Aripiprazole Lauroxil 2-Month Formulation for Acute Schizophrenia: A Post Hoc Analysis of PANSS Factor Scores in the ALPINE Study

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INTRODUCTION

- Aripiprazole lauroxil (AL), a prodrug of aripiprazole, is a US Food and Drug Administration–approved atypical long-acting injectable (LAI) antipsychotic for the treatment of schizophrenia in adults[1]
- The randomized, active-controlled, phase 3b ALPINE (Aripiprazole Lauroxil and Paliperidone palmitate: INItiation Effectiveness; NCT03345979) study evaluated the efficacy and safety of a 2-month formulation of AL in patients hospitalized for an acute exacerbation of schizophrenia[2]
  - AL was initiated using 1 intramuscular injection of the NanoCrystal Dispersion formulation of AL (AL_{NCD}) plus one 30 mg dose of oral aripiprazole on day 1, followed by AL 1064 mg 1 week later
  - Paliperidone palmitate (PP) was included as an active control[1]
  - ALPINE was not designed as or powered for a direct comparison between AL and PP
- In the AL group, mean baseline Positive and Negative Syndrome Scale (PANSS) total score (94.1) significantly improved with treatment, with a mean change of −17.4 points at week 4 (P<0.001)
  - Improvement continued in observed cases through week 9 (mean change, −19.8 points) and week 25 (mean change, −23.3 points) (P<0.001 at each time point)[2]
  - Likewise, PANSS Positive, Negative, and General Psychopathology subscale scores also improved throughout the study[4]
- In the PP group, mean baseline PANSS total score (94.6) significantly improved with treatment, with a mean change at week 4 of −20.1 points (P<0.001)
  - Improvement continued in observed cases through week 9 (mean change, −22.5 points) and week 25 (mean change, −21.7 points) (P<0.001 at each time point)
  - Likewise, PANSS Positive, Negative, and General Psychopathology subscale scores also improved throughout the study
- Although the 30-item PANSS,[5] with its 3 subscales (Positive, Negative, and General Psychopathology), is often used in clinical trials to assess antipsychotic efficacy, the PANSS can be deconstructed into 5 factors that are relatively independent of each other[6]
  - These factors (dimensions, domains) include positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression (see QR code for PANSS Item mapping to the 5 factors)[7]

OBJECTIVE

- To assess the efficacy of AL and PP separately based on PANSS factor scores from patients enrolled in the ALPINE study

METHODS

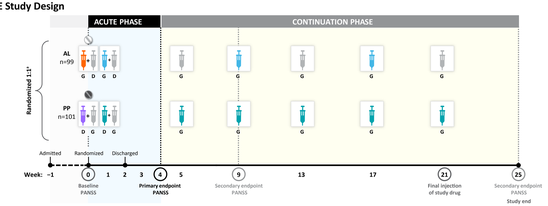
Study Population

- The ALPINE study enrolled adults aged 18–65 years who met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), criteria for schizophrenia and were experiencing an acute exacerbation or relapse of symptoms requiring hospitalization, with onset of acute symptoms <2 months prior to screening[2,8]
- Additional enrollment criteria were reported in the primary ALPINE publication[2]

Study Design

- Patients were enrolled and randomized as inpatients during an acute exacerbation of schizophrenia, discharged after 2 weeks if clinically stable, and followed as outpatients for the remainder of the 25 weeks[2]
- All patients received injections (active drug and/or placebo) at day 1, day 8, and then monthly, as shown in the figure below

ALPINE Study Design



[a]Because AL initiation required gluteal injection and PP initiation required deltoid injection, placebo injections were administered in patients' deltoid and gluteal muscles, respectively, during initiation to maintain blinding. The AL group also received placebo injections at weeks 5, 13, and 21 to match the PP dosing schedule, and the PP group received an oral placebo tablet on day 1 to match the oral dose of aripiprazole in the AL initiation regimen.
AL, aripiprazole lauroxil; AL_{NCD}, NanoCrystal Dispersion formulation of AL; D, deltoid; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INItiation Effectiveness; G, gluteal; IM, intramuscular; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

Assessments

- Baseline and week 4, 9, and 25 PANSS assessments were included in the analysis
- Respective PANSS items mapping to the 5 factor dimensions as published by Marder et al (see QR code) are rated from 1 (absent) to 7 (extreme)[7]

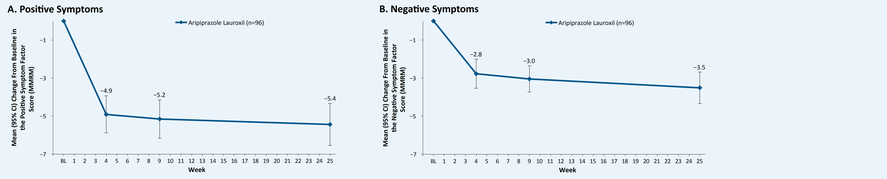
Statistical Analysis

- Changes from baseline in each PANSS factor were analyzed for AL and PP through week 25 using a mixed model with repeated measures (MMRM)

RESULTS

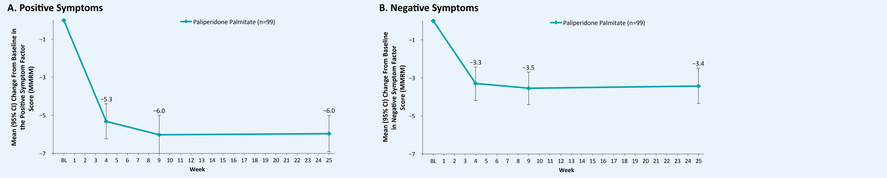
Improvement from baseline in PANSS 5 factor scores was consistent with previously reported change in PANSS total and subscale scores

Aripiprazole Lauroxil



BL, baseline; CI, confidence interval; MMRM, mixed model with repeated measures; PANSS, Positive and Negative Syndrome Scale.

Paliperidone Palmitate



BL, baseline; CI, confidence interval; MMRM, mixed model with repeated measures; PANSS, Positive and Negative Syndrome Scale.

Baseline Demographics and Clinical Characteristics (Safety Population)[2,a]

Characteristics	AL (n=99)	PP (n=101)
Age, mean (SD), years	43.5 (9.7)	43.4 (10.8)
Sex, male, n (%)	73 (73.7)	76 (75.2)
Race, n (%)		
Black	72 (72.7)	78 (77.2)
White	25 (25.3)	17 (16.8)
Asian	2 (2.0)	4 (4.0)
Multiple races[b]	0	2 (2.0)
Ethnicity		
Hispanic or Latino	8 (8.1)	11 (10.9)
Weight, mean (SD), kg	84.8 (19.8)	85.0 (18.8)
BMI, mean (SD), kg/m^2	28.2 (5.5)	27.9 (5.1)
Prior antipsychotic exposure, n (%)		
Aripiprazole	5 (5.1)	7 (6.9)
Risperidone[c]	31 (31.3)	31 (30.7)
Both aripiprazole and risperidone[c]	51 (51.5)	49 (48.5)
Neither aripiprazole nor risperidone[c]	12 (12.1)	14 (13.9)
PANSS total score, mean (SD)[d]	94.1 (9.0)	94.6 (8.4)

[a]Safety population (patients who received ≥1 dose of study drug). AL: 96 patients had ≥1 postbaseline PANSS assessment and were included in the PANSS factor analysis (93 completed the treatment period). [b]A patient who reported ≥1 race is counted once under this category. [c]"Risperidone" includes risperidone or paliperidone (oral or long-acting injectable). [d]Based on patients with ≥1 postbaseline PANSS assessment (aripiprazole lauroxil, n=96; paliperidone palmitate, n=99). Baseline was defined as the last nonmissing assessment before the first dose of study drug on day 1.
AL, aripiprazole lauroxil; BMI, body mass index; PANSS, Positive and Negative Syndrome Scale total score; PP, paliperidone palmitate; SD, standard deviation.

LIMITATIONS

- This was a post hoc analysis; analysis of PANSS factors was not specified in the study protocol
- The ALPINE study was not powered for a direct comparison between AL and PP; PP in the blinded control group provided an active control with known efficacy
- A placebo group was not included, thus limiting interpretation of the findings of this analysis
- Results from the ALPINE study may not be generalizable to the real-world population of patients who are started on an LAI antipsychotic during hospitalization for an acute exacerbation of schizophrenia

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CONCLUSIONS

- In this post hoc analysis from the ALPINE study, patients with schizophrenia who initiated AL or PP in the hospital and continued treatment during outpatient care experienced improvement in schizophrenia symptoms, as measured by PANSS factor scores, consistent with previously reported changes in PANSS total and subscale scores
- Improvement from baseline was observed across all PANSS factors among patients in AL and PP treatment groups

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PANSS Item Mapping to the Five Factors as Described by Marder et al[5,7]

Original PANSS Item Number	Item Name
Positive symptoms (8 items)	
P1	Delusion
P3	Hallucinatory behavior
P5	Grandiosity
P6	Suspiciousness/persecution
N7	Stereotyped thinking
G1	Somatic concern
G9	Unusual thought content
G12	Lack of insight
Negative symptoms (7 items)	
N1	Blunted affect
N2	Emotional withdrawal
N3	Poor rapport
N4	Passive social withdrawal
N6	Lack of spontaneity and flow of conversation
G7	Motor retardation
G16	Active social avoidance
Disorganized thought (7 items)	
P2	Conceptual disorganization
N5	Difficulty with abstract thinking
G5	Mannerisms and posturing
G10	Disorientation
G11	Poor attention
G13	Disturbance of volition
G15	Preoccupation
Uncontrolled hostility/excitement (4 items)	
P4	Excitement
P7	Hostility
G8	Uncooperativeness
G14	Poor impulse control
Anxiety/depression (4 items)	
G2	Anxiety
G3	Guilt feelings
G4	Tension
G6	Depression

P, Positive subscale; PANSS, Positive and Negative Syndrome Scale; N, Negative subscale; G, General Psychopathology subscale.

AUTHOR DISCLOSURES

LC has served as consultant to AbbVie/Allergan, Acadia, Adamas, Alkermes (including during conduct of this study), Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, Impel, INmune Bio, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, MedAvante-ProPhase, Marvin, Merck, Mitsubishi-Tanabe Pharma, Neurelis, Neurocrine, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, University of Arizona, Vanda, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; received speaker fees from AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies; received fees/royalties/publishing income for work with Elsevier (Topic Editor, Psychiatry, *Clinical Therapeutics*), Springer Healthcare (book), Taylor & Francis (Editor-in-Chief, *Current Medical Research and Opinion*, 2022-date), *UpToDate* (reviewer), and Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019); owns a small number of shares of common stock (purchased >10 years ago) in Bristol Myers Squibb, Eli Lilly, J&J, Merck, and Pfizer; and has stock options with Reviva.

JAM and **MD** are employees of Alkermes, Inc., and may own stock/options in the company.

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