnosis [*n* (%)]	
Schizophrenia	909 (97.6)
Schizoaffective disorder	22 (2.4)
Number of previous episodes or exacerbations of schizophrenia in the last 24 months [*n* (%)]	
0	238 (26.2)
1	283 (31.2)
2	212 (23.3)
3	74 (8.1)
4	34 (3.7)
≥ 5	67 (7.4)
Age of onset of first episode schizophrenia (years) [mean (SD)]	25.25 (8.60)

LAI, long-acting injectable; *n*, number of affected patients; *N*, total number of patients; SD, standard deviation.

Table 2 Frequency of injection dosages (mg) and injection intervals (utilized in $\geq 1\%$ of injections) for olanzapine long-acting injection

Injection dosage (mg)	Injection interval	Number of injections ($N=45662$) [*n* (%)]
300	Q2W	13 064 (28.6)
405	Q4W	8623 (18.9)
210	Q2W	3838 (8.4)
300	Q4W	3370 (7.4)
210	Q4W	2675 (5.9)
300	Q3W	2264 (5.0)
210	Q3W	1133 (2.5)
150	Q4W	774 (1.7)
150	Q2W	766 (1.7)
330	Q4W	449 (1.0)

A total of 47 429 injections were administered, but only 45 662 of these reported a prescribed interval.
N, total number of injections; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

Patient disposition

The mean duration of patient exposure was 1073.4 days ($\sim$3 years) with the longest duration of 2204 days ($\sim$6 years). Overall olanzapine LAI exposure was 2735.9 patient-years. Figure 1 shows the time to discontinuation. Patient disposition is presented in Table 3, shown as rates reported and also in terms of a post-hoc analysis correction for patient completion as a result of the product becoming commercially available. In the original analysis 39.7% ($n=370$) and in the post-hoc analysis 42.2% ($n=393$) of patients completed the study.

The most frequently reported AEs leading to discontinuation were schizophrenia [15 (1.6%) patients], weight increase [8 (0.9%) patients], and psychotic disorder [7 (0.8%) patients].

Olanzapine plasma concentrations

Steady-state olanzapine LAI plasma concentrations remained consistent over time, with no evidence of continuing accumulation over the course of 6 years of treatment (Fig. 2). The median dose-normalized olanzapine plasma concentration was 2.25 (ng/ml)/(mg/day), with a 10th–90th percentile range of 1.01–4.26 (ng/ml)/(mg/day).

Safety

Table 4 shows TEAEs reported by at least 5% of the patients. Overall, 670 (72.0%) patients reported at least one TEAE during the study. The five most commonly reported TEAEs were increased weight, anxiety, insomnia, somnolence, and nasopharyngitis. A total of 170 (18.3%) patients reported at least one SAE. The most frequently reported SAEs were schizophrenia ($n=35$), psychotic disorder ($n=20$), sedation ($n=12$), suicidal ideation ($n=8$), agitation ($n=6$), anxiety ($n=6$), depression ($n=5$), paranoia ($n=5$), and somnolence ($n=5$).

There were 11 deaths (Table 3), including one suicide, reported during the study. Of the 11 deaths, 10 were considered by the investigators to be unrelated to treatment with the study drug or to protocol procedures, and one patient's death from myocardial infarction was considered to be possibly related to the study drug. The other causes of death were alcoholic cardiomyopathy, myocardial ischemia, mesenteric ischemia and septic shock, trauma as a result of a road traffic accident, pneumonia, leptospirosis, hypertrophic cardiomyopathy, renal cell carcinoma, and essential hypertension.

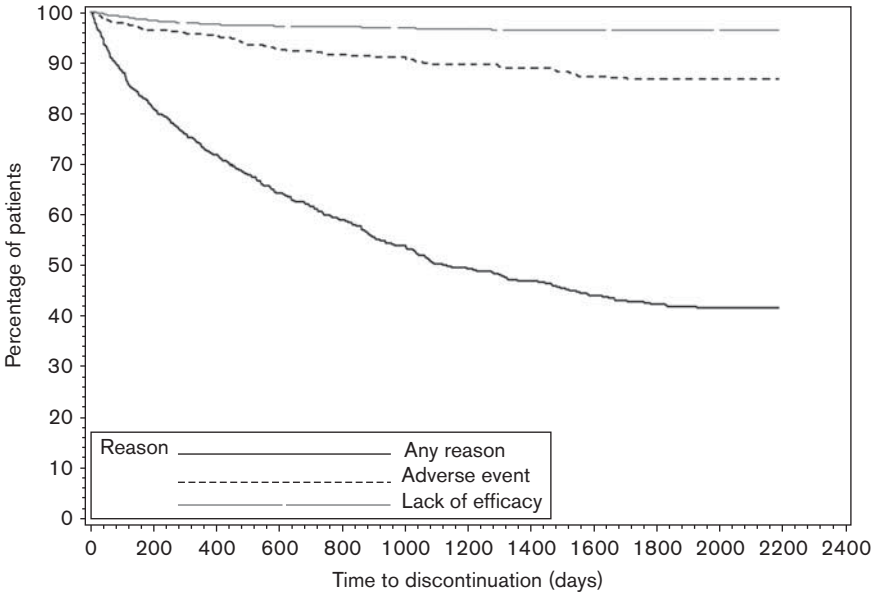
Overall, the incidence of injection-site AEs was low, reported in 36 (3.9%) patients. The most frequently reported injection-site AE was injection-site pain, reported in 18 (1.9%) patients. All other AEs were reported in less than 1% of patients.

During the course of the study, 36 PDSS events occurred in 35 patients; one patient experienced two events. These patients experienced temporary symptoms of delirium and/or excessive sedation following possible inadvertent intravascular injection of a portion of the dose of olanzapine LAI. Clinical presentation varied but was consistent with symptoms reported in cases of oral olanzapine overdose. There were no fatalities, and all patients recovered within 72 h of receiving the injection. Of the patients who experienced PDSS events, 25 (71.4%) continued to receive further injections of olanzapine LAI. In this study, PDSS events occurred in $\sim$0.08% of olanzapine LAI injections administered.

Laboratory analytes

Mean changes in metabolic and hepatic laboratory analyte levels and prolactin levels are presented in Table 5. Overall, mean changes in these and all other laboratory analyte levels were small and not clinically significant.

Fig. 1



Kaplan–Meier time to discontinuation.

Table 3 Patient disposition in the olanzapine LAI group

	Olanzapine LAI group ($N=931$)	
	Original analysis [*n* (%)]	Post-hoc analysis [*n* (%)][a]
Completed	370 (39.7)	393 (42.2)
Subject decision	290 (31.1)	279 (30.0)
Adverse event	77 (8.3)	77 (8.3)
Lost to follow-up	57 (6.1)	57 (6.1)
Physician decision	45 (4.8)	42 (4.5)
Sponsor decision	37 (4.0)	28 (3.0)
Lack of efficacy	27 (2.9)	27 (2.9)
Protocol violation	17 (1.8)	17 (1.8)
Death	11 (1.2)	11 (1.2)

LAI, long-acting injection; *n*, number of affected patients; *N*, total number of patients; US, United States.
[a]A post-hoc analysis was carried out to correct for patient completion as a result of the product becoming commercially available. Non-US patients who discontinued because of patient, physician, or sponsor decision within 90 days of product launch in their country or 90 days before 31 December 2010 were considered to have completed the trial. US patients who discontinued because of patient, physician, or sponsor decision on or after 31 December 2009 were considered to have completed the trial.

However, a number of patients experienced treatment-emergent abnormal changes. A total of 22.6% ($n=97$, $N=430$) of patients showed high prolactin levels (> 1050.2 pmol/l for female patients; >814.6 pmol/l for male patients). Treatment-emergent significant changes from normal to high (≥ 6.993 mmol/l) fasting glucose levels were seen in 3.6% of patients, and changes from normal to impaired (≥ 5.55 and <6.993 mmol/l) glucose levels were seen in 29.7% of patients. For total cholesterol, 3.3% of patients showed changes from normal to high levels (≥ 6.21 mmol/l) and 21.2% from normal to borderline levels (≥ 5.17 and <6.21 mmol/l). For triglycerides, 16.1% of patients showed changes from normal to borderline levels (≥ 1.69 and <2.26 mmol/l), 9.3% showed changes from normal to high levels (≥ 2.26 mmol/l), and 0.4% showed changes from normal to extremely high levels (≥ 5.65 mmol/l).

Vital signs, weight, and electrocardiograms

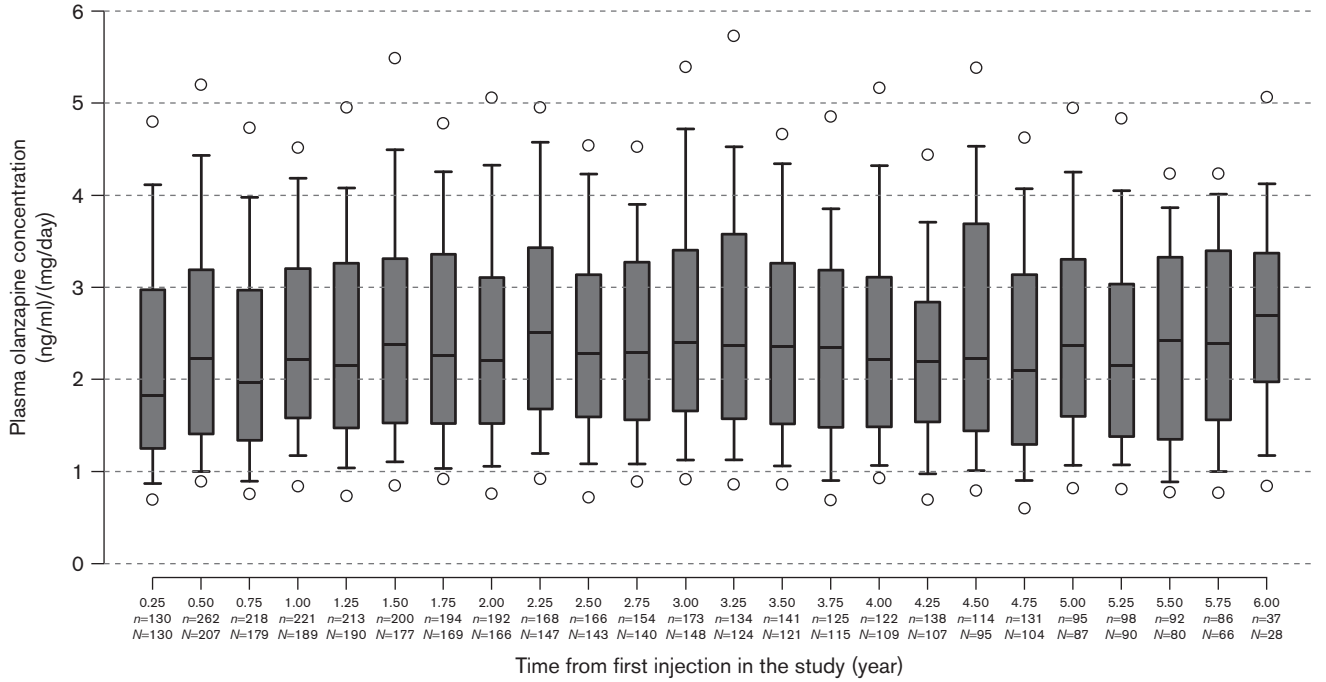
Small, clinically insignificant mean changes were observed in vital signs (blood pressure, pulse, and temperature). A total of 83 (10.3%) patients experienced orthostatic hypotension [≥ 30 mmHg decrease in systolic blood pressure (supine to standing) during the study]. Other categorical changes in vital signs were assessed as not clinically significant. The baseline-to-endpoint mean change in weight was 2.10 kg (SD = 7.81, $P<0.001$). During the study, 373 patients (40.6%) experienced an increase of at least 7% in baseline body weight, whereas 199 patients (21.7%) experienced a decrease of at least 7% in baseline body weight.

There was a small mean increase in the QT interval when corrected using the Fridericia method (QTcF), but this increase was not clinically significant (1.26 ms, $P=0.022$). Few patients experienced QTcF increases that were 60 ms or higher (< 1%), and there were no clinically significant cardiac events observed with these changes.

Extrapyramidal symptoms

Mean changes in the individual extrapyramidal scales were small [SAS: −0.15 (SD = 1.53, $P=0.005$); BAS: 0.0 (SD = 0.48, $P=0.832$); AIMS: −0.08 (SD = 1.52, $P=0.127$)]. The percentage of patients with treatment-emergent parkinsonism was 8.1% at anytime during the

Fig. 2



Plasma olanzapine concentration versus time from first injection for year 1 through year 6. *N*, number of patients in the specified category; *n*, number of observations. 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 95th and 5th percentiles, and data points outside the whiskers represent points beyond the 95th and 5th percentiles.

Table 4 Treatment-emergent adverse events in at least 5% of patients

	Olanzapine LAI group (*N*=931) [*n* (%)]
Patients with ≥ 1 TEAEs	670 (72.0)
Weight increased	134 (14.4)
Anxiety	95 (10.2)
Insomnia	90 (9.7)
Somnolence	89 (9.6)
Nasopharyngitis	74 (7.9)
Headache	68 (7.3)
Depression	53 (5.7)
Dizziness	53 (5.7)
Sedation	49 (5.3)

LAI, long-acting injection; *n*, number of affected patients; *N*, total number of patients; TEAEs, treatment-emergent adverse events.

study (2.6% at endpoint), with akathisia was 4.0% at anytime (1.5% at endpoint), and with dyskinesia was 3.3% at anytime (2% at endpoint). Two patients discontinued treatment after development of tardive dyskinesia, one patient discontinued because of symptoms of moderate dyskinesia, and one patient discontinued because of mild EPS. There were no reported cases of neuroleptic malignant syndrome.

Efficacy

Patients on average were 'mildly ill' (Leucht *et al.*, 2005) at study entry with a mean PANSS total score of 54.54 (SD = 17.69) and a CGI-S total score of 2.92 (SE = 0.03). The baseline-to-endpoint mean change in PANSS total score was 0.30 (SD = 16.4, $P = 0.590$); the PANSS negative score was −0.08 (SD = 5.14, $P = 0.637$); the PANSS positive score was 0.21 (SD = 4.69, $P = 0.190$); and the PANSS general psychopathology total score was 0.19 (SD = 8.51, $P = 0.510$). A review of the individual item scores on the PANSS scale showed small mean changes from baseline to endpoint. There were statistically significant baseline-to-endpoint decreases for active social avoidance (−0.11, SD = 1.08, $P = 0.003$) and mannerisms and posturing (−0.09, SD = 0.78, $P < 0.001$), and baseline-to-endpoint increases for poor impulse control (0.11, SD = 0.90, $P < 0.001$) and suspiciousness (0.08, SD = 1.10, $P = 0.038$). There were small mean improvements in the CGI-S score over the duration of the study (mean change −0.17, from baseline to LOCF endpoint). These improvements were significant ($P \leq 0.001$) starting at week 3 and for all subsequent measured time points (Fig. 3).

Health outcomes/quality of life

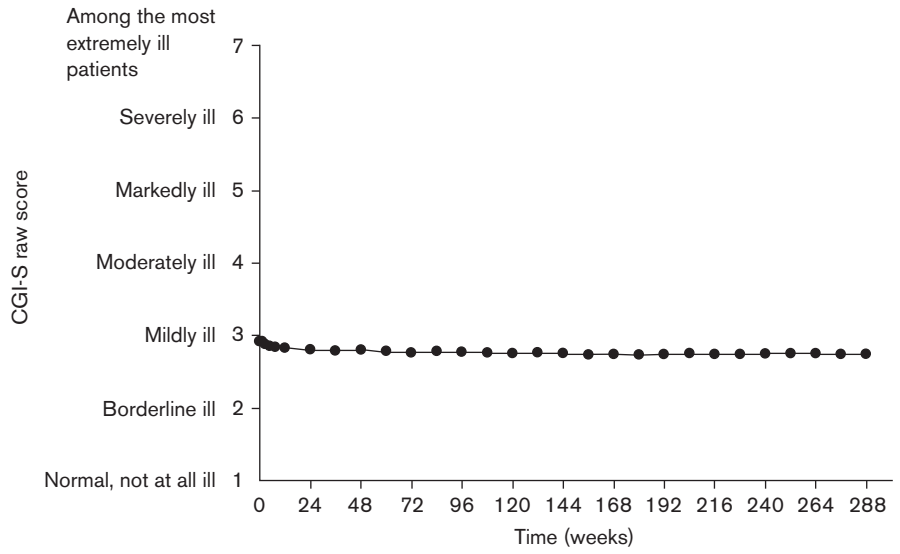
The PSMQ was analyzed at endpoint for all patients. Overall, the majority of patients responding to this medication satisfaction questionnaire ($N = 931$) indicated favorable responses for olanzapine LAI compared with previous oral therapy. For the current use of depot

Table 5 Laboratory analysis: mean change from baseline to LOCF endpoint

	N	Baseline mean (SD)	Mean change (SD)	*P*-value
Glucose, fasting (mmol/l)	868	5.40 (1.25)	0.33 (1.62)	<0.001
Total cholesterol (mmol/l)	879	5.13 (1.10)	0.05 (0.95)	0.128
HDL cholesterol (mmol/l)	877	1.13 (0.32)	0.04 (0.27)	<0.001
LDL cholesterol (mmol/l)	872	3.15 (0.96)	−0.01 (0.83)	0.763
Triglycerides (mmol/l)	879	1.92 (1.24)	−0.01 (1.29)	0.834
Prolactin (pmol/l)	591	844.13 (1182.65)	62.50 (1062.00)	0.154
Total bilirubin (μmol/l)	916	7.91 (4.54)	0.06 (3.82)	0.648
Alkaline phosphatase (U/l)	916	84.74 (27.05)	−2.81 (19.29)	<0.001
AST/SGOT (U/l)	916	24.30 (13.81)	−0.12 (13.93)	0.791
ALT/SGPT (U/l)	916	29.40 (27.30)	−1.14 (24.10)	0.154
Weight (kg)	919	80.34 (17.5)	2.10 (7.8)	<0.001

ALT/SGPT, alanine transaminase/serum glutamic pyruvic transaminase; AST/SGOT, aspartate aminotransferase/serum glutamic–oxaloacetic transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LOCF, last observation carried forward.

Fig. 3



The Clinical Global Impression-Severity of Illness (CGI-S) visitwise mean score for all 931 patients enrolled in the olanzapine LAI open-label extension study (mean baseline = 2.92, mean endpoint = 2.74). LAI, long-acting injection.

medication, 73.2% ($n = 629$) of patients were either somewhat or very satisfied. For preference of olanzapine LAI versus previous oral medications, 66.8% ($n = 575$) of patients preferred or much preferred olanzapine LAI. For side effects with olanzapine LAI versus previous oral therapy, 73.3% ($n = 630$) of patients thought olanzapine LAI use resulted in less or much less side effects.

During the study period, 255 patients (27.4%) were hospitalized, with the majority of hospital days attributed to psychiatric care (13.01 days/patient-year) rather than to regular care (0.87 days/patient-year) or intensive care unit care (0.05 days/patient-year).

Discussion

This 6-year open-label study represents the longest clinical trial to evaluate the safety and efficacy of olanzapine LAI in patients with schizophrenia, as well as in a small number of patients with schizoaffective disorder. The safety profile of olanzapine LAI was generally consistent with the known safety profile of oral olanzapine (Kantrowitz and Citrome, 2008), except for the incidence of injection-site-related AEs and PDSS events. The mean weight gain was 2.10 kg, which was statistically significant, and more than one-third of patients experienced potentially clinically significant weight gain (≥ 7% baseline body weight). Treatment-emergent significant changes in the levels of glucose, lipids, prolactin, and hepatic enzymes, as well as in other laboratory values and ECG readings, were consistent with the known safety profile of the olanzapine molecule. The rate of treatment-emergent parkinsonism, akathisia, and dyskinesia reported at anytime during the study is higher than that previously reported by a 6-month study (Beasley Jr *et al.*, 2003) on oral olanzapine (0.9, 1.8, and 0.5%, respectively). However, this difference is more than

likely due to the much longer term exposure seen in this study. The endpoint values for the same measures are lower than and similar to those previously reported on treatment with oral olanzapine. Only four patients discontinued the study because of possible EPS-related events. Pharmacokinetic analyses revealed no indication of systemic accumulation of olanzapine after 6 years of treatment, and the olanzapine concentrations delivered by the LAI formulation were within the expected therapeutic range that would be seen for patients treated with oral olanzapine (Bergstrom *et al.*, 2000; Perry *et al.*, 2001; Citrome *et al.*, 2009).

The injection-site-related AEs occurred at a similar rate to those seen with other intramuscular injection products (Hamann *et al.*, 1990; Jones *et al.*, 1998). The PDSS events are thought to be related to the inadvertent intravascular injection of a portion of the olanzapine dose, resulting in symptoms consistent with an olanzapine overdose (Detke *et al.*, 2010; McDonnell *et al.*, 2010). A review of PDSS events reported that events occurred after 0.07% of injections (Detke *et al.*, 2010). In the current study, PDSS events occurred after 0.08% of injections. All patients recovered from the events within 72 h. The majority of patients continued treatment with olanzapine LAI after experiencing their respective PDSS events. A regression analysis of pooled olanzapine LAI studies (Detke *et al.*, 2010) indicated that lower body mass index (BMI) and/or higher age could increase the risk of a PDSS event. However, these events have occurred in patients at many different ages and BMIs, and thus the recommendation is that a PDSS event can potentially occur at any injection in any patient, suggesting the need to monitor all patients (regardless of risk factors) for its possible occurrence.

The efficacy analyses were carried out to evaluate maintenance of the treatment effect from previous studies. Although efficacy cannot be established in an open-label study, olanzapine LAI appeared to show sustained effectiveness in maintaining clinical stability for the duration of the study. Patients were, on average, mildly ill at study entry, and changes in PANSS total and subscale scores and CGI-S scores remained small throughout the study, indicating that patients, in general, were able to maintain their status.

For patients with schizophrenia, treatment with antipsychotics is typically necessary for the long term, but persistence on treatment is often poor, resulting in frequent relapses with potentially serious consequences (Robinson *et al.*, 1999; Weiden *et al.*, 2004). Reports indicate that up to 70% of patients with schizophrenia, in clinical trials, are partially noncompliant with treatment by 2 years (Thieda *et al.*, 2003; Lieberman *et al.*, 2005). In this long-term study, over 40% of patients treated with olanzapine LAI stayed on treatment until study completion, with a mean treatment duration of ~3 years and the longest duration of ~6 years. Although ideally all patients would remain on treatment, the completion rate is high considering the maximum possible duration of the study. Observational studies in the United States of America, Spain, Australia, and Belgium on risperidone LAI for a duration of 24 months have reported completion rates ranging from 39 to 63% (Lambert *et al.*, 2011). A relatively high retention rate for olanzapine LAI treatment was observed despite the risk of PDSS events, as well as the requirement that all patients be observed at the healthcare facility for 3 h after the injection and be accompanied to their destination after leaving the facility.

Data from the present study also appear to indicate that not only will patients with schizophrenia stay on an injectable antipsychotic regimen for the long term, but that they may actually prefer this method of treatment. There have been perceptions reported in the literature that many patients do not want to take an injectable long-acting antipsychotic medication (Patel *et al.*, 2003; Gray *et al.*, 2009). However, other studies have shown that patients treated with a long-acting medication prefer to remain on that medication (Pereira and Pinto, 1997) or prefer the long-acting medication compared with a previous treatment (Wistedt, 1995). In keeping with those findings, a majority of patients in this study were satisfied with their treatment with olanzapine LAI. The level of satisfaction was similar to that reported by patients treated with oral antipsychotic medications (Gray *et al.*, 2005; Bitter *et al.*, 2010).

The current study includes patients treated for ~6 years with olanzapine LAI, representing one of the longest long-acting injectable treatment studies of an atypical antipsychotic to date. These results provide data on safety and tolerability for patients on maintenance treatment with olanzapine LAI. The study design attempted to mimic real-world prescribing practices with few restrictions on the use of concomitant medications, including supplementation with oral olanzapine. The oral supplementation seen in this study indicates intermittent and infrequent use. A previous analysis of the interim data from this study indicated that the limited and targeted supplementation of olanzapine LAI with oral olanzapine functioned as a rescue medication, selectively aimed at more severely ill patients at baseline (Ascher-Svanum *et al.*, 2011).

Limitations of this study include the open-label design and lack of comparators, making it difficult to draw conclusions with regard to relative safety and efficacy. Patients who entered this study were from three different feeder studies (acute study, maintenance study, and pharmacokinetic study), which may have led to varied patient characteristics at baseline. Although changes in total PANSS and CGI-S scores were observed to be small in this study, patients who experienced worsening of

symptoms may have discontinued from the study before the maximum score was recorded, resulting in changes in these scores being understated. The majority of patients had previously been treated with olanzapine LAI before entering this study. Detection of any potential safety signals unique to the injectable formulation was limited, as oral olanzapine and other concomitant medications were permitted during the study.

Conclusion

In summary, these results provide long-term safety and tolerability information on a long-acting injectable antipsychotic. The safety profile of olanzapine LAI was generally consistent with the known safety profile of oral olanzapine with the exception of the AEs associated with the method of administration (e.g. injection site AEs and PDSS events). Of note, in this long-term study it was found that ~40% of patients experienced potentially clinically significant weight gain. Efficacy results need to be interpreted cautiously because of the open-label study design. However, patients receiving olanzapine LAI showed very little change in PANSS total scores and CGI-S scores, suggesting that olanzapine LAI was effective in long-term maintenance of treatment effect. Further, pharmacokinetic analyses revealed no indication of long-term systemic accumulation of olanzapine, even after ~6 years of treatment. Patient satisfaction with the injectable medication was high. Treatment with olanzapine LAI must be weighed against the known risks associated with olanzapine treatment in addition to the risk of PDSS events occurring after ~0.07% of injections. However, for patients with schizophrenia who tolerate treatment with oral olanzapine but have difficulty adhering to oral treatment, olanzapine LAI represents an important treatment option.

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Conflicts of interest

All authors are full-time employees of Eli Lilly and Company and stockholders of Eli Lilly and Company.

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