Safety and Efficacy of Aripiprazole Lauroxil in an Outpatient Setting After Initiation During Hospitalization for an Acute Exacerbation of Schizophrenia

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BACKGROUND

- Inpatient treatment typically focuses on stabilization of acute symptoms, but effective care must also ensure continuity of symptom control after discharge[1]
- Patients discharged after an acute schizophrenia exacerbation enter a high-risk period marked by medication nonadherence, suicide risk, and frequent relapse and rehospitalization[2-6]
- Long-acting injectable (LAI) antipsychotics offer an opportunity to bridge the transition from inpatient care to the establishment of effective outpatient care; however, they have been underutilized during acute care[7]
- Aripiprazole lauroxil (AL) is an LAI that can be initiated during hospitalization,[8] providing relevant plasma concentrations that extend postdischarge and help to bridge inpatient stabilization and outpatient maintenance[9]
- The ALPINE study (ClinicalTrials.gov identifier NCT03345979) was a 25-week, phase 3b, double-blind, randomized trial assessing the efficacy and safety of AL every-2-months initiated with the 1-day regimen during a 2-week inpatient period and in the 23 weeks after discharge[10]
  - At the week 4 primary endpoint, AL treatment was associated with a statistically significant reduction in Positive and Negative Syndrome Scale (PANSS) Total score[10]
  - The study included an active LAI control with known efficacy for treating symptoms of schizophrenia (paliperidone palmitate [PP])

OBJECTIVE

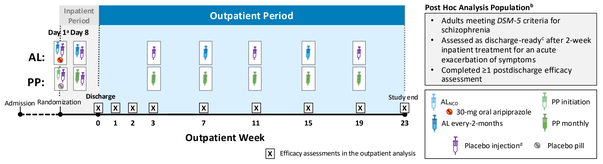
- The objective of this post hoc analysis was to examine 23-week outpatient efficacy, safety, and tolerability of AL, including the discharge-to-next-dose transition period, following inpatient initiation

METHODS

Study Design

- Details of the ALPINE study design have been published previously[10]
- AL and PP initiation and results from the 2-week inpatient period are presented in a companion poster [Poster #1]

Figure 1. ALPINE Study Design, Treatment, and Outpatient Assessments



[a]AL was initiated on study day 1 using a 1-day regimen (AL_{ACD} and a single 30-mg oral dose of aripiprazole) followed by administration of AL every-2-months on day 8. Patients assigned to PP received PP 234 mg on study day 1 and PP 156 mg monthly starting on study day 8. [b]Post hoc criteria were chosen consistent with a patient successfully converted to an LAI and attending the first postdischarge appointment using no oral antipsychotic supplementation, with relevant plasma concentrations from the LAI onboarding. [c]Patients were assessed as ready for discharge based on the Readiness for Discharge Questionnaire, evaluated daily from day 4 to discharge. [d]Because AL and PP use different injection sites, day 1 and day 8 injections were given with a placebo injection in the opposite site to maintain blinding. Because the 1-day AL initiation regimen includes a 30-mg oral dose of aripiprazole, patients assigned to PP were administered an oral placebo tablet.
AL, aripiprazole lauroxil; AL_{ACD}, aripiprazole lauroxil NanoCrystal Dispersion formulation; *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; LAI, long-acting injectable; PP, paliperidone palmitate.

Assessments

- Efficacy was assessed based on the PANSS Total score and PANSS Marder Factor scores[11]
- Safety was assessed based on adverse events (AEs)

Post Hoc Analysis

- Data from the day of discharge, weeks 1, 2, and 3, and monthly visits thereafter were included in this post hoc analysis
- PANSS and CGI-S data were analyzed using a mixed model for repeated measures approach
- Given the post hoc nature of the analysis, no statistical testing was conducted

Patients

Table 1. Demographics at ALPINE Study Baseline: Outpatient Analysis Population[a]

Characteristic	Aripiprazole Lauroxil (n=84)	Paliperidone Palmitate (n=93)
Age, mean (SD), years	43.6 (9.8)	43.2 (10.6)
Sex, male, n (%)	64 (76.2)	71 (76.3)
Race,[b] n (%)		
Black or African American	61 (72.6)	73 (78.5)
White	21 (25.0)	14 (15.1)
Asian	2 (2.4)	4 (4.3)

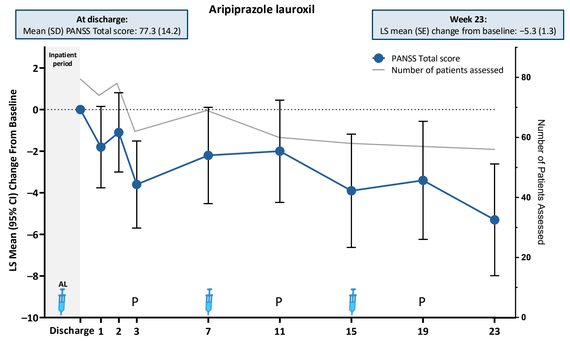
[a]A total of 200 patients were randomized in ALPINE (aripiprazole lauroxil, n=99; paliperidone palmitate, n=101); the outpatient analysis population included patients who were discharged from the inpatient period and completed ≥1 postdischarge efficacy assessment. [b]Two patients in the paliperidone palmitate group reported >1 race and were reported as "multiple races."

RESULTS

AL treatment initiated during acute hospitalization was assessed through the transition to outpatient care

Outpatient Durability of Response

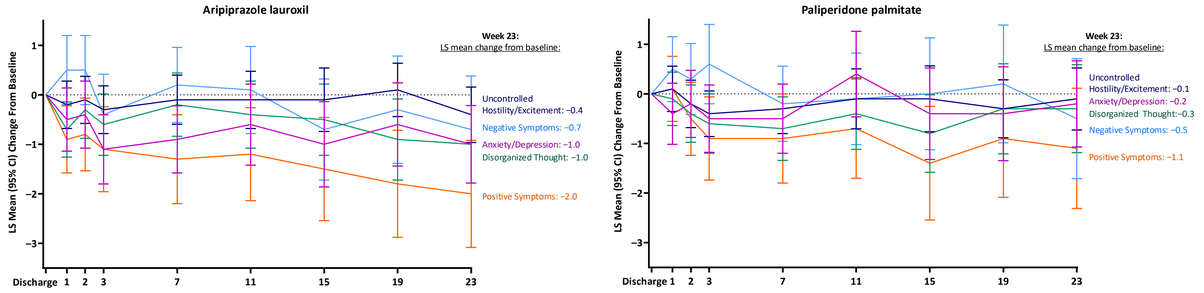
Figure 2. Changes From Discharge in PANSS Total Score to During Outpatient Treatment



AL, aripiprazole lauroxil; LS, least squares; P, placebo injection; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

- **AL treatment was associated with a durable response in the outpatient period**

Figure 3. Changes from Discharge in Marder Factor Scores During Outpatient Treatment[a]



[a]Marder factors include positive symptom items: delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness (P6), stereotyped thinking (N7), somatic concern (G1), unusual thought content (G9), and lack of judgment and insight (G12); negative symptom items: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16); disorganized thought items: conceptual disorganization (P2), difficulty in abstract thinking (N5), mannerisms and posturing (G5), poor attention (G11), disturbance of volition (G13), preoccupation (G15), and disorientation (G10); uncontrolled hostility/excitement items: excitement (P4), hostility (P7), uncooperativeness (G8), and poor impulse control (G14); and anxiety/depression items: anxiety (G2), guilt (G3), tension (G4), and depression (G6).[11]
LS, least squares.

Outpatient Safety

- Serious AEs were reported for 6 AL-treated patients and 7 PP-treated patients (worsening schizophrenia [AL, n=4; PP, n=2], psychotic disorder [AL, n=2], suicide attempt [AL, n=1; PP, n=1], suicidal ideation, hypercalcemia, leukocytosis, and renal failure [AL, n=1 each], and depression, dystonia, psychotic symptom, overdose, alcohol poisoning, bone deformity, and road traffic accident [PP, n=1 each])

Table 2. Summary of AEs Reported During the Outpatient Period

Patients, n (%)	Aripiprazole Lauroxil (n=84)	Paliperidone Palmitate (n=93)
Patients with any AE	42 (50.0)	44 (47.3)
AEs reported by ≥3% of patients in either treatment group		
Weight increased	9 (10.7)	14 (15.1)
Worsening schizophrenia	4 (4.8)	2 (2.2)
Headache	3 (3.6)	2 (2.2)
Blood pressure increased	3 (3.6)	1 (1.1)
Injection site pain	3 (3.6)	0
Blood creatine phosphokinase increased	1 (1.2)	3 (3.2)
Erectile dysfunction	0	3 (3.2)
AEs leading to study discontinuation[a]	6 (7.1)	5 (5.4)
SAEs leading to death	0	1 (1.1)[b]

[a]AEs leading to study discontinuation worsening schizophrenia (AL, n=4; PP, n=1), psychotic disorder (AL, n=2), suicide attempt (AL, n=1; PP, n=1), suicidal ideation (AL, n=1), akathisia (PP, n=1), dystonia (PP, n=1), overdose (PP, n=1), and road traffic accident (PP, n=1). [b]One patient assigned to paliperidone palmitate died as a result of a road traffic accident.
AE, adverse event; AL, aripiprazole lauroxil; PP, paliperidone palmitate; SAE, serious adverse event.

- Movement-related disorders were reported in few patients during the inpatient period based on Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS) criteria (BARS global score ≥2; SAS total score >3)

Figure 4. Proportions of Patients With BARS Global Score ≥2 (A) and SAS Total Score >3 (B)

BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale.

LIMITATIONS

- This post hoc analysis excluded patients who discontinued treatment during the inpatient period; therefore, the results may not generalize to all patients started on treatment with AL 1064 mg every-2-months
- The study was not designed for between-group comparisons; the primary study objective was to assess the AL formulations, which were investigational at the time of the study, using PP as an active control
- These outpatient findings were specific to AL and PP and may not generalize to treatment with other LAI antipsychotics

CONCLUSIONS

- These post hoc analysis findings support the use of AL or PP through the transition from acute inpatient treatment of schizophrenia to outpatient maintenance care
  - Schizophrenia symptom severity remained stable from discharge through 23 weeks of outpatient AL or PP treatment based on PANSS Total scores
  - Safety and tolerability of outpatient AL and PP treatment were consistent with their known profiles, with no new safety signals among patients discharged from the hospital fully initiated on AL or PP
- Having LAI antipsychotic onboarded at discharge ensures relevant drug levels during this high-risk transition period, providing support for a durable treatment response

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Supported by funding from Alkermes, Inc.

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DISCLOSURES

PJW is a former employee of Alkermes, Inc., and has been a consultant for Alkermes, Lyndra, MapLight, and Teva.
JK is the founder of Altea Research Institute and a cofounder of Excell Research and is a consultant and/or serves on advisory boards for AstraZeneca, Bristol-Myers Squibb, Janssen, Novartis, Otsuka, Pfizer, and Sunovion.
SL, DJK, and **JAM** are or were employees of Alkermes, Inc., and may own stock/options in the company.

ACKNOWLEDGMENTS

This study was sponsored by Alkermes, Inc., Waltham, MA, USA. Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc

Key Contributors
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the poster; gave final approval of the version to be presented; and agree to be accountable for all aspects of the work.