Inpatient Initiation of the Long-Acting Injectable Antipsychotic Aripiprazole Lauroxil for the Treatment of Acute Exacerbations of Schizophrenia

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BACKGROUND

- Long-acting injectable (LAI) antipsychotic formulations are used for maintenance treatment of patients with schizophrenia but are considered less frequently for managing acute symptom exacerbations[1]
- Early LAI antipsychotic formulations were limited, requiring a prolonged period of daily oral antipsychotic supplementation to quickly achieve therapeutic plasma concentrations after initiation[2,3]
- Advances in formulation technology now allow rapid attainment of target plasma levels within days, reducing or eliminating the need for oral supplementation at initiation[2]
  - The LAI antipsychotic aripiprazole lauroxil (AL) has a 1-day initiation option that allows full onboarding of the LAI within a short hospital stay[4]
- Despite these advances, many clinicians rely solely on oral antipsychotic therapy in the inpatient setting[5,6]
- 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[7]
  - AL treatment was associated with statistically significant reductions in Positive and Negative Syndrome Scale (PANSS) Total score at the 4- and 25-week endpoints
  - The study included an active LAI control with known efficacy for treating symptoms of schizophrenia (paliperidone palmitate [PP])

OBJECTIVE

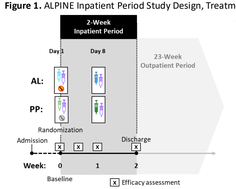
- The objective of this post hoc analysis was to evaluate the initial response to AL, initiated using the 1-day regimen, during a 2-week inpatient hospitalization for the treatment of acute schizophrenia

METHODS

Study Design

- Details of the ALPINE study design have been published previously[7]
  - This post hoc analysis focuses on the 2-week inpatient period; the outpatient period is assessed in a companion poster [Poster #2]
- Patients randomly assigned to AL received the 1-day initiation regimen on day 1, followed by their first dose of AL 1064 mg every-2-months on day 8 (**Figure 1**)
  - Initiation regimen: 1 injection of AL NanoCrystal Dispersion formulation (AL_{NCD}) and a single 30-mg oral dose of aripiprazole
  - No oral supplementation was given after day 1
- The active control was paliperidone palmitate (PP)

Figure 1. ALPINE Inpatient Period Study Design, Treatment, and Patient Population



Study Treatments

LAI	Day 1 (Initiation)	Day 8[a]	
		Dosage	Coverage Duration
AL	AL_{NCD} 1 30-mg dose OA	AL 1064 mg	2 months
PP	PP 234 mg	PP 156 mg	1 month

Placebo injection[b]

Placebo pill[b]

Study Population:

- Adults meeting *DSM-5* criteria for schizophrenia
- Hospitalized for acute symptoms (onset ≤2 months)
- PANSS Total score of 80–120

[a]The first AL injection can be administered on the same day as AL_{NCD} or ≤10 days afterward. The first PP 156-mg injection must be administered 8 days after the PP 234-mg injection; therefore, AL was administered on day 8 in ALPINE. [b]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. [c]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_{NCD}, AL NanoCrystal Dispersion formulation; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; OA, oral aripiprazole; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

Assessments

- Efficacy was assessed based on the PANSS Total score and PANSS Marder Factors[8]; early response was defined as ≥20% reduction in PANSS Total score from baseline to discharge
- Safety was assessed based on adverse events (AEs)

Post Hoc Analysis

- Data from the baseline (day 1, predose) and day 4, 8, and 15 assessments were included in the post hoc analysis
- Efficacy outcomes were analyzed using a mixed model for repeated measures approach

Patients

Table 1. Demographics and Baseline Clinical Characteristics[a]

Characteristic	Aripiprazole Lauroxil (n=99)	Paliperidone Palmitate (n=101)
Age, mean (SD), years	43.5 (9.7)	43.4 (10.8)
Sex, male, n (%)	73 (73.7)	76 (75.2)
Race,[b] n (%)		
Black or African American	72 (72.7)	78 (77.2)
White	25 (25.3)	17 (16.8)
Asian	2 (2.0)	4 (4.0)
BMI, mean (SD), kg/m^2	28.2 (5.5)	27.9 (5.1)

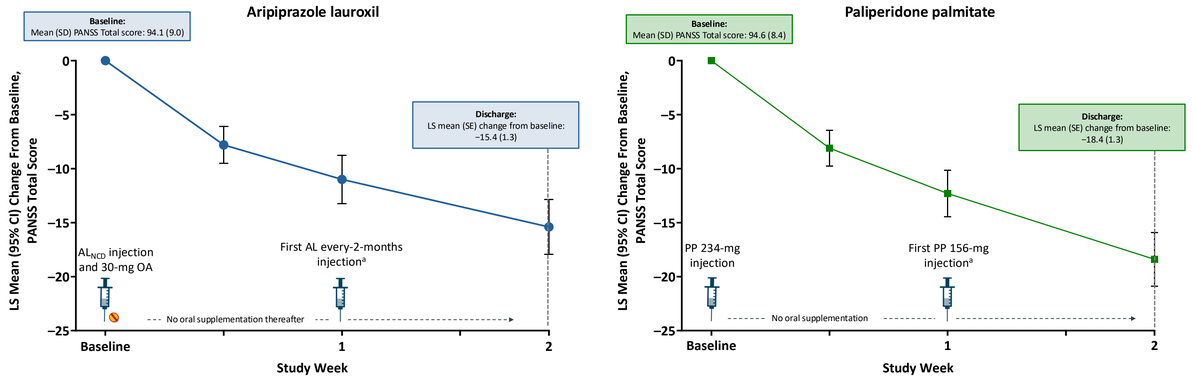
[a]Safety population (patients who received ≥1 dose of study drug). [b]Two patients in the paliperidone palmitate group reported >1 race and were reported as "multiple races."
BMI, body mass index.

RESULTS

AL treatment of acute schizophrenia was initiated using a 1-day regimen during a 2-week inpatient period

2-Week Efficacy

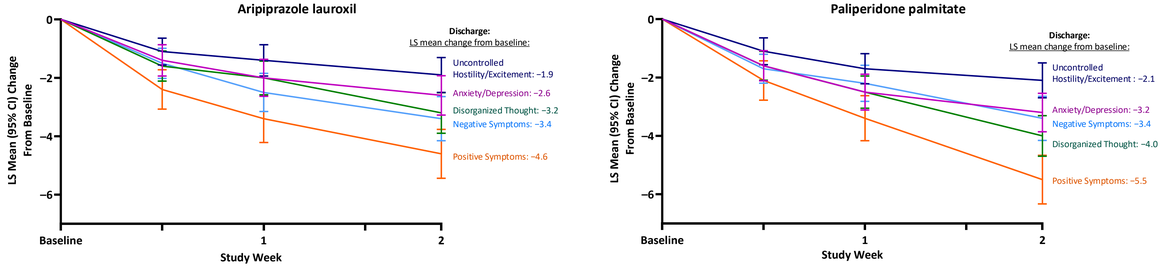
Figure 2. LS Mean Changes From Baseline in PANSS Total Score During the 2-Week Inpatient Period



[a]The first AL injection can be administered on the same day as AL_{NCD}, or up to 10 days afterward. The first PP 156-mg injection must be administered 8 days after the PP 234-mg injection; therefore, AL was administered on day 8 in ALPINE.
AL aripiprazole lauroxil; AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion formulation; LS, least squares; OA, oral aripiprazole; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

- **No statistically significant differences in PANSS Total scores were observed between AL and PP at any assessment**
- **By discharge, 55.2% (53/96) of AL-treated patients had met the early treatment response criterion of ≥20% improvement from baseline in PANSS Total score during the inpatient period (PP, 60.6% [60/99])**

Figure 3. LS Mean Changes From Baseline in Marder Factor[a] Scores During the 2-Week Inpatient Period



[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).[8]
AL, aripiprazole lauroxil; LS, least squares; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

2-Week Safety

- Most AEs reported in the first 2 weeks of treatment were mild (AL, 43.4%; PP, 29.7%) or moderate (AL, 8.1%; PP, 22.8%) in severity
- Serious AEs were reported for 2 AL-treated patients (generalized tonic-clonic seizure, worsening schizophrenia) and 0 PP-treated patients

Table 2. AEs Reported During the 2-Week Inpatient Period

Patients, n (%)	Aripiprazole Lauroxil (n=99)	Paliperidone Palmitate (n=101)
Patients with any AE	**53 (53.5)**	**53 (52.5)**
AEs reported by ≥3% of patients in either treatment group		
Injection site pain	15 (15.2)	25 (24.8)
Akathisia	9 (9.1)	10 (9.9)
Headache	5 (5.1)	6 (5.9)
Somnolence	4 (4.0)	7 (6.9)
Dystonia[a]	4 (4.0)	6 (5.9)
Constipation	3 (3.0)	3 (3.0)
Dizziness	3 (3.0)	3 (3.0)
Agitation	3 (3.0)	1 (1.0)
Myalgia	3 (3.0)	1 (1.0)
Injection site induration	3 (3.0)	0
Increased appetite	2 (2.0)	3 (3.0)
Weight increased	1 (1.0)	6 (5.9)
Arthralgia	1 (1.0)	3 (3.0)
AEs leading to study discontinuation[b]	4 (4.0)[c]	6 (5.9)

[a]Includes Medical Dictionary for Regulatory Activities version 21.1 preferred terms of dystonia and oromandibular dystonia. [b]AEs leading to study discontinuation included injection site pain (n=2) and generalized tonic-clonic seizure and worsening schizophrenia (n=1 each) for aripiprazole lauroxil and injection site pain, abdominal pain upper, akathisia, blood prolactin increased, dizziness, galactorrhea, and oromandibular dystonia (n=1 each) for paliperidone palmitate. [c]One patient assigned to aripiprazole lauroxil discontinued due to injection site pain associated with a placebo injection.
AE, adverse event.

LIMITATIONS

- This post hoc analysis was limited to the inpatient period to specifically address early response; however, efficacy and safety results for the 23-week outpatient period of ALPINE are reported in a companion poster [Poster #2]
- 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 inpatient findings were specific to AL and PP and may not generalize to treatment with other LAI antipsychotics

CONCLUSIONS

- To our knowledge, this is the first clinical study to evaluate the safety and efficacy of using the 2 LAIs that could be initiated without required prolonged oral coverage and therefore were suited for inpatient initiation in patients entering the hospital already exposed to the respective oral formulation
- Early response to AL or PP over 2 weeks was robust based on improvement in PANSS Total score and on symptom domains of clinical interest
- Safety and tolerability following 1-day initiation were consistent with the known profile of oral aripiprazole (with the addition of injection site pain) and with that of AL initiated using 3 weeks of oral aripiprazole supplementation
  - The 2-week safety of PP was also consistent with its known profile
- These post hoc analysis findings support the existing evidence for inpatient initiation of LAI treatment for acute exacerbations of schizophrenia that require hospitalization

REFERENCES

1. Citrome L. *CNS Spectr*. 2021;26:118-29. DOI: 10.1017/S1092852921000730. 2. Jain R, et al. *CNS Spectr*. 2020;25(3):323-30. DOI: 10.1017/S1092852919000816. 3. Krishna A, et al. *J Am Board Fam Med*. 2024;37(4):773-83. DOI: 10.3122/jabfm.2022.220425r1. 4. Sommi RW, et al. *J Clin Psychiatry*. 2024;85:23m15132. DOI: 10.4088/JCP.23m15132. 5. Velligan D, et al. *BMC Psychiatry*. 2025;25(1):232. DOI: 10.1186/s12888-025-06566-1. 6. Olayinka O, et al. *Psychiatry J*. 2019;2019:8629030. DOI: 10.1155/2019/8629030. 7. Weiden PJ, et al. *J Clin Psychiatry*. 2020;81:19m13207. DOI: 10.4088/JCP.19m13207. 8. Marder SR, et al. *J Clin Psychiatry*. 1997;58(12):538-46. DOI: 10.4088/jcp.v58n1205.

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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.

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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.

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