ORIGINAL RESEARCH

Switching to olanzapine long-acting injection from either oral olanzapine or any other antipsychotic: comparative post hoc analyses

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Background: A considerable proportion of patients suffering from schizophrenia show suboptimal responses to oral antipsychotics due to inadequate adherence. Hence, they are likely to benefit from switching to a long-acting injectable formulation. These post hoc analyses assessed the clinical effects of switching to olanzapine long-acting injection (OLAI) from either oral olanzapine (OLZ) or other antipsychotics (non-OLZ).

Methods: Post hoc analyses were done based on two randomized studies (one short-term, one long-term) conducted in patients suffering from schizophrenia and treated with OLAI. The short-term study was an 8-week placebo-controlled, double-blind trial in acute patients, and the long-term study was a 2-year, oral olanzapine-controlled, open-label, follow-up of stabilized outpatients.

Results: These analyses used data from 62 OLAI-treated patients (12 switched from OLZ, 50 from non-OLZ) from the short-term study and 190 OLAI-treated patients (56 switched from OLZ, 134 from non-OLZ) from the long-term study. Kaplan–Meier survival analyses of time to all-cause discontinuation of OLAI treatment did not differ significantly between OLZ and non-OLZ patients in the short-term study ($P=0.209$) or long-term study ($P=0.448$). Similarly, the proportions of OLZ and non-OLZ patients that discontinued OLAI were not statistically different in the short-term (16.7% versus 36.0%, respectively; $P=0.198$) or long-term (57.1% versus 47.8% respectively; $P=0.238$) studies. In the short-term study, no significant differences were detected between the patient groups in mean change in Positive and Negative Syndrome Scale (PANSS) total score (−13.4 OLZ versus −20.8 non-OLZ; $P=0.166$). In the long-term study, mean change in PANSS total score (3.9 OLZ versus −3.6 non-OLZ; $P=0.008$) was significantly different between the non-OLZ and OLZ groups. Rates of treatment-emergent adverse events were similar in OLZ and non-OLZ groups per study.

Conclusion: These post hoc analyses suggest that no significant differences in clinical effectiveness were seen after switching from non-OLZ or OLZ to OLAI. However, these findings should be interpreted with care, due to small sample sizes and differences in patients' clinical profiles.

Keywords: schizophrenia, olanzapine, long-acting injection, depot formulation

Introduction

Long-term treatment with antipsychotic medication is a mainstay therapeutic approach in patients with schizophrenia. However, partial or total nonadherence to oral antipsychotic therapy continues to be a major problem in the long-term management of the disease,[1] affecting approximately 50% of patients.[2,3] Antipsychotic nonadherence often leads to negative outcomes, including symptom exacerbation, relapse, more emergency room admissions, and rehospitalizations.[4]

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In clinical practice, long-acting injectable formulations are a good option to improve treatment adherence, and thus improve the effectiveness of antipsychotic treatment, particularly in patients with a suboptimal response to previous oral treatments by ensuring delivery of the medication and simplifying administration.[5–7]

Olanzapine long-acting injection (OLAI), the intramuscular depot formulation of olanzapine, is currently available for the treatment of patients with schizophrenia. The therapeutic efficacy of OLAI has been demonstrated in two pivotal Phase III randomized controlled trials. The short-term effectiveness of OLAI was established in an 8-week, placebo-controlled Phase III trial in adult patients (n=404) who were experiencing acute psychotic symptoms and met *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV or DSM-IV-TR criteria for schizophrenia.[8] In the other pivotal Phase III trial, the longer-term noninferiority of OLAI was demonstrated in adult patients with schizophrenia (n=1,065) over a 24-week period (following randomization either to continue their current oral olanzapine dose or to switch to OLAI, after remaining stable for 4–8 weeks on open-label oral olanzapine).[9] Additionally, in a third study (Phase IIIB), adult outpatients (n=524) with schizophrenia were randomized to receive OLAI (n=264) or oral olanzapine (n=260) for up to 2 years of open-label treatment.[10,11] In the latter study, median times to all-cause discontinuation (primary outcome measure) did not differ significantly between the treatment groups.[10,11]

This paper reports on a post hoc analysis from the 8-week pivotal Phase III randomized controlled trial in acute patients (hereafter referred to as the "short-term study") and from the 2-year randomized open-label Phase IIIB study in outpatients (hereafter referred to as the "long-term study") suffering from schizophrenia (according to DSM-IV criteria). The main objective of these post hoc analyses was to assess what clinical effects would be observed after switching from either oral olanzapine (OLZ) or from any other antipsychotic medication (non-OLZ) to OLAI.

Materials and methods

The two Phase III studies were selected for these post hoc analyses because they were the only studies with appropriate data available that allowed comparison between OLZ-pretreated and non-OLZ-pretreated patients who switched to OLAI. Both studies were conducted in compliance with the ethical principles laid down in the Declaration of Helsinki, good clinical practices, and applicable laws and regulations. For each investigational site, ethical review boards provided written approval of the study protocols and the patient informed consent documents.

Source studies: main objectives and treatment groups

Complete descriptions of the two trials, including details of study design and patient populations, have been previously reported,[8,10,11] the methodologic details of each study are summarized in Figure 1.

The main objectives of the two source studies were to determine the efficacy and tolerability of OLAI relative to placebo (short-term study) or oral olanzapine (long-term study). Patients receiving oral olanzapine in combination with another antipsychotic medication before switching to OLAI and patients randomized to the placebo or oral olanzapine groups were not included in the present post hoc analyses (Figure 1).

Post hoc analyses: main objective and treatment groups

The main objective of these post hoc analyses was to assess what clinical effects would be observed after switching from either oral olanzapine (OLZ) or from any other antipsychotic medication (non-OLZ) to OLAI. For these analyses, two groups of patients were identified per source study based on their previous treatment before randomization to OLAI, ie, patients who switched from oral olanzapine monotherapy to OLAI and patients who switched from any other antipsychotic medication to OLAI (Figure 1).

Post hoc measures

Given that poor adherence to oral antipsychotic therapy is a major problem in the long-term management of schizophrenia,[1] completion/discontinuation of treatment is recognized as a proxy measure of a medication's effectiveness in treating schizophrenia.[12–14] Thus, time to all-cause discontinuation, rate of discontinuation, and reasons for discontinuation were used as proxy measures of effectiveness. Disease severity measures included mean change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative scores[15] and mean change in Clinical Global Impression Severity (CGI-S) score. Safety/tolerability measures included incidence of treatment-emergent adverse events occurring in ≥5% and two or more patients; incidence of treatment-emergent serious adverse events occurring in two or more patients; categorical changes in metabolic parameters (ie, weight, fasting glucose, fasting triglycerides, total cholesterol, high-density lipoprotein cholesterol, and
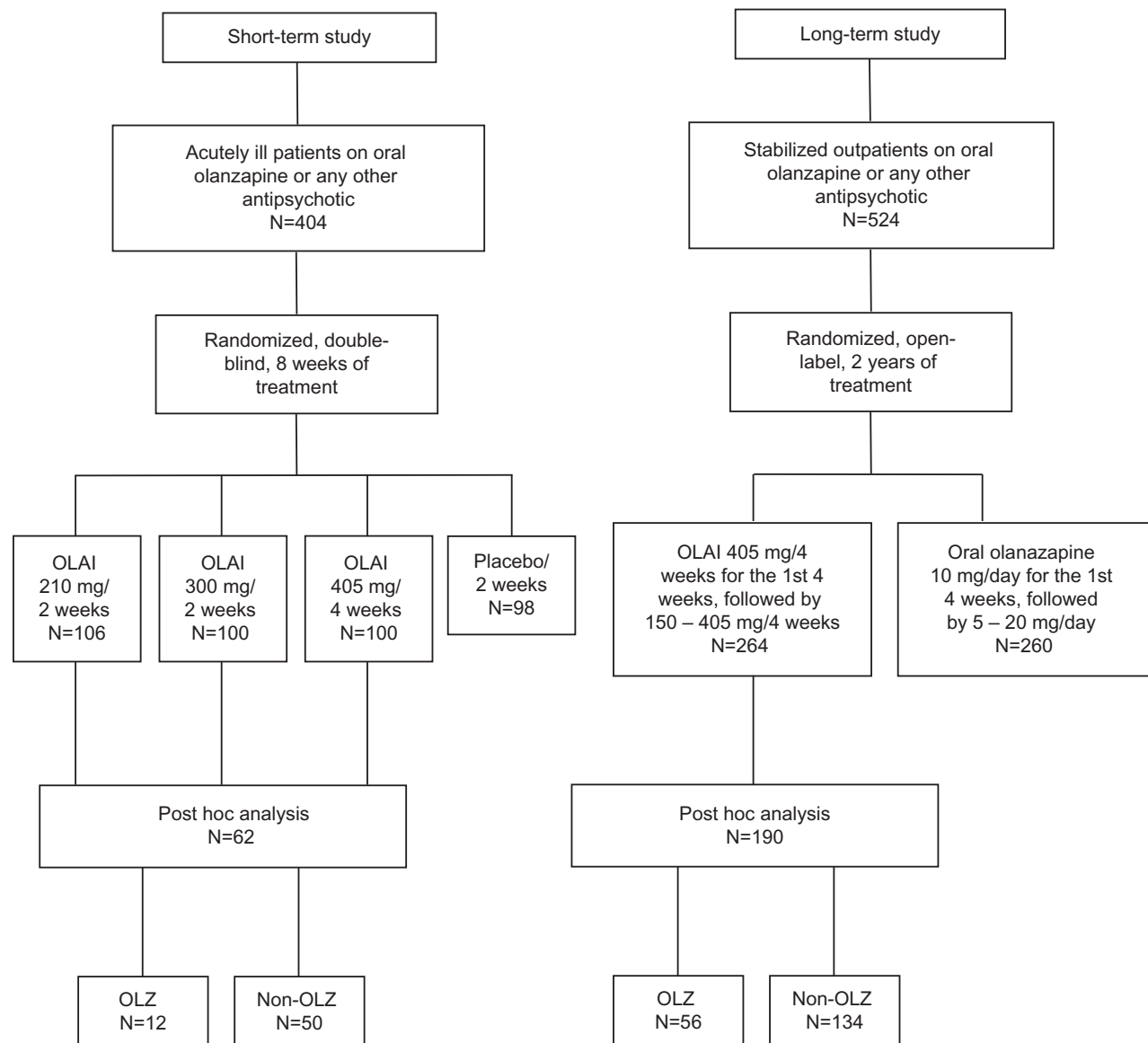
Figure 1 Patients' treatments before and during the original studies, and patient groups in the post hoc analyses. Only patients who had used OLZ or non-OLZ immediately before randomization to OLAI were included in the post hoc analyses.
Abbreviations: OLAI, olanzapine long-acting injection; OLZ, switched to OLAI from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication; N, number of patients.

low-density lipoprotein cholesterol); incidence of treatment-emergent extrapyramidal symptoms (ie, dyskinesia, akathisia, and parkinsonism); and mean change in extrapyramidal symptom scores, assessed using the Abnormal Involuntary Movements Scale (for dyskinesia),[16] Barnes Akathisia Scale,[17] and Simpson-Angus Scale (for parkinsonism).[18]

Statistical analyses

For the purpose of these post hoc analyses, the two patient groups (ie, patients who switched to OLAI from oral olanzapine monotherapy versus those who switched to OLAI from any other antipsychotic medication) were assessed

using Kaplan–Meier tests, t-tests, and chi-square tests, as appropriate, without adjusting for any baseline variables, because the focus was to describe the outcomes of treatment with OLAI for both pretreatment groups. Mean changes from baseline (ie, start of OLAI treatment) to endpoint were analyzed using t-tests applying the last-observation-carried-forward (LOCF) approach. Statistical significance was defined as $P<0.05$ (two-sided), without adjustment for multiplicity, and should be viewed as indicative only. Data from both studies were statistically analyzed and are presented here separately. All post hoc statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

As shown in Figure 1, data for 62 hospitalized patients with acute psychotic symptoms were included in the post hoc analyses from the short-term study (8 weeks of OLAI treatment); 12 of them switched to OLAI from oral olanzapine (hereafter referred to as the OLZ group) and 50 switched to OLAI from any other antipsychotic medication (hereafter referred to as the non-OLZ group). Separately from the short-term study analyses, data for 190 stabilized outpatients from the long-term study (2 years of OLAI treatment) were also analyzed, ie, 56 in the OLZ and 134 in the non-OLZ patient groups (Figure 1). OLAI was given as 210 mg/2 weeks, 300 mg/2 weeks, or 405 mg/4 weeks in the short-term study, and 150–405 mg/4 weeks in the long-term study. The antipsychotic medications used by patients immediately before switching to OLAI are shown in Table 1.

Overall, patient demographics were similar at baseline between the OLZ and non-OLZ pretreatment groups in the short-term and long-term studies (Table 2). In each study group, most patients were male (63%–75%) and Caucasian (42%–68%) or African-American (10%–50%), with mean (± standard deviation) ages between 39 ± 11.5 years and 44 ± 11.4 years and a mean body mass index between 27.3 ± 7.0 kg/m^2 and 29.2 ± 5.8 kg/m^2. The only statistically significant difference in patient demographics was observed with body weight in the long-term study; patients in the OLZ group were heavier than in the non-OLZ group (mean 85.1 ± 20.44 kg versus 78.2 ± 21.61 kg; P=0.039).

Table 1 Antipsychotic medications used immediately before starting the olanzapine long-acting injection

	Short-term study		Long-term study	
	OLZ (N=12)	Non-OLZ (N=50)	OLZ (N=56)	Non-OLZ (N=134)
Any previous APS, n (%)	12 (100.0)	50 (100.0)	56 (100.0)	134 (100.0)
Risperidone	0	20 (40.0)	0	45 (33.6)
Aripiprazole	0	8 (16.0)	0	9 (6.7)
Depot APS	0	15 (30.0)	0	4 (3.0)
Haloperidol	0	4 (8.0)	0	24 (17.9)
Olanzapine	12 (100.0)	0	56 (100.0)	0
Quetiapine	0	2 (4.0)	0	17 (12.7)
Ziprasidone	0	1 (2.0)	0	12 (9.0)
Other typical APS	0	5 (10.0)	0	35 (26.1)
Other atypical APS	0	0	0	18 (13.4)

Abbreviations: APS, antipsychotic medication; OLZ, switched to olanzapine long-acting injection (OLAI) from oral olanzapine monotherapy; Non-OLZ, switched to OLAI from any other antipsychotic medication; N, number of patients who switched to OLAI treatment; n, number of patients who used any APS before switching to OLAI treatment.

As shown in Table 3, mean PANSS total scores were significantly different in the OLZ pretreatment groups compared with the non-OLZ groups in each study (short-term, 95.0 versus 105.9; long-term, 51.7 versus 56.9). The mean baseline CGI-S scores were not significantly different between the pretreatment groups, but were numerically lower in the OLZ patients compared with non-OLZ patients in the short-term study (4.8 versus 4.9, respectively) and in the long-term study (3.0 versus 3.3, respectively, see Table 3).

Discontinuation rates

As shown in Figure 2, the Kaplan–Meier survival analysis of time to all-cause discontinuation of OLAI treatment did not differ between OLZ patients and non-OLZ patients in the short-term study or long-term study. Similarly, as shown in Figure 3, OLAI discontinuation rates did not differ between OLZ patients and non-OLZ patients in the short-term study and long-term study at endpoints. As expected, OLAI discontinuation rates were generally lower in the short-term (8-week) study than in the long-term (2-year) study at endpoints (Figures 2 and 3). In addition, the reasons for discontinuation did not differ between the OLZ patients and non-OLZ patients in the short-term study or long-term study (Figure 3). The most common reasons for discontinuation of OLAI treatment were: lack of efficacy in the short-term study and clinical relapse in the long-term study, subject decision, adverse events in both studies, and, in the long-term study alone, lost to follow-up most probably due to the longer study design (Figure 3). In the long-term study, clinical relapse was defined as: hospitalization related to schizophrenia, or increase ≥25% from baseline in total PANSS score (if baseline score was >40) or an increase of 10 points (if baseline score was ≤40), and at least a one-point increase from baseline score on the CGI-S, if the increase resulted in a CGI-S score ≥4, deliberate self-injury or injury of others, or discontinuation from the study because of worsening psychosis.[11]

Disease severity at study endpoints

As shown in Table 4, at LOCF endpoints, no significant differences were detected in any disease severity measures (mean PANSS total, positive and negative, and CGI-S scores) between non-OLZ and OLZ pretreated patients in the short-term study or long-term study. However, numerical reductions in PANSS total and CGI-S scores were detected at endpoint (Table 4) relative to baseline (Table 3). Similarly, in the short-term study, no statistically significant differences were detected in mean change from baseline to LOCF

Table 2 Baseline patient demographics

	Short-term study			Long-term study		
	OLZ (N=12)	**Non-OLZ (N=50)**	*P*-value	**OLZ (N=56)**	**Non-OLZ (N=134)**	*P*-value
Age (years), mean (SD)	39.2 (11.5)	43.7 (11.4)	0.233	40.7 (12.6)	42.2 (10.5)	0.437
Male, %	9 (75.0)	35 (70.0)	0.732	40 (71.4)	84 (62.7)	0.249
Ethnicity, %			0.085			0.123
Caucasian	5 (41.7)	34 (68.0)		29 (51.8)	91 (67.9)	
African	6 (50.0)	15 (30.0)		7 (12.5)	13 (9.7)	
Hispanic	1 (8.3)	0		8 (14.3)	11 (8.2)	
Native American	0	0		2 (3.6)	0	
East Asian	0	1 (2.0)		8 (14.3)	14 (10.4)	
West Asian	0	0		2 (3.6)	5 (3.7)	
BMI (kg/m^2), mean (SD)	29.1 (5.9)	28.5 (6.7)	0.769	29.2 (5.8)	27.3 (7.0)	0.058
Weight (kg), mean (SD)	84.7 (16.8)	85.6 (24.3)	0.872	85.1 (20.4)	78.2 (21.6)	0.039

Abbreviations: BMI, body mass index; OLZ, switched to olanzapine long-acting injection (OLAI) from oral olanzapine monotherapy; Non-OLZ, switched to OLAI from any other antipsychotic medication; N, number of patients who switched to OLAI treatment; SD, standard deviation.

endpoint PANSS and CGI-S scores in the OLZ and non-OLZ groups. In the long-term study, statistically significant differences in reductions of the mean change from baseline of PANSS total and negative scores were detected in non-OLZ patients, relative to OLZ patients.

Safety and tolerability assessments

There were no statistically significant differences in the proportions of patients experiencing any treatment-emergent adverse event between the OLZ group and non-OLZ groups in the short-term study (91.7% versus 72.0%, respectively) or long-term study (66.1% versus 69.4%, respectively). Treatment-emergent adverse events in ≥5% and two or more OLZ or non-OLZ patients in either of the studies included diarrhea, increased weight, somnolence, and insomnia (see Table 5).

In the short-term study, no statistically significant difference in the proportion of patients who experienced a treatment-emergent serious adverse event was found between OLZ and non-OLZ pretreatment groups. In the long-term study, a significantly higher proportion of patients in the OLZ pretreatment group than in the non-OLZ pretreatment group (19.6%

versus 5.2%, respectively) experienced a treatment-emergent serious adverse event. The main serious treatment-emergent adverse events recorded in either/both studies were schizophrenia, anxiety, and psychotic disorder (Table 6).

Potentially clinically significant changes in metabolic parameters from baseline to endpoint were defined as any such changes that were larger than in a set of predefined values. The predefined values were: weight gain, ≥7% increase from baseline; fasting glucose, ≥7 mmol/L following baseline of <5.56 mmol/L; fasting triglycerides, ≥2.26 mmol/L following baseline of <1.69 mmol/L; total fasting cholesterol, ≥6.21 mmol/L following baseline of <5.17 mmol/L; fasting low-density lipoprotein cholesterol, ≥4.13 mmol/L following baseline <2.58 mmol/L; and fasting high-density lipoprotein cholesterol, <1.03 mmol/L following baseline of ≥1.03 mmol/L. These changes were assessed in patients in both the short-term and long-term studies (see Figure 4). Of these parameters, only increase in body weight from baseline in the short-term study was statistically significant, with a greater proportion of patients in the OLZ pretreatment group (58.3%) experiencing weight increases than in the non-OLZ pretreatment group (26.0%).

Table 3 Baseline disease characteristics

	Short-term study			Long-term study		
	OLZ (N=12)	**Non-OLZ (N=50)**	*P*-value	**OLZ (N=56)**	**Non-OLZ (N=134)**	*P*-value
Episodes in previous 24 months, mean (SD)	5.3 (3.2)	3.1 (3.0)	0.056	2.8 (2.2)	2.6 (1.3)	0.448
Length of current episode (months), mean (SD)	1.9 (1.9)	3.3 (6.2)	0.181	7.2 (4.6)	5.3 (5.0)	0.011
PANSS total score, mean (SD)	95.0 (10.3)	105.9 (18.1)	0.009	51.7 (10.8)	56.9 (9.5)	0.003
CGI-S score, mean (SD)	4.8 (0.6)	4.9 (0.8)	0.540	3.0 (1.0)	3.3 (0.7)	0.062

Abbreviations: CGI-S, Clinical Global Impression Severity; OLZ, switched to olanzapine long-acting injection (OLAI) from oral olanzapine monotherapy; Non-OLZ, switched to OLAI from any other antipsychotic medication; PANSS, Positive and Negative Syndrome Scale; N, number of patients who switched to OLAI treatment; SD, standard deviation.
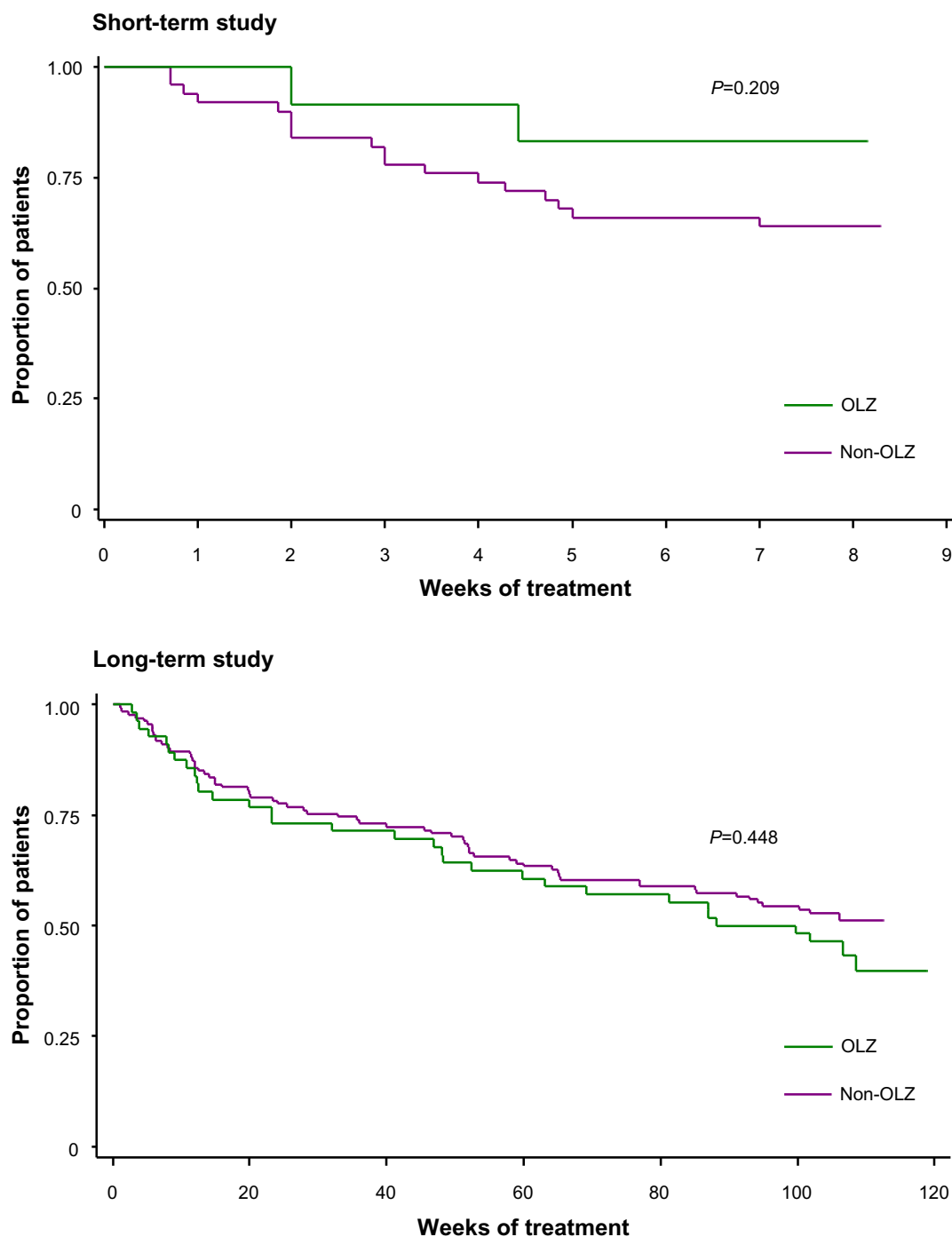
Short-term study

Long-term study

Figure 2 Kaplan–Meier survival analysis of time to all-cause discontinuation from OLAI treatment. No statistically significant differences were detected in times to all-cause discontinuation in the short-term study or in the long-term study.
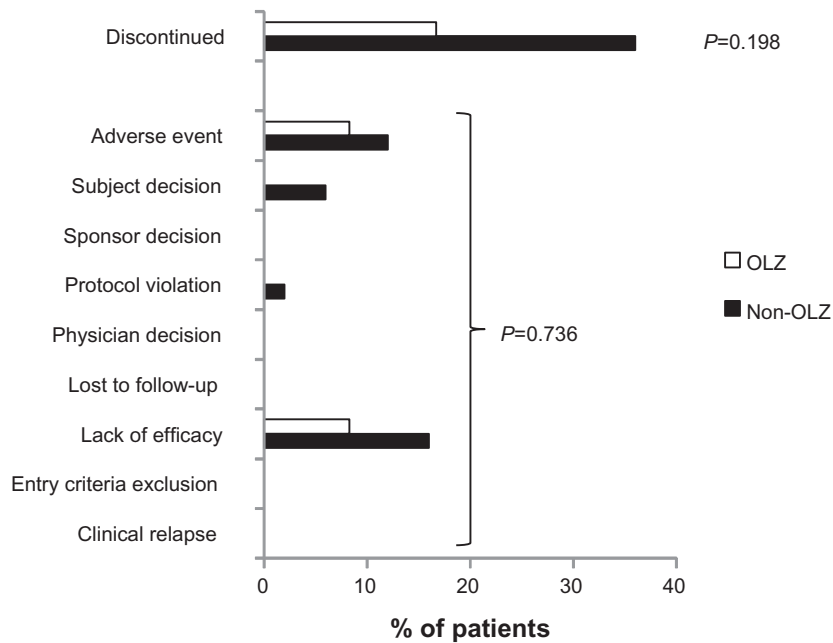**Abbreviations:** OLAI, olanzapine long-acting injection; OLZ, switched to OLAI from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication.

After identifying potentially clinically significant changes in metabolic parameters, the investigators decided whether these changes were clinically significant, and if so, these changes were classified as adverse events. Metabolic changes based on adverse event reporting, rather than solely based on laboratory or clinical measurements, are shown in Table 5.

Extrapyramidal symptoms

In the short-term and long-term studies, some potentially clinically significant differences were detected in extrapyramidal symptoms, which occurred at any time after switching to OLAI treatment. Specifically, potentially clinically significant changes that were
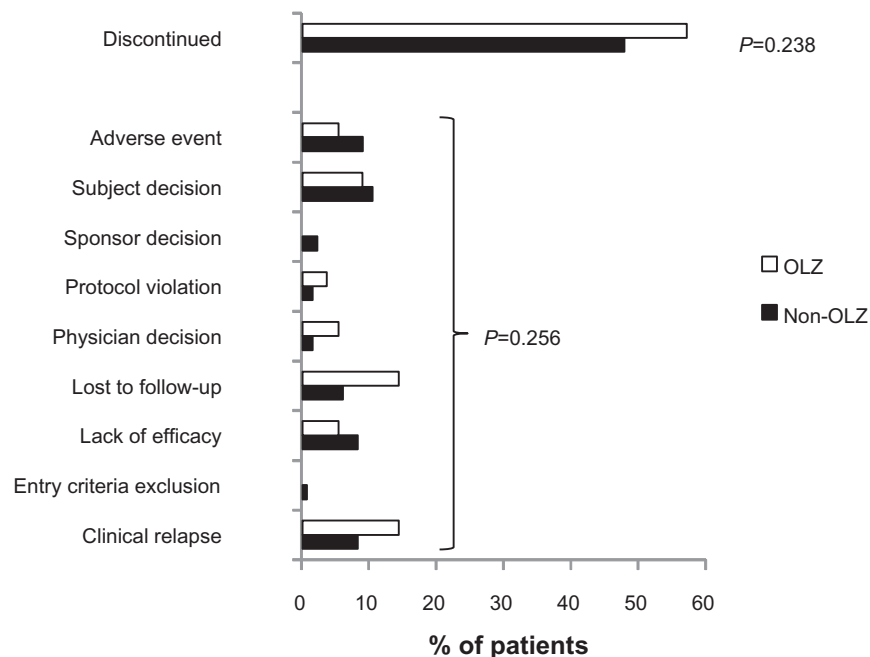
Short-term study

Long-term study

Figure 3 Rates of discontinuation and reasons for discontinuation from OLAI treatment. No statistically significant differences were detected in discontinuation rates in the short-term study or in the long-term study.
Abbreviations: OLAI, olanzapine long-acting injection; OLZ, switched to OLAI from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication.

significantly more frequent in OLZ patients than non-OLZ patients were: akathisia in the short-term study (33.3% versus 10.0%) and long-term study (8.9% versus 1.5%); and parkinsonism in the long-term study (8.9% versus 2.2%, Figure 5).

In the short-term study, mean extrapyramidal symptom scores (for dyskinesia, akathisia, and parkinsonism) decreased from baseline to endpoints in OLZ and non-OLZ groups, with the exception of a mean 0.9 increase in Simpson-Angus total score (for parkinsonism) in the OLZ

Table 4 Disease severity measures after treatment with olanzapine long-acting injection

	Short-term study			Long-term study		
	OLZ (N=12; n=10)	**Non-OLZ** (N=50; n=32)	*P*-value	**OLZ** (N=56; n=24)	**Non-OLZ** (N=134; n=70)	*P*-value
LOCF endpoint in disease severity measures						
PANSS total score, mean (SD)	79.4 (13.7)	73.3 (19.7)	0.288	48.0 (10.9)	45.1 (11.6)	0.280
PANSS positive, mean (SD)	19.6 (6.2)	16.3 (6.4)	0.170	9.9 (2.7)	9.3 (2.9)	0.347
PANSS negative, mean (SD)	20.2 (3.2)	19.6 (5.7)	0.672	15.0 (5.3)	13.3 (4.3)	0.166
CGI-S, mean (SD)	4.1 (0.7)	3.6 (0.8)	0.066	2.6 (0.9)	2.5 (0.8)	0.412
	OLZ (N=12; n=12)	**Non-OLZ** (N=50; n=50)	*P*-value	**OLZ** (N=56; n=47)	**Non-OLZ** (N=134; n=126)	*P*-value
Mean change from baseline to LOCF endpoint in disease severity measures						
PANSS total (SD)	−13.4 (13.4)	−20.8 (25.0)	0.166	3.9 (15.9)	−3.6 (16.4)	0.008
PANSS positive (SD)	−4.3 (4.5)	−6.6 (7.5)	0.175	0.7 (5.0)	−0.9 (4.5)	0.061
PANSS negative (SD)	−1.8 (3.5)	−4.5 (6.0)	0.054	1.2 (4.4)	−1.6 (4.7)	<0.001
CGI-S (SD)	−0.4 (1.1)	−0.7 (1.1)	0.367	−0.1 (0.8)	−0.3 (1.0)	0.112

Abbreviations: CGI-S, Clinical Global Impression Severity; LOCF, last-observation-carried-forward; OLZ, switched to olanzapine long-acting injection (OLAI) from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication; N, number of patients who switched to OLAI treatment; n, number of patients at the LOCF endpoint; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

group (Figure 6). However, no extrapyramidal symptom scores differed significantly in non-OLZ patients versus OLZ patients in the short-term study. In the long-term study, mean extrapyramidal symptom scores decreased from baseline in the non-OLZ group, but there was no clinically significant difference in OLZ patients. Thus, mean Barnes scores for akathisia were significantly lower for non-OLZ patients than for OLZ patients (–0.6 versus 0.0), although extrapyramidal

symptom scores did not differ significantly between the pretreatment groups for parkinsonism or dyskinesia in the long-term study.

Discussion

These post hoc analyses suggest that patients suffering from schizophrenia and switching from non-OLZ to OLAI did not experience lower tolerability or less effectiveness compared

Table 5 Treatment-emergent adverse events occurring in >5.0% and two or more patients

	Short-term study			Long-term study		
	OLZ (N=12)	**Non-OLZ** (N=50)	*P*-value	**OLZ** (N=56)	**Non-OLZ** (N=134)	*P*-value
Any treatment-emergent adverse events, n (%)	11 (91.7)	36 (72.0)	0.153	37 (66.1)	93 (69.4)	0.652
Diarrhea	0	2 (4.0)		3 (5.4)	5 (3.7)	
Dyspepsia	0	3 (6.0)		0	1 (0.7)	
Nasopharyngitis	1 (8.3)	2 (4.0)		4 (7.1)	7 (5.2)	
Upper respiratory tract infection	1 (8.3)	1 (2.0)		3 (5.4)	3 (2.2)	
Weight decreased	0	0		1 (1.8)	11 (8.2)	
Weight increased	0	2 (4.0)		7 (12.5)	24 (17.9)	
Hyperlipidemia	2 (16.7)	0		0	0	
Increased appetite	0	0		1 (1.8)	8 (6.0)	
Headache	4 (33.3)	10 (20.0)		3 (5.4)	7 (5.2)	
Lethargy	2 (16.7)	0		1 (1.8)	1 (0.7)	
Sedation	1 (8.3)	4 (8.0)		2 (3.6)	2 (1.5)	
Somnolence	0	1 (2.0)		5 (8.9)	14 (10.4)	
Agitation	2 (16.7)	5 (10.0)		2 (3.6)	3 (2.2)	
Anxiety	3 (25.0)	1 (2.0)		8 (14.3)	12 (9.0)	
Insomnia	2 (16.7)	7 (14.0)		6 (10.7)	17 (12.7)	
Schizophrenia	0	0		5 (8.9)	2 (1.5)	
Cough	2 (16.7)	0		0	1 (0.7)	
Pharyngolaryngeal pain	3 (25.0)	1 (2.0)		0	0	

Abbreviations: OLZ, switched to olanzapine long-acting injection (OLAI) from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication; N, number of patients who switched to OLAI treatment; n, number of patients who experienced at least one treatment-emergent adverse event.

Table 6 Treatment-emergent serious adverse events occurring in two or more patients

	Short-term study			Long-term study		
	OLZ (N=12)	Non-OLZ (N=50)	P-value	OLZ (N=56)	Non-OLZ (N=134)	P-value
Any treatment-emergent serious adverse events, n (%)	3 (25.0)	4 (8.0)	0.095	11 (19.6)	7 (5.2)	0.002
Any psychiatric disorder	2 (16.7)	1 (2.0)		8 (14.3)	6 (4.5)	
Anxiety	1 (8.3)	0		2 (3.6)	0	
Psychotic disorder	0	1 (2.0)		1 (1.8)	3 (2.2)	
Schizophrenia	0	0		5 (8.9)	2 (1.5)	

Abbreviations: OLZ, switched to olanzapine long-acting injection (OLAI) from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication; N, number of patients who switched to OLAI treatment; n, number patients of who experienced at least one treatment-emergent serious adverse event.
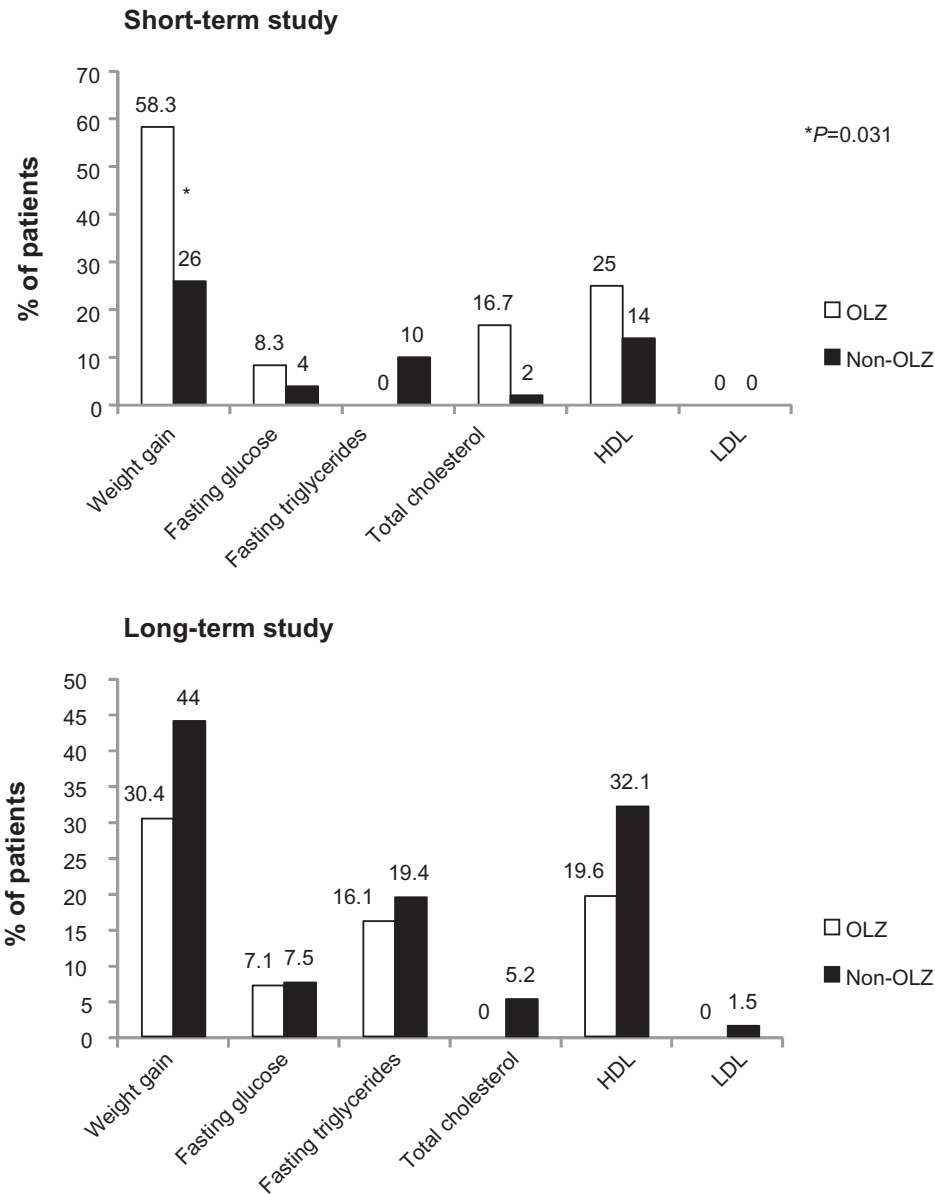
Figure 4 Potentially clinically significant changes in metabolic parameters after switching to OLAI treatment. The only statistically significant difference detected in potentially clinically significant changes was "weight gain" in the short-term study. Definitions: weight gain, ≥7% increase from baseline; fasting glucose, ≥7 mmol/L following baseline of <5.56 mmol/L; fasting triglycerides, ≥2.26 mmol/L following baseline of <1.69 mmol/L; total fasting cholesterol, ≥6.21 mmol/L following baseline of <5.17 mmol/L; fasting LDL, ≥4.13 mmol/L following baseline <2.58 mmol/L; fasting HDL, <1.03 mmol/L following baseline of ≥1.03 mmol/L.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLAI, olanzapine long-acting injection; OLZ, switched to OLAI from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication.
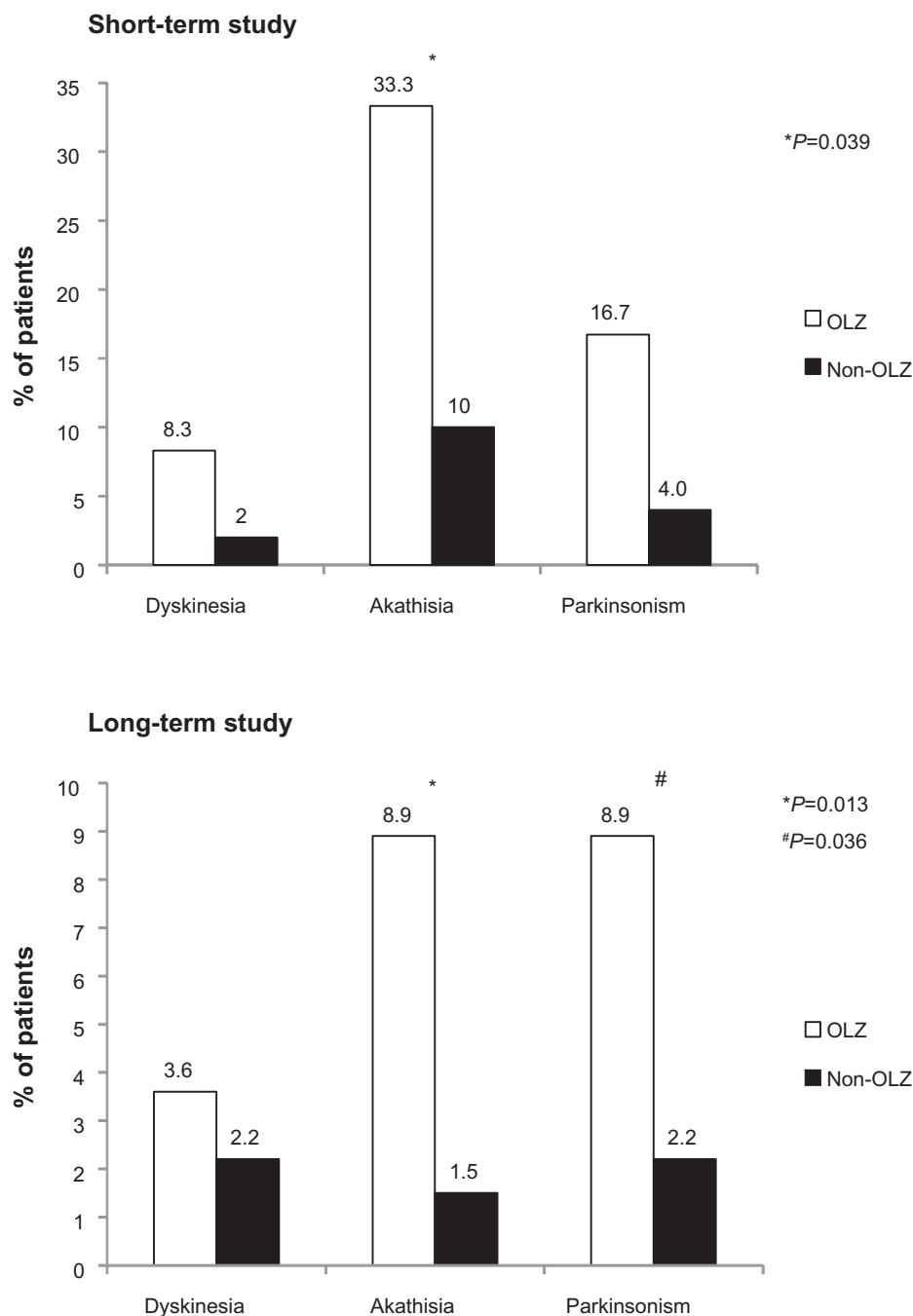
Short-term study

Long-term study

Figure 5 Potentially clinically significant changes in extrapyramidal symptoms at any time after switching to OLAI treatment. Statistically significant differences were detected in akathisia (in the short-term and long-term studies) and parkinsonism (in the long-term study).
Abbreviations: OLAI, olanzapine long-acting injection; OLZ, switched to OLAI from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication.

with patients switching from oral OLZ to OLAI in either short-term (8-week) or long-term (2-year) studies. However, these findings should be interpreted with care, particularly due to the small sample size (eg, only 12 patients in the OLZ group from the short-term study) and differences in patients' clinical profiles.

Given that poor adherence to oral antipsychotic therapy is a major problem in the long-term management of schizophrenia,[1] completion/discontinuation of treatment is recognized as a proxy measure of a medication's effectiveness in treating schizophrenia.[12–14] In addition, measuring discontinuation is said to integrate "patients' and clinicians' judgments of efficacy, safety, and tolerability into a global measure of effectiveness that reflects their evaluation of therapeutic benefits in relation to undesirable effects".[12]
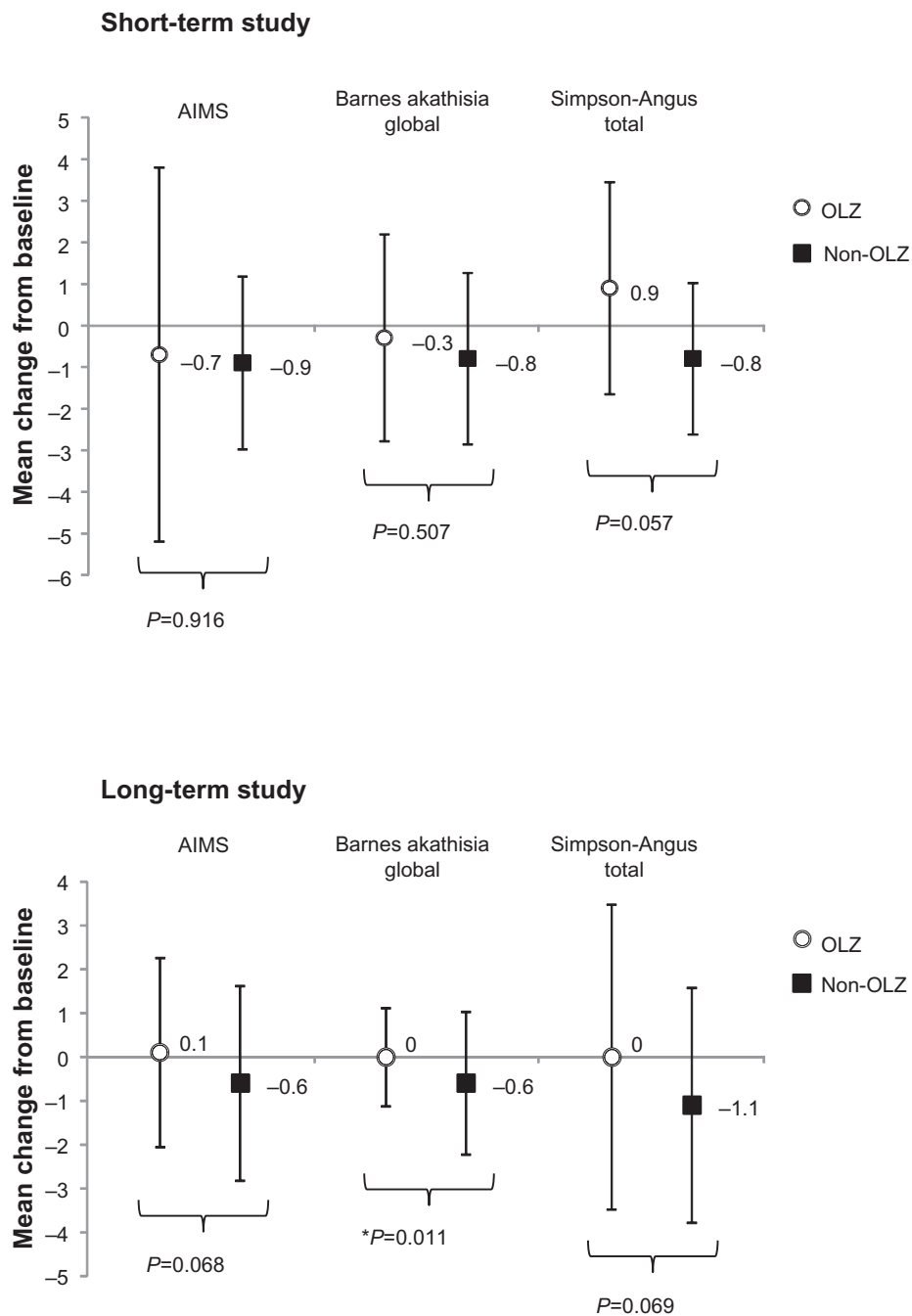
Short-term study

Long-term study

Figure 6 Mean (SD) changes in extra pyramidal symptom scores. The only statistically significant difference was detected in the Barnes Akathisia Rating Scale in the long-term study.
Abbreviations: OLAI, olanzapine long-acting injection; OLZ, switched to OLAI from oral olanzapine monotherapy; non-OLZ, switched to OLAI from any other antipsychotic medication; SD, standard deviation; AIMS, Abnormal Involuntary Movement Scale.

In our analysis, time to all-cause discontinuation, percentages of patients who discontinued OLAI treatment, and reasons for discontinuation (eg, lack of efficacy, adverse events) were similar for OLZ patients and non-OLZ patients. Hence, the effectiveness of OLAI (as shown by treatment discontinuation) did not appear to be affected by the type of antipsychotic treatment that patients switched from. These findings are compatible with those from several other

studies[12,13,19,20] that suggest the effectiveness of olanzapine (shown by treatment discontinuation) is equal to and often greater than the effectiveness of a range of other typical and atypical antipsychotics.

In the current analyses, we also measured disease severity using PANSS and CGI-S scores. Mean PANSS total scores were different at baseline (non-OLZ patients had symptoms that were more severe than those of OLZ patients) in both the

short-term and long-term studies, while baseline mean CGI-S scores did not differ significantly between pretreatment groups. However there were no statistically significant differences in mean PANSS total scores, or between mean CGI-S scores, at the end of the 8-week or 2-year follow-up periods. Thus, non-OLZ patients may have noninferior or even greater clinical benefit (ie, potentially with better control of psychotic symptoms) after starting treatment with OLAI than OLZ patients. Moreover, in the 2-year study, mean changes from baseline to endpoint in PANSS total and in PANSS negative scores confirmed that these patients may have experienced noninferior or greater clinical benefit than oral OLZ patients by starting treatment with OLAI. Regarding the differences in baseline PANSS between the non-OLZ and OLZ groups, these may have been due to the fact that our post hoc analyses were based on nonrandomized comparisons.

While it should be reiterated that these analyses were complicated by non-OLZ patients having a higher mean PANSS total score (and thus more severe symptoms) at baseline than OLZ patients, these data may indicate that the non-OLZ group had more room for improvement in symptom control. Moreover, this is not an unexpected result, because the non-OLZ treatments may not have been as effective as oral OLZ before switching to OLAI. This suggestion is based on the clinical improvements (by means of PANSS scores) of olanzapine being greater than those of various other typical and atypical antipsychotics in two large meta-analyses,[21,22] as well as the aforementioned similar or greater effectiveness (discontinuation rates) of oral OLZ versus non-OLZ treatments.[12,13,19,20] Similarly, the greater room for improvement and potentially greater effectiveness of olanzapine may also explain why symptoms in non-OLZ patients improved to a greater extent relative to symptoms in OLZ patients when they were administered OLAI.

In terms of safety, there were no statistically significant differences in the percentages of non-OLZ-pretreated patients versus OLZ-pretreated patients with treatment-emergent adverse events in the short-term or long-term studies. In addition, the adverse events detected were similar to those described in the oral olanzapine Summary of Product Characteristics (SPC) and OLAI SPC.[23,24] Serious adverse events were significantly more frequent in patients pretreated with oral OLZ than in those treated with non-OLZ in the long-term study. However, given the limited number of patients who experienced serious adverse events, these findings should be interpreted with caution. In addition, although the frequency of adverse events was similar in OLZ patients versus non-OLZ patients, mean extrapyramidal symptom scores tended

to decrease to a greater extent in non-OLZ patients than in OLZ patients in both studies, reaching statistical significance for akathisia symptoms in the long-term study. From a clinical perspective, larger decreases in extrapyramidal symptom scores in non-OLZ patients versus OLZ patients are to be expected, given that olanzapine has a lower risk of extrapyramidal symptoms when compared with other antipsychotic medications.[25–27] Also, the differences in these changes might be explained by the different baseline values for the pretreatment groups.

In addition, while the incidence of clinically significant changes in fasting glucose, fasting triglycerides, and total, high-density lipoprotein, and low-density lipoprotein cholesterol levels were similar between OLZ patients and non-OLZ patients in each study, a significantly greater number of patients treated with OLZ compared with non-OLZ patients in the short-term study reported potentially clinically significant weight gain ($\geq$7%). The latter result was unexpected because it is likely that at least some patients in the OLZ group would have experienced an increase in body weight before switching to OLAI, relative to non-OLZ patients, because greater weight gain has been reported during treatment with olanzapine compared with some other antipsychotics.[28] Thus, in theory, after switching to OLAI, OLZ-pretreated patients should not experience significantly more increases in body weight when compared with non-OLZ-pretreated patients. In contrast, based on literature reports, non-OLZ-pretreated patients may have a greater risk of weight gain when exposed to olanzapine, regardless of the formulation used.[28]

Several limitations may affect these current analyses, so our findings should be interpreted with care. Firstly, because these were post hoc analyses, they should be considered exploratory. A prospective study design, if at all possible, could be a more ideal approach to compare the effects of switching from different antipsychotic medications on the effectiveness and safety of OLAI. This is particularly relevant for comparing changes over time as well as endpoint values between the two pretreatment groups, given that OLZ-pretreated and non-OLZ-pretreated patients often had different baseline values.

Secondly, our analyses were limited to a small number of patients. In particular, our analysis of the 8-week study was limited to only 12 patients in the OLZ group, which may be responsible for the lack of statistical significance with PANSS scores, despite trends towards lower values in the non-OLZ group versus the OLZ group. However, while 97 patients used oral olanzapine in the 8-week source study, only 12 of these patients were taking

olanzapine as monotherapy. Exclusion of patients using additional non-OLZ antipsychotic medications from the OLZ group thus ensured that we could ascribe the results of the current post hoc analyses solely to OLZ, although the number of patients was limited by this.

Thirdly, the patients in our analyses had differing clinical profiles. Patients who switched to OLAI from any non-OLZ therapy were analyzed in one group per study, rather than being subdivided into individual groups per non-OLZ drug. Thus, potential differences in clinical outcomes between patients switching from different non-OLZ drugs were not detected. Another example of patient differences, which may have influenced safety and effectiveness outcomes, is exposure to different doses of OLAI (ie, 210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks in the short-term study versus 150–405 mg/4 weeks in the long-term study). Indeed, greater efficacy and larger changes in metabolic safety measures (eg, greater weight gain) have been reported at higher doses of OLAI.[29]

Fourthly, the short-term and long-term changes during treatment with OLAI were examined in two separate studies and in two different patient populations, rather than in one longitudinal investigation. As with the third limitation, differences between the two studies, which may have influenced safety and effectiveness outcomes, include exposure to different medications before each study and the different doses of OLAI used in each study. Hence, it was not possible to combine or directly compare the effectiveness and safety outcomes of the two studies, and the current analyses were performed separately per study.

Conclusion

These post hoc analyses suggest that patients switching from non-OLZ to OLAI did not experience lower tolerability or less effectiveness (measured by time to all-cause discontinuation, rates and reasons for discontinuation, and mean changes in PANSS and CGI-S scores) compared with patients switching from oral OLZ to OLAI. This was the case both with acutely ill patients (8-week OLAI treatment) and stabilized patients (2-year OLAI treatment). However, these findings should be interpreted with care, particularly due to the small sample sizes and differences in patients' clinical profiles.

Author contributions

AC, MC, AS, EA, and EP assisted with study design, interpretation of the study results, and manuscript preparation. AS and LB were responsible for data analysis and statistical

consulting. All authors approved the final version of the submitted manuscript.

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