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Efficacy and safety of aripiprazole lauroxil in schizophrenic patients presenting with severe psychotic symptoms during an acute exacerbation☆

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ABSTRACT

Aripiprazole lauroxil (AL), a new long-acting injectable antipsychotic, demonstrated safety and efficacy in treating acute exacerbation symptoms of schizophrenia in a 12-week placebo-controlled trial of two doses of AL (441 mg and 882 mg) administered every 4 weeks. We performed a post hoc analysis of this trial to evaluate the efficacy of AL in the subgroup of patients with severe psychotic symptoms, defined as those with baseline Positive and Negative Syndrome Scale (PANSS) Total score above the median score of 92 (n = 309). Change from baseline to Day 85 in PANSS Total score; Positive, Negative, and General Psychopathology subscale scores; and overall response rate were assessed. Statistically significant and clinically meaningful improvements in PANSS Total score were demonstrated with AL 441 mg and AL 882 mg, with placebo-adjusted differences of −14.7 ($p < 0.0001$) and −16.6 ($p < 0.0001$), respectively. Significant and clinically meaningful findings with both doses of AL were also demonstrated for the PANSS subscales and responder rates. Overall responder rates at Day 85 were significantly greater for AL 441 mg (49%; $p < 0.001$) and 882 mg (61%; $p < 0.001$) groups vs. placebo (18%). Common adverse events (>5%) were schizophrenia, akathisia, headache, insomnia, and anxiety. AL demonstrated robust efficacy in treatment of the subgroup of patients experiencing severe psychotic symptoms. Both doses (441 mg and 882 mg) were effective, with numerically greater improvement in symptoms and proportion of responders favoring the higher dose arm. Both doses had a side effect profile consistent with the known safety profile of aripiprazole.

1. Introduction

Symptoms of schizophrenia, including positive, negative, and cognitive, cause extreme emotional distress and disruption to the lives of patients (Alphs et al., 2011), with symptom severity determined to be among the most significant predictors of poor treatment outcome (Mohr et al., 2004). In addition, symptom severity has been found to be highly correlated with nonadherence to medication among patients with schizophrenia (Higashi et al., 2013). Research has shown that the greater the severity of symptoms, the more likely a person with schizophrenia is to have impaired clinical insight, poor social adjustment, increased need for medication, and increased use of nicotine (Buckley et al., 2007; Krishnadas et al., 2012; Gerretsen et al., 2013).

The goals of treatment during an acute psychotic episode are to prevent harm, control disturbed behavior, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggression), and effect a rapid return to the best level of functioning possible (Andreasen et al., 2005).

Relapse is a time to reevaluate the pharmacologic treatment plan to consider whether the current episode represents a failure of efficacy of the prior antipsychotic, or for oral medications, covert medication nonadherence. Because relapse requires a greater level of care, it can be an ideal time to initiate a long-acting antipsychotic medication as it does not need to be administered as frequently and thus may address efficacy issues related to non-adherence.

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Aripiprazole lauroxil (AL) is an injectable, extended-release formulation that is converted in vivo to aripiprazole, an atypical antipsychotic. AL was approved for the treatment of schizophrenia in 2015 and is available in three doses, 441 mg, 662 mg, and 882 mg. All three doses are administered monthly, and the 882-mg dose has the option of being administered at 6-week dose intervals. In a large, randomized, placebo-controlled study, both doses of AL evaluated (441 mg and 882 mg) administered every 4 weeks over the course of 12 weeks demonstrated robust efficacy compared with placebo (Meltzer et al., 2015). Results of that study are consistent with earlier studies of oral aripiprazole, which also showed efficacy for the acute treatment of schizophrenia at oral doses ranging from 10 to 30 mg per day (Potkin et al., 2003; Kane et al., 2002).

Despite these and other studies showing comparability of the aripiprazole moiety with other first-line antipsychotics for the acute treatment of schizophrenia, many clinicians have raised concerns about the relative efficacy of aripiprazole for more severe or symptomatic patients, in part based on its partial agonism at D2 dopamine receptors. To address the question of AL efficacy for the more symptomatic patients participating in the 12-week pivotal trial (Meltzer et al., 2015), we performed a post hoc analysis of the major response and outcome parameters in patients with the most severe symptoms at baseline. Safety, tolerability, and dose-response were also evaluated.

2. Methods

The primary study was conducted across seven countries during the period December 2011 to March 2014, and written informed consent was obtained from all participants before study participation. The study was registered at clinicaltrials.gov (NCT01469039). The primary results have been published (Meltzer et al., 2015).

2.1. Study design

This multicenter, randomized, double-blind, placebo-controlled study evaluated AL in patients experiencing an acute relapse of schizophrenia. Detailed methods were previously reported (Meltzer et al., 2015) and are summarized briefly. Patients satisfying screening eligibility criteria were admitted to an inpatient study unit. Currently prescribed antipsychotics were discontinued after screening and before administration of study drug. Aripiprazole-naïve patients were administered a test dose of oral aripiprazole 5 mg daily for 2 days before randomization to assess tolerability.

Patients were randomized to AL 441 mg, AL 882 mg or placebo (fat emulsion for human use; Intralipid) injected into the gluteal muscle once monthly (Days 1, 29 and 57). Patients assigned to the active treatment arms also received oral aripiprazole 15 mg daily for the first three weeks of the study (the placebo arms received blinded oral placebo). Both intramuscular (IM) injections (AL 441 mg, AL 882 mg, or placebo) and oral drugs (oral aripiprazole 15 mg or placebo for 21 days) were administered under double-blind conditions.

2.2. Initial patient selection

Eligible patients were 18 to 70 years of age with a primary psychiatric diagnosis of schizophrenia and who were admitted to an inpatient psychiatric unit for treatment of an acute psychotic episode. Details of the inclusion/exclusion criteria and procedures can be found in the primary manuscript (Meltzer et al., 2015), and the key elements of the inclusion/exclusion criteria are summarized as follows: after signing informed consent forms, the primary clinical diagnosis of schizophrenia based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria was confirmed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trial Version (SCID-CT; First et al., 2007). Patients with a primary diagnosis of a mood disorder, schizoaffective disorder, or other Axis 1 disorder, including primary drug or alcohol disorder, were excluded. All patients had to meet clinical criteria for psychiatric hospitalization and met a priori criteria of having an acute psychotic episode within the prior 2 months. After consenting, patients had to meet screening symptom severity criteria of a Clinical Global Impression-Severity (CGI-S) score ≥ 4 and a Positive and Negative Syndrome Scale (PANSS) Total score of 70 to 120 as well as a score of ≥4 for two or more key positive symptom items to qualify for randomization. Key positive symptom items included: Item 1 (P1; delusions), Item 2 (P2; conceptual disorganization), Item 3 (P3; hallucinatory behavior) and Item 6 (P6; suspiciousness/persecution). Pharmacologic history required having a history of responding to a therapeutic trial of a first-line (non-clozapine) antipsychotic.

2.3. Study assessments

The PANSS and CGI-S scales were administered at screening and on days 1, 8, 15, 22, 29, 57, and 85. The primary outcome studied was the mean change from baseline to Day 85 in PANSS Total score. Mean change from baseline in PANSS Total score and subscale (Positive, Negative, General) scores at all post baseline visits were assessed. Categorical responder rate (defined as ≥30% improvement in PANSS Total score or a final CGI-I score of ≤2 [very much or much improved]) was assessed.

Safety was evaluated based on standard procedures for a placebo-controlled antipsychotic randomized clinical trial, (Meltzer et al., 2015) and was assessed in all patients with PANSS Total scores >92 who received at least one dose of study drug.

2.4. Post hoc categorization of "severe" status

The original efficacy analysis for the full study included 596 patients who entered and received at least one follow-up efficacy assessment. The baseline PANSS Total scores for the full study cohort ranged from 65 to 143, with a mean (SD) of 92.8 (10.8) and median of 92. To define the post-hoc "severe" sample for this current analysis, we used a baseline PANSS Total score of >92 as the cutoff criterion. This PANSS score cutoff was selected because it was the median entry score and is consistent with a CGI-S score of markedly ill (Santor et al., 2007; Leucht et al., 2005).

2.5. Statistical analysis

Efficacy analyses were performed in patients who received at least one dose of study drug and had at least one follow-up efficacy assessment. Changes from baseline in PANSS Total score and PANSS Positive, Negative, and General Psychopathology subscale scores at each post baseline visit for AL 441 mg and AL 882 mg were compared with placebo using mixed-model repeated measures analyses based on the observed data. These models included change from baseline scores at each post baseline visit as the dependent outcome, and covariates included baseline scores, treatment, and study region. The overall responder rate was analyzed using a logistic regression model with last observation carried forward. This model included study region and treatment group as factors and baseline PANSS Total score as a covariate.

Descriptive statistics were generated for the safety outcomes. To assess magnitude of improvement in the more severe subgroup, effect sizes of PANSS improvement at Day 85 were calculated for the PANSS ≤ 92 and PANSS > 92 subgroups. Cohen's *d* was used to report the effect size, and calculated as the difference between two least square means from the mixed-model repeated analysis divided by a pooled standard deviation.

Patients assigned to the active treatment arms (441 mg and 882 mg) also received oral aripiprazole 15 mg daily for the first three weeks of the study (the placebo arms received blinded oral placebo). Therefore, it is difficult to disentangle the effects of active oral aripiprazole from active AL during this period. To address this problem, the same efficacy analyses for PANSS Total score were repeated using the Day 22 PANSS score as a new "baseline" ($n = 247$, or 84% of the original PANSS > 92 sample used for efficacy analyses)

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testing for the change from Day 22 to Day 85 using the same models (including effect size).

3. Results

3.1. Patient disposition and baseline characteristics

A total of 309 patients out of the total sample population in the original study ($N = 622$) had a baseline PANSS Total score of >92 and were considered severely ill. Out of 309 patients 294 had at least one follow-up efficacy assessment and were included in efficacy analyses. Demographic and baseline characteristics for the placebo, AL 441 mg, and AL 882 mg groups are shown in Appendix 1 and Appendix 2. Of these 294 patients, 163 (55.4%) completed the treatment period (Appendix 1). A greater percentage of patients in the placebo group discontinued from the study (66%) compared with the AL 441 mg (37%) and 882 mg (31%) groups. Reasons for discontinuation in the placebo group were most commonly due to a lack of efficacy (25%), adverse event (21%), or withdrawal by patient (9%). The main reasons for discontinuation among severely ill patients assigned to the AL 441 mg dose were withdrawal by patient (15%) and adverse event (10%), whereas in the AL 882 mg group, the most common reasons were lack of efficacy (10%) and withdrawal by patient (9%). Baseline PANSS Total scores (mean ± SD) were similar among the three groups: 102.7 ± 7.9, 101.3 ± 6.0, and 101.0 ± 6.4 for placebo, AL 441 mg, and 882 mg, respectively (Appendix 2).

3.2. Safety

The most common adverse events (≥5% in any treatment group) in severely ill patients were schizophrenia, akathisia, headache, insomnia, and anxiety. Table 1 shows all adverse events occurring in >2% patients in any treatment group.

3.3. Efficacy

Statistically significant and clinically meaningful improvements in PANSS Total score were demonstrated for both doses of AL from baseline to Day 85. The placebo-adjusted differences were −14.7 ($p < 0.0001$) for AL 441 mg and −16.6 for AL 882 mg. PANSS Total score also decreased significantly at every post baseline visit after Day 15 for AL 441 mg and Day 8 for AL 882 mg (Fig. 1).

Table 1
Adverse events experienced by >2% in any treatment group of severely ill patients.[a]

		Aripiprazole Lauroxil	
	Placebo ($n = 105$) n (%)	441 mg ($n = 100$) n (%)	882 mg ($n = 104$) n (%)
Akathisia	5 (4.8)	15 (15.0)	12 (11.5)
Nausea	1 (1.0)	3 (3.0)	4 (3.8)
Diarrhea	3 (2.9)	3 (3.0)	2 (1.9)
Dyspepsia	1 (1.0)	4 (4.0)	1 (1.0)
Asthenia	1 (1.0)	0	4 (3.8)
Injection site pain	4 (3.8)	3 (3.0)	3 (2.9)
Bronchitis	1 (1.0)	3 (3.0)	0
Viral upper respiratory tract infection	0	3 (3.0)	0
Weight increased	1 (1.0)	3 (3.0)	2 (1.9)
Dizziness	5 (4.8)	2 (2.0)	2 (1.9)
Schizophrenia	16 (15.2)	5 (5.0)	3 (2.9)
Agitation	5 (4.8)	0	2 (1.9)
Psychotic	4 (3.8)	2 (2.0)	1 (1.0)
Oropharyngeal pain	2 (1.9)	3 (3.0)	1 (1.0)
Headache	9 (8.6)	10 (10.0)	8 (7.7)
Insomnia	11 (10.5)	6 (6.0)	12 (11.5)
Anxiety	5 (4.8)	4 (4.0)	6 (5.8)

[a] Study population with baseline PANSS Total scores > 92 who received at least one dose of study drug (AL 441 mg, AL 882 mg or PBO) ($N = 309$).

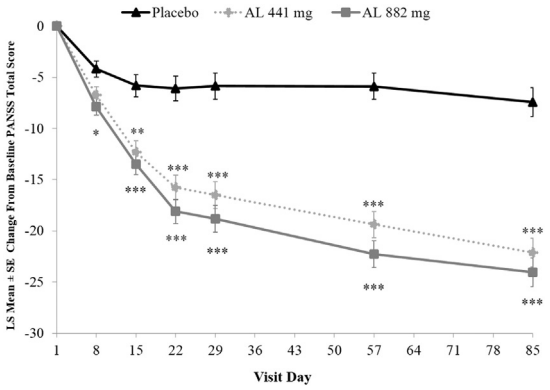

Fig. 1. Mean change from baseline in PANSS Total score. Change from baseline was analyzed at each post baseline visit using mixed-model repeated measures analyses, with covariates including baseline, treatment, and study region, in severely ill patients with at least one follow-up efficacy assessment ($N = 294$). *$p \le 0.01$, **$p \le 0.001$, ***$p \le 0.0001$. AL, aripiprazole lauroxil; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Consistent findings with both AL doses vs. placebo were demonstrated in the PANSS Positive, Negative, and General Psychopathology subscales (Fig. 2). Significant differences vs. placebo in mean change from baseline were observed at each assessment time point after Day 15 for all three subscales. For the PANSS Positive subscale, the placebo-adjusted differences at Day 85 were −4.38 for AL 441 mg and −5.34 for AL 882 mg (both $p < 0.001$). For the PANSS Negative subscale, the placebo-adjusted differences at Day 85 were −2.66 for AL 441 mg and −3.20 for AL 882 mg ($p = 0.0035$ and $p = 0.0004$, respectively). For the PANSS General Psychopathology subscale, the placebo-adjusted differences at Day 85 were −7.10 for AL 441 mg and −7.8 for AL 882 mg (both $p < 0.0001$).

The efficacy analysis with baseline at Day 22 shows that both active AL doses still separate from the placebo group for the remaining 9 weeks. The placebo–adjusted difference for PANSS Total scores were −5.7 (SE 2.8, $p = 0.045$, effect size = 0.303) for the AL 441 mg group and −5.9 (SE 2.74, $p = 0.03$, effect size = 0.313) for the AL 882 mg group.

The overall responder rates at Day 85 were significantly greater for both the AL 441 mg group (49% [$p < 0.001$]) and AL 882 mg group (61% [$p < 0.001$]) compared with placebo (18%) (Fig. 3).

The effect size estimates shown in Table 2 compare the effect sizes in the less symptomatic (PANSS ≤ 92) subgroup with those in the more symptomatic (PANSS > 92) subgroup. The effect size for both doses of AL was marginally greater for the more symptomatic subgroup compared with the less symptomatic subgroup. In addition, the effect size for the higher-dose arm was greater than that for the lower-dose arm for the more symptomatic subgroup (0.58 for AL 441 mg vs. 0.66 for AL 882 mg) but not for the less symptomatic subgroup (0.50 for AL 441 mg vs. 0.45 for AL 882 mg).

4. Discussion

The present post hoc analyses demonstrated robust efficacy of both doses of AL in severely ill patients (PANSS Total score > 92 at baseline). Statistically significant and clinically meaningful improvements were demonstrated for all efficacy parameters for both doses of AL in patients with severe psychotic symptoms.

These results were consistent with the early and durable improvements seen for all parameters in the total population (Meltzer et al., 2015). Although statistical testing between dose groups was not done due to the post hoc nature of this analysis, the AL 882 mg group experienced numerically greater improvements in PANSS total and subscale scores, as well as a greater proportion of categorical responders (61 vs. 49%) suggesting that the higher dose may offer additional benefit in some patients, particularly in those with more severe illness.

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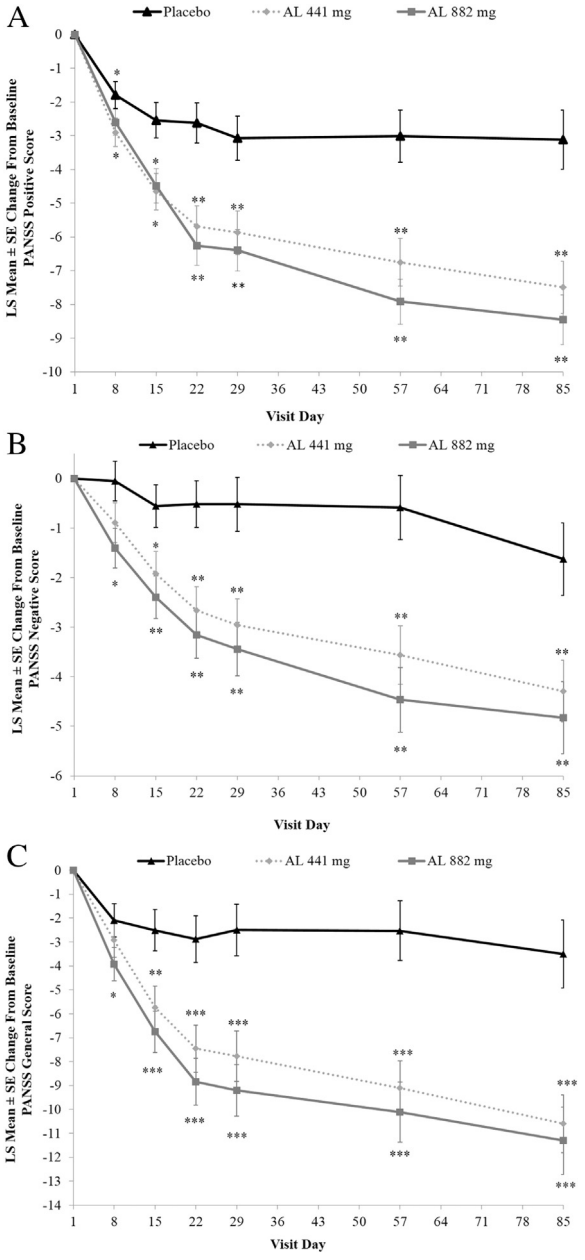

Fig. 2. Change from baseline in (A) PANSS Positive subscale score, (B) PANSS Negative subscale score, and (C) PANSS General Psychopathology subscale score. Change from baseline was analyzed at each study visit for all three subscales using mixed-model repeated measures analyses, with covariates including baseline, treatment, and study region, in severely ill patients with at least one follow-up efficacy assessment ($N = 294$). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. AL, aripiprazole lauroxil; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

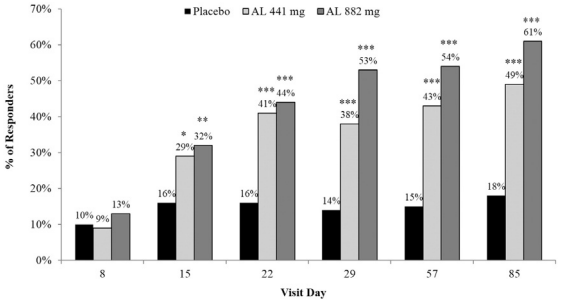

Fig. 3. Overall proportion of responders by visit. The proportion of responders (PANSS Total score ≥ 30% decrease [improvement of symptoms] from baseline or CGI-I score of 2 [much improved] or 1 [very much improved]) was analyzed using a logistic regression model with last observation carried forward for the severely ill patients ($N = 294$) at each postbaseline visit. The logistic regression model includes the study region and treatment group as factors and the baseline PANSS Total score as a covariate. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. AL, aripiprazole lauroxil; PANSS, Positive and Negative Syndrome Scale.

Consistent with the efficacy data, there were fewer adverse events of psychosis/schizophrenia in the high- dose group and more in the placebo group, compared with the low-dose group. There is frequently a trade-off between greater efficacy with higher dosing but more side effects. The dose/tolerability relationship did not seem pronounced, and was not always consistent. For example, insomnia was more frequent for the higher dose arm (11.5% for the 882 mg and 6% for the 441 mg groups, respectively), but the reverse was true for akathisia with a 15% observed adverse event rate for the 441 mg group compared with 11.5% for the 882 mg group.

There are many factors to be considered in determining the choice of antipsychotic and whether to start a long-acting formulation during an acute episode. Some believe that oral aripiprazole may not be effective in very symptomatic patients and thus question whether AL will be effective in these more symptomatic patients. Some have questioned whether drugs with partial agonism at the D2 dopamine receptor can have robust efficacy in severely ill patients. The present study suggests that AL has robust efficacy in more severely symptomatic patients, given the larger effect size in the PANSS >92 subgroup compared with the PANSS ≤92 subgroup. In other words, we found no evidence to support the common belief of AL's decreased efficacy among the subgroup of more symptomatic patients.

There are several limitations to this analysis. There may be ceiling effects on symptom severity, given that, at some point, patients become too symptomatic to enter a clinical trial, and therefore not amenable to this kind of study. Patients with known histories of treatment-resistant schizophrenia (e.g. prior clozapine treatment) were excluded, so this study cannot address the efficacy of aripiprazole for patients who are known to respond poorly to first-line (non-clozapine) antipsychotics. Other limitations in drawing inferences on relative efficacy across levels of symptom severity include the post hoc nature of this analysis, and the data-driven selection of a baseline PANSS score of 92 by median split as a cutoff for patients with more severe symptoms. The imbalance in terms of N numbers and disease severity, and the use of a categorical cut-off point for PANSS Total score (when symptom severity could arguably be considered a continuous variable) also pose limitations to the responder analysis. In addition, it is possible that regression to the mean could bias the effect size comparison in favor of the greater severity subgroup; however, since all groups (including placebo) had similar baseline PANSS severity scores, regression to the mean should similarly affect all groups.

The results with both AL doses are consistent with results from studies in which oral antipsychotics were used in patients experiencing severe symptoms during an acute episode. (Fleischhacker et al., 2014, Ishigooka et al., 2015; Gopal et al., 2011; Turner et al., 2004, Potkin et al., 2003).

In summary, this post hoc analysis demonstrated robust efficacy of both doses of AL in patients with severe psychotic symptoms. The numerically greater improvement seen with AL 882 mg suggests that the higher dose of AL may offer additional benefit for patients experiencing more severe symptoms. Both doses of AL were generally safe and well tolerated; the most commonly reported adverse effects were akathisia, headache, insomnia and anxiety.

Contributors

All authors participated in the design, execution, and analysis of this study as well as in preparation of the manuscript.

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Table 2
Change from baseline in PANSS Total score at Day 85.

	Not severely ill (PANSS ≤ 92)			Severely ill (PANSS > 92)[a]		
	Placebo ($n = 97$)	AL 441 mg ($n = 104$)	AL 882 mg ($n = 101$)	Placebo ($n = 99$)	AL 441 mg ($n = 95$)	AL 882 mg ($n = 100$)
LS mean (SE)	−12.28 (1.92)	−21.61 (1.84)	−20.70 (1.84)	−7.44 (2.76)	−22.14 (2.40)	−24.05 (2.27)
LS mean difference (SE)		−9.33 (2.64)	−8.42 (2.64)		−14.70 (3.49)	−16.61 (3.42)
P value[b]		0.0005	0.0017		<0.0001	<0.0001
Effect size[c]		0.495	0.450		0.576	0.659

Abbreviations: AL, aripiprazole lauroxil; PANSS, Positive and Negative Syndrome Scale; SE, standard error.
[a] Study population with baseline PANSS Total score > 92 who received at least one dose of study drug and at least one follow-up efficacy assessment.
[b] Vs. placebo-arm.
[c] Cohen's *d*, see text for details.

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Conflict of interest

Dr. Potkin has received funding, honoraria, or has been a paid consultant to Acadia, Allergan, Alkermes, Eisai, Eli Lilly, FORUM Pharmaceuticals, Lundbeck, Neurim, Novartis, Pfizer, Otsuka, Sunovion, Roche, Toyama Pharmaceuticals, and vTv Therapeutics. Dr Potkin has received grants from Allergan (Grant ID#11594) and Otsuka (GRTMEDSCZ22920).

Drs. Risinger, Du, Bose, Silverman, and Ehlrich are employees of Alkermes, Inc. Dr. Stankovic and Ms. Zummo are previous employees of Alkermes, Inc.

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Appendix 1. Disposition table for severely ill patients.

N (%)	Treatment group			
		Aripiprazole lauroxil		
	Placebo ($n = 99$)	441 mg ($n = 95$)	882 mg ($n = 100$)	Total ($N = 294$)
Completed treatment period	34 (34.3)	60 (63.2)	69 (69.0)	163 (55.4)
Adverse event	21 (21.2)	9 (9.5)	2 (2.0)	32 (10.9)
Death	1 (1.0)	0	0	1 (0.3%)
Lack of efficacy	25 (25.3)	4 (4.2)	10 (10.0)	39 (13.3)
Lost to follow-up	6 (6.1)	4 (4.2)	7 (7.0)	17 (5.8)
Noncompliance with study drug	1 (1.0)	0	0	1 (0.3)
Other	1 (1.0)	0	1 (1.0)	2 (0.7)
Physician decision	0	2 (2.1)	0	2 (0.7)
Protocol violation	1 (1.0)	2 (2.1)	2 (2.0)	5 (1.7)
Withdrawal by patient	9 (9.1)	14 (14.7)	9 (9.0)	32 (10.9)

Appendix 2. Demographic and baseline characteristics for severely ill patients.

			Aripiprazole lauroxil		
		Placebo ($n = 99$)	441 mg ($n = 95$)	882 mg ($n = 100$)	Total ($N = 294$)
Gender	Female	31 (31.3%)	30 (31.6%)	30 (30.0%)	91 (31.0%)
	Male	68 (68.7%)	65 (68.4%)	70 (70.0%)	203 (69.0%)
Region	Asia	6 (6.1%)	3 (3.2%)	7 (7.0%)	16 (5.4%)
	Europe	41 (41.4%)	45 (47.4%)	49 (49.0%)	135 (45.9%)
	North America	52 (52.5%)	47 (49.5%)	44 (44.0%)	143 (48.6%)
Country	Bulgaria	9 (9.1%)	13 (13.7%)	11 (11.0%)	33 (11.2%)
	Malaysia	3 (3.0%)	1 (1.1%)	3 (3.0%)	7 (2.4%)
	Philippines	3 (3.0%)	2 (2.1%)	4 (4.0%)	9 (3.1%)
	Romania	3 (3.0%)	2 (2.1%)	5 (5.0%)	10 (3.4%)
	Russia	11 (11.1%)	12 (12.6%)	16 (16.0%)	39 (13.3%)
	Ukraine	18 (18.2%)	18 (18.9%)	17 (17.0%)	53 (18.0%)
	United States	52 (52.5%)	47 (49.5%)	44 (44.0%)	143 (48.6%)
Race	Asia	8 (8.1%)	3 (3.2%)	7 (7.0%)	18 (6.1%)
	Black or African American	46 (46.5%)	35 (36.8%)	35 (35.0%)	116 (39.5%)
	White	45 (45.4%)	57 (60.0%)	58 (58.0%)	160 (54.4%)
Ethnicity	Hispanic or Latino	3 (3.0%)	5 (5.3%)	2 (2.0%)	10 (3.4%)
	Not Hispanic or Latino	96 (97.0%)	90 (94.7%)	98 (98.0%)	284 (96.6%)
BMI	Normal	35 (35.4%)	36 (37.9%)	37 (37.0%)	108 (36.7%)
	Obese	33 (33.3%)	33 (34.7%)	26 (26.0%)	92 (31.3%)
	Overweight	31 (31.3%)	26 (27.4%)	37 (37.0%)	94 (32.0%)
PANNS total	Mean (SD)	102.7 (7.9)	101.3 (6.0)	101.0 (6.4)	101.7 (6.8)
Age	Mean (SD)	39.9 (12.1)	40.4 (9.9)	38.8 (10.8)	39.7 (11.0)
Weight (kg)	Mean (SD)	81.3 (19.0)	80.3 (17.2)	79.0 (17.3)	80.2 (17.8)
Height (cm)	Mean (SD)	171.5 (9.5)	171.2 (9.9)	171.1 (9.3)	171.2 (9.5)
BMI	Mean (SD)	27.5 (5.3)	27.4 (5.3)	26.94 (5.1)	27.3 (5.2)

Demographic and baseline characteristics were described for patients determined to be severely ill (Positive and Negative Syndrome Scale [PANSS] Total score > 92 at baseline) and who completed one or more primary efficacy assessment (PANSS Total score) after receiving study drug ($N = 294$).
Abbreviations: BMI, body mass index; SD, standard deviation.

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