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SHORT REPORT

# Aripiprazole Lauroxil Every 2 Months or Paliperidone Palmitate Monthly for Acute Schizophrenia: A Post Hoc Analysis of PANSS Five-Factor Scores in the ALPINE Trial

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**Purpose:** The randomized, controlled Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness (ALPINE) study (NCT03345979) evaluated the efficacy and safety of aripiprazole lauroxil (AL) administered every-2-months in patients with schizophrenia. Primary results indicating significant improvement in Positive and Negative Syndrome Scale (PANSS) total scores with AL or active control (paliperidone palmitate [PP] monthly) were reported previously. In this post hoc analysis, treatment effects based on a PANSS five-factor model were assessed.

**Patients and Methods:** Adult patients with an acute exacerbation of schizophrenia were enrolled as inpatients, randomized to AL (1064 mg every 2 months) or PP (156 mg monthly), discharged after 2 weeks, and then followed as outpatients through week 25. PANSS five-factor scores at baseline and weeks 4, 9, and 25 were analyzed in this post hoc analysis. Within-group changes from baseline were summarized by treatment group using the last-observation-carried-forward method for imputation; no formal testing of statistical significance was performed.

**Results:** Of 200 patients randomized to AL (n=99) or PP (n=101), 99 patients (AL, n=56; PP, n=43) completed study treatment. Improvement in PANSS factor scores was observed with AL from baseline to week 25. Mean (standard error [SE]) changes at week 25 were −3.5 (0.42) (negative); −5.4 (0.56) (positive); −3.4 (0.39) (disorganized thought); −1.9 (0.32) (uncontrolled hostility/excitement); and −3.1 (0.37) (anxiety/depression). For PP, week 25 PANSS factor improvements (mean [SE]) for the negative, positive, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression factors were −3.4 (0.48), −6.0 (0.49), −4.0 (0.35), −2.2 (0.30), and −3.5 (0.41), respectively.

**Conclusion:** In this post hoc analysis of patients with acutely exacerbated schizophrenia treated with AL 1064 mg every-2-months or PP 156 mg monthly, numerical improvements in PANSS five-factor scores were observed over time. These results support the primary efficacy findings based on PANSS total score and suggest that efficacy extends to these clinically important symptom domains.

**Keywords:** antipsychotic agents, treatment efficacy, symptom assessment

## Introduction

Long-acting injectable (LAI) antipsychotic medications provide continuous antipsychotic exposure for maintenance treatment but also are effective as a first-line option for acute symptoms of schizophrenia.[1] In a phase 3b, randomized, placebo-controlled study assessing the LAI aripiprazole lauroxil (AL [Aristada, Alkermes, Inc, Waltham, MA, USA]) 441 mg and 882 mg monthly regimens, AL was efficacious in the treatment of acutely exacerbated schizophrenia.[2] Statistically significant improvement from baseline in Positive and Negative Syndrome Scale[3] (PANSS) total score was observed in both AL dose groups, with separation from placebo as early as day 8.[2] Subsequently, the efficacy and safety of AL using the 1064 mg every-2-months regimen was evaluated in patients with acute schizophrenia in the 25-week randomized active-controlled ALPINE (Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness)

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study[4] using paliperidone palmitate (PP [Invega Sustenna, Janssen Pharmaceuticals, Inc, Titusville, NJ]) as an active control with known effectiveness.[5] In ALPINE, within-group PANSS total scores improved significantly from baseline at the primary (week 4) and secondary (weeks 9 and 25) endpoints in both the AL and PP groups (Supplemental Figure 1).[4]

Assessments of change in symptoms of schizophrenia based on a PANSS five-factor model as reported by Marder et al[6] ("Marder factors") can provide a more detailed characterization of treatment effects than symptom severity based on the PANSS total score alone. PANSS five-factor scores differentiate effects of antipsychotic medications across important and distinct symptom domains,[6–9] including negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression.[6] The five-factor structure may represent a more valid distribution of the items than the original three PANSS subscales,[10] and baseline factor scores are better predictors of remission than the PANSS total score.[11] Additionally, changes in PANSS factor scores with antipsychotic treatment may reflect meaningful improvement in patient functioning, as positive and negative symptom factor scores have been correlated with measures of function[12] and reductions in disorganized thought factor scores are associated with improvements in measures of cognition.[13]

The primary efficacy findings for the AL 441 mg and 882 mg monthly regimens were supported and extended by results of a post hoc PANSS five-factor analysis, in which statistically significant improvements from baseline were observed in all five symptom domains.[7] The objective of the current post hoc analysis was to assess improvement across multiple symptom domains captured by PANSS five-factor scores in patients treated with the AL 1064 mg every-2-months regimen or PP monthly in the ALPINE study. Our aim was to determine whether treatment with AL was associated with improvement across five symptom domains consistently identified in patients with schizophrenia.[9]

## Materials and Methods

This is a post hoc analysis of data from the randomized, double-blind, active-controlled phase 3b ALPINE study; detailed descriptions of the study design and enrollment criteria were previously reported[4] and are summarized briefly here. The study was conducted in accordance with the principles of Good Clinical Practice derived from the Declaration of Helsinki and in accordance with local regulations and the International Conference on Harmonisation guidelines. The study protocol was approved by the Copernicus Group's institutional review board. Written informed consent was obtained from each participant before any study-specific procedures were conducted.

### ALPINE Patients and Study Design

Adult patients (aged 18–65 years) with an acute exacerbation of schizophrenia (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[14]) were enrolled as inpatients, randomized to AL or PP, discharged after 2 weeks, and then followed as outpatients through week 25 (Figure 1). Patients with a history of hypersensitivity or intolerance to aripiprazole, risperidone, or paliperidone were excluded. For patients without prior exposure to aripiprazole and/or paliperidone/risperidone, tolerability to test doses was assessed during screening.

Patients were randomized 1:1 to AL or PP on study day 1 by an interactive web response system using randomization codes prepared by an independent biostatistician. Randomization was stratified by antipsychotic medication exposure history to ensure balance between the two treatment groups. Patients assigned to AL received 1064 mg every 2 months, initiated using a single intramuscular (IM) 675 mg injection of a NanoCrystal Dispersion formulation of AL (Aristada Initio [Alkermes, Inc]) and a single 30 mg oral dose of aripiprazole on day 1. An IM injection of AL 1064 mg was then administered on day 8 and every 8 weeks thereafter. Patients assigned to PP received a 234 mg IM injection and an oral placebo tablet on day 1 and a 156 mg IM injection on day 8 and every 4 weeks thereafter. Placebo injections were used to maintain study blinding; the timing of injections is shown in Figure 1. Primary and secondary efficacy endpoints in ALPINE were changes from baseline in PANSS total score at week 4 and at weeks 9 and 25, respectively.[4]

### Post Hoc Analysis

This post hoc analysis of PANSS five-factor scores was exploratory in nature, as the factor scores were not prespecified study endpoints. The analysis included all randomized patients who received at least 1 dose of AL or PP and underwent at least 1 postbaseline PANSS assessment. Scores for each factor (negative symptoms, positive symptoms, disorganized

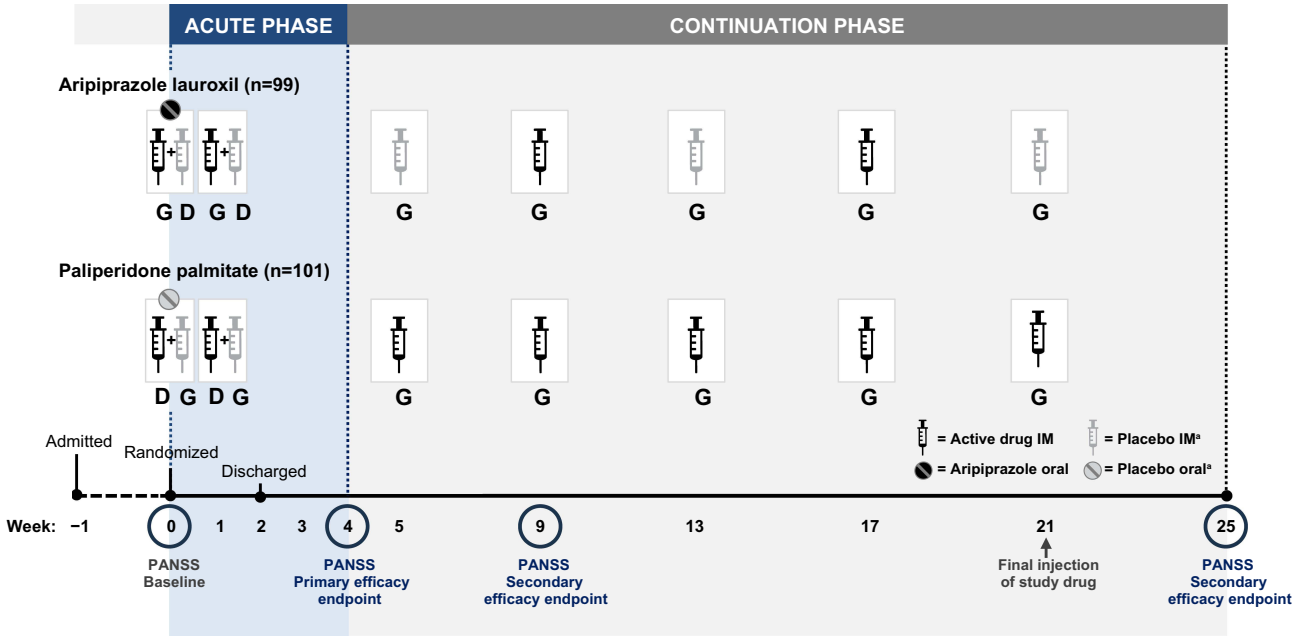


**Figure 1** ALPINE study design. [a]Because AL initiation required gluteal injection and PP initiation required deltoid injection, both groups were administered placebo injections during initiation (days 1 and 8) to maintain blinding; the AL group also received a placebo injection at weeks 5, 13, and 21 to match the PP dosing schedule. The PP group received an oral placebo tablet on day 1 to match the oral dose of aripiprazole in the AL initiation regimen. Adapted with permission from Weiden PJ, Claxton A, Kunovac J, et al. Efficacy and safety of a 2-month formulation of aripiprazole lauroxil with 1-day initiation in patients hospitalized for acute schizophrenia transitioned to outpatient care: phase 3, randomized, double-blind, active control ALPINE study. *J Clin Psychiatry.* 2020;81(3):19m13207.[4]
**Abbreviations**: AL, aripiprazole lauroxil; D, deltoid; G, gluteal; IM, intramuscular; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

thought, uncontrolled hostility/excitement, and anxiety/depression[6]) were calculated from their component item scores (Table 1) at baseline and at weeks 4, 9, and 25. Mean changes from baseline and standard errors (SEs) were calculated for each PANSS factor score by treatment group at baseline and weeks 4, 9, and 25 using the last-observation-carried-forward method for imputation. The study was not powered to formally test between-group differences. No statistical modeling was conducted in this analysis; only summary statistics were calculated.

Safety was assessed in all patients who received at least 1 dose of AL or PP. Adverse events (AEs) reported in the primary publication were summarized.

**Table 1** PANSS Item Mapping to the Five Factors as Described by Marder et al[6]

| Original PANSS Item Numbers | Item Name |
|---|---|
| **Negative symptoms (7 items; range, 7–49)** | |
| 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 |

(*Continued*)


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**Table 1** (Continued).

| Original PANSS Item Numbers | Item Name |
|---|---|
| **Positive symptoms (8 items; range, 8–56)** | |
| P1 | Delusion |
| P3 | Hallucinatory behavior |
| P5 | Grandiosity |
| P6 | Suspiciousness |
| N7 | Stereotyped thinking |
| G1 | Somatic concern |
| G9 | Unusual thought content |
| G12 | Lack of judgment and insight |
| **Disorganized thought (7 items; range, 7–49)** | |
| 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, range: 4–28)** | |
| P4 | Excitement |
| P7 | Hostility |
| G8 | Uncooperativeness |
| G14 | Poor impulse control |
| **Anxiety/depression (4 items; range, 4–28)** | |
| G2 | Anxiety |
| G3 | Guilt feelings |
| G4 | Tension |
| G6 | Depression |

**Abbreviations**: P, positive subscale; PANSS, Positive and Negative Syndrome Scale; N, negative subscale; G, general psychopathology subscale.

## Results

Of the 200 patients randomized to AL or PP treatment, 96 patients assigned to AL and 99 patients assigned to PP underwent at least 1 postbaseline PANSS assessment and were included in the PANSS five-factor analysis. Baseline demographics and disease severity were similar between treatment arms (Table 2). Mean (SD) baseline PANSS total scores for the included patients were 94.1 (9.0) and 94.6 (8.4) for the AL and PP groups, respectively. PANSS five-factor scores at baseline were similar for the AL and PP groups (Table 2).

**Table 2** Baseline Demographics and Clinical Characteristics (Safety Population[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) |
| 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/paliperidone | 31 (31.3) | 31 (30.7) |
| Both aripiprazole and risperidone/paliperidone | 51 (51.5) | 49 (48.5) |
| Neither aripiprazole nor risperidone/paliperidone | 12 (12.1) | 14 (13.9) |
| PANSS total score, mean (SD)[c] | 94.1 (9.0) | 94.6 (8.4) |
| PANSS five-factor scores, mean (SD)[c] | | |
| Negative symptoms | 22.6 (3.9) | 22.6 (4.0) |
| Positive symptoms | 29.7 (4.0) | 29.6 (3.6) |
| Disorganized thought | 20.7 (4.5) | 20.8 (3.3) |
| Uncontrolled hostility/excitement | 9.6 (2.8) | 9.5 (2.7) |
| Anxiety/depression | 11.4 (3.4) | 12.1 (3.1) |

**Notes**: [a]Safety population (patients who received ≥1 dose of study drug). [b]Patients who reported ≥1 race are counted once under this category. [c]Based on the full analysis set, which included patients who underwent ≥1 postbaseline PANSS assessment (AL, n=96; PP, n=99). Baseline was defined as the last nonmissing assessment before the first dose of study drug on day 1.
**Abbreviations**: AL, aripiprazole lauroxil; BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

Changes from baseline in PANSS five-factor scores during the 25-week treatment with AL or PP are presented in Figure 2. The pattern of change from baseline in PANSS factor scores during AL or PP treatment was consistent with change in the PANSS total score (Supplemental Figure 1); for each factor score, change from baseline was numerically greatest between baseline and week 4, and improvement was maintained through week 25.

Among patients treated with AL, the mean (SD) negative symptoms factor score was 22.6 (3.9) at baseline with a mean (SE) change of −3.5 (0.42) at week 25. Mean (SE) change in the positive symptoms factor score was −5.4 (0.56) at week 25 (baseline mean [SD], 29.7 [4.0]). Mean (SE) changes from baseline at week 25 were −3.4 (0.39) for the disorganized thought factor score (baseline mean [SD], 20.7 [4.5]), −1.9 (0.32) for uncontrolled hostility/excitement (baseline mean [SD], 9.6 [2.8]), and −3.1 (0.37) for anxiety/depression (baseline mean [SD], 11.4 [3.4]).

Similar changes in PANSS five-factor scores were observed with AL and PP treatment (Figure 2). Among patients treated with PP, mean (SE) changes from baseline in factor scores at week 25 were −3.4 (0.48) for negative symptoms,

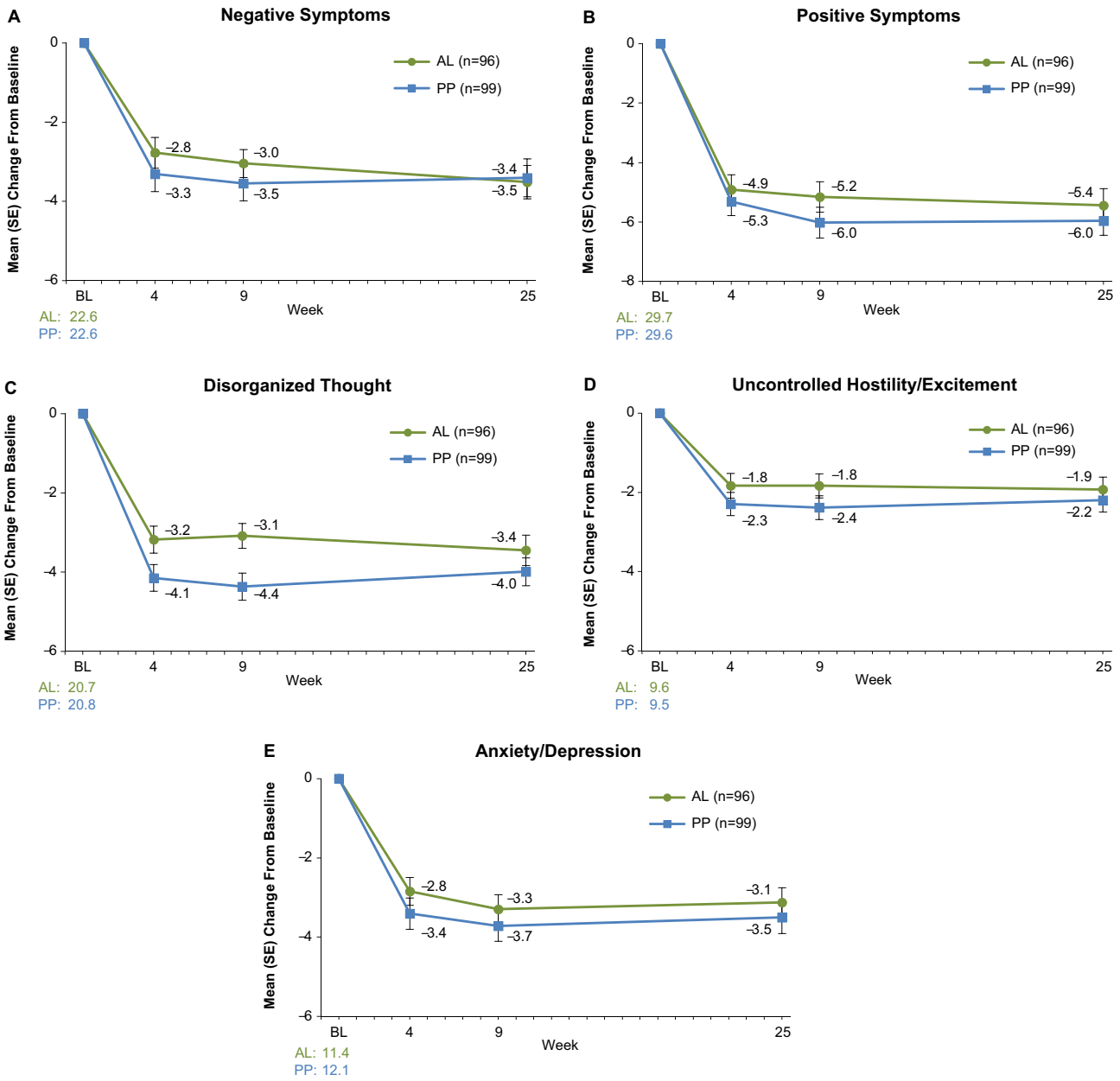


**Figure 2** Changes from baseline in PANSS five-factor scores: (**A**) factor 1, negative symptoms; (**B**) factor 2, positive symptoms; (**C**) factor 3, disorganized thought; (**D**) factor 4, uncontrolled hostility/excitement; and (**E**) factor 5, anxiety/depression. Baseline factor scores are shown below the X-axis.
**Abbreviations**: AL, aripiprazole lauroxil; BL, baseline; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

−6.0 (0.49) for positive symptoms, −4.0 (0.35) for disorganized thought, −2.2 (0.30) for uncontrolled hostility/excitement, and −3.5 (0.41) for anxiety/depression.

The proportions of patients in the AL and PP groups who reported 1 or more AE during the 25-week treatment were 69.7% and 71.3%, respectively.[4] The most common AEs (reported by ≥5% of patients in either treatment group) were injection site pain (AL, 17.2%; PP, 24.8%), increased weight (AL, 9.1%; PP, 16.8%), akathisia (AL, 9.1%; PP, 10.9%), headache (AL, 8.1%; PP, 7.9%), worsening of schizophrenia (AL, 5.1%; PP, 2.0%), somnolence (AL, 4.0%; PP, 6.9%), and dystonia (including oromandibular dystonia; AL, 4.0%; PP, 7.9%), consistent with the known profiles of AL and PP.[4] A more complete report of safety and tolerability results from ALPINE was published previously.[15]

## Discussion

In this post hoc analysis, AL treatment was associated with improvement from baseline in all PANSS factor scores. Changes observed at weeks 4, 9, and 25 were consistent with findings from separate short-term, placebo-controlled studies of AL[7] and PP[5,16] in which statistically significant improvements in each of the five PANSS factor scores were reported. The magnitude of changes across the five PANSS factor scores in the current analysis is within the range observed during treatment with other antipsychotic medications, including risperidone,[6,17] olanzapine,[17] risperidone LAI,[18] and xanomeline–trospium,[8] in shorter-duration trials. Taken together, these results suggest that both AL and PP may be efficacious for treating symptoms of schizophrenia in terms of reducing overall severity of symptoms[4] and improving scores across all five symptom domains during both acute and extended treatment.

The clinical importance of the observed decreases in PANSS factor scores could not be determined directly in the current analysis. The ALPINE study did not include function assessments at baseline or the Clinical Global Impression–Improvement (CGI-I), which is commonly used to anchor an analysis of minimal clinically important difference (MCID).[19,20] Although no comprehensive analysis of MCID for these five factors has been published to our knowledge, the MCID for negative factor scores has been explored.[19,20] Changes in PANSS negative factor score corresponding to CGI-I = 3 (minimally improved) were estimated as −3.8 and −5.0 points in separate studies.[19,20] It should be noted that MCID estimates are valid for the dataset for which they are calculated, and previous analyses included patients with predominantly negative symptoms of schizophrenia.[19,20] The clinical meaningfulness of changes in factor scores was inferred alternatively based on corresponding improvements in function.[13,21] With 52-week risperidone LAI treatment, a −1-point change from baseline in disorganized thought factor score was associated with statistically significant improvement in neurocognitive composite score,[13] and a mean change of –8.9 in negative symptoms factor score during 26-week cariprazine treatment was associated with 14-point improvement in the Personal and Social Performance Scale score in patients with predominantly negative symptoms.[21]

This analysis has several limitations. First, use of last-observation-carried-forward methodology for handling missing data can introduce bias if responsive or nonresponsive patients differentially discontinue from the trial. Only approximately 25% of the patients included in the analysis were female; therefore, the results may not generalize equally to female patients with schizophrenia. Although changes in factor scores during AL treatment were consistent with those observed with the active control, interpretation of these results is limited by the lack of a placebo comparison. Additionally, the ALPINE study was not powered for direct comparisons between the AL and PP treatment groups, and PANSS five-factor scores were not prespecified study outcomes and, therefore, are exploratory in nature. No formal testing of statistical significance was performed, and only summary statistics were calculated in this analysis. Future studies powered to formally test between-group differences would be needed to confirm the symptom domain improvements observed with AL treatment. Studies comparing changes in PANSS factor scores and functional outcome measures could provide clinical context for improvements observed during treatment with AL or PP, and an examination of relationships between PANSS factor scores and treatment response and remission would offer valuable information about residual symptoms within specific domains during long-term antipsychotic treatment.

## Conclusions

In patients with schizophrenia treated with AL 1064 mg every 2 months or PP 156 mg monthly in the ALPINE study, the PANSS five-factor scores all improved over time, consistent with previously reported changes in PANSS total score. The active control, PP, provided clinical context for improvements observed in factor scores with AL treatment. The results of this post hoc analysis support the primary efficacy findings for the AL 1064 mg every-2-months regimen and the PP active control based on PANSS total score[4] and suggest that efficacy extends to the clinically important symptom domains represented by the PANSS five-factor scores.

## Abbreviations

AE, adverse event; AL, aripiprazole lauroxil; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; IM, intramuscular; LAI, long-acting injectable; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

## Data Sharing Statement

The data collected in this study are proprietary to Alkermes, Inc. Alkermes, Inc, is committed to public sharing of data in accordance with applicable regulations and laws.

## Ethics Approval and Informed Consent

The institutional review board/independent ethics committee for each study site approved the study protocol before patient enrollment. The study was conducted in accordance with Good Clinical Practice guidelines and ethical principles derived from the Declaration of Helsinki. All study participants provided written informed consent before participating in study procedures.

## Consent for Publication

All authors have approved the details of the manuscript to be published, and all authors providing consent have reviewed the article contents to be published.

## Informed Consent Statement

Written informed consent was obtained from each participant before any study-specific procedures were conducted.

## Author Contributions

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 article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The decision to submit the manuscript was the sole decision of the authors.

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## Disclosure

Leslie Citrome has served as consultant to AbbVie/Allergan, Acadia, Adamas, Alkermes (including during conduct of this study), Angelini, Astellas, Avanir, Axsome, Biogen, BioXcel, Boehringer Ingelheim, Bristol Myers Squibb, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, MedAvante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, and Wells Fargo and for one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; received speaker fees from AbbVie, Acadia, Alkermes, Angelini, Axsome, BioXcel, Bristol Myers Squibb, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, and Teva and for CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies; and 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. James A. McGrory and Martin Dunbar are employees of Alkermes, Inc, and may own stock/options in the company. The authors report no other conflicts of interest in this work.

## References


1. Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry*. 2016;77(suppl 3):1–24. doi:10.4088/JCP.15032su1
2. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085–1090. doi:10.4088/JCP.14m09741
3. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276. doi:10.1093/schbul/13.2.261
4. Weiden PJ, Claxton A, Kunovac J, et al. Efficacy and safety of a 2-month formulation of aripiprazole lauroxil with 1-day initiation in patients hospitalized for acute schizophrenia transitioned to outpatient care: phase 3, randomized, double-blind, active control ALPINE study. *J Clin Psychiatry*. 2020;81(3):19m13207. doi:10.4088/JCP.19m13207
5. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacol*. 2010;30(3):235–244. doi:10.1097/JCP.0b013e3181dd3103
6. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997;58(12):538–546. doi:10.4088/jcp.v58n1205
7. Citrome L, Risinger R, Cutler AJ, et al. Effect of aripiprazole lauroxil in patients with acute schizophrenia as assessed by the Positive and Negative Syndrome Scale-supportive analyses from a phase 3 study. *CNS Spectr*. 2018;23(4):284–290. doi:10.1017/s1092852917000396
8. Weiden PJ, Breier A, Kavanagh S, Miller AC, Brannan SK, Paul SM. Antipsychotic efficacy of KarXT (xanomeline-trospium): post hoc analysis of positive and negative syndrome scale categorical response rates, time course of response, and symptom domains of response in a Phase 2 study. *J Clin Psychiatry*. 2022;83(3):21m14316. doi:10.4088/JCP.21m14316
9. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophr Res*. 2012;137(1–3):246–250. doi:10.1016/j.schres.2012.01.031
10. Lehoux C, Gobeil M-H, Lefèbvre -A-A, Maziade M, Roy M-A. The five-factor structure of the PANSS: a critical review of its consistency across studies. *Clin Schizophr Relat Psychoses*. 2009;3(3):103–110.
11. Nash AI, Turkoz I, Savitz AJ, Mathews M, Kim E. Predictors of achieving remission in schizophrenia patients treated with paliperidone palmitate 3-month formulation. *Neuropsychiatr Dis Treat*. 2019;15:731–737. doi:10.2147/ndt.s194264
12. Si TM, Zhang YL, Feng Y, Zhuo JM, Cai S, Zhang L. Association between symptom control and functional improvement in patients with acute schizophrenia: a post hoc analysis of an open-label, single-arm, multi-center study of paliperidone-extended release formulation. *Psychiatry Res*. 2019;274:301–305. doi:10.1016/j.psychres.2019.02.036
13. Pandina G, Bilder R, Turkoz I, Alphs L. Identification of clinically meaningful relationships among cognition, functionality, and symptoms in subjects with schizophrenia or schizoaffective disorder. *Schizophr Res*. 2013;143(2–3):312–318. doi:10.1016/j.schres.2012.11.031
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5*. American Psychiatric Publishing; 2013.
15. Citrome L, Yagoda S, Bidollari I, Wang M. Safety and tolerability of starting aripiprazole lauroxil with aripiprazole lauroxil NanoCrystal Dispersion in 1 day followed by aripiprazole lauroxil every 2 months using paliperidone palmitate monthly as an active control in patients with schizophrenia: a post hoc analysis of a randomized controlled trial. *J Clin Psychiatry*. 2024;85(1):23m15095. doi:10.4088/JCP.23m15095
16. Gopal S, Hough DW, Xu H, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *Int Clin Psychopharmacol*. 2010;25(5):247–256. doi:10.1097/YIC.0b013e32833948fa
17. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2001;158(5):765–774. doi:10.1176/appi.ajp.158.5.765
18. Le Moigne A, Csernansky J, Leadbetter RA, et al. PANSS individual item and Marder dimension analyses from a pivotal trial of RBP-7000 (monthly extended-release risperidone) in schizophrenia patients. *J Clin Psychiatry*. 2021;82(5):21m13906. doi:10.4088/JCP.21m13906
19. Czobor P, Sebe B, Acsai K, et al. What is the minimum clinically important change in negative symptoms of schizophrenia? PANSS based post-hoc analyses of a Phase III clinical trial. *Front Psychiatry*. 2022;13:816339. doi:10.3389/fpsyt.2022.816339
20. Leucht S, Barabássy Á, Laszlovszky I, et al. Linking PANSS negative symptom scores with the Clinical Global Impressions Scale: understanding negative symptom scores in schizophrenia. *Neuropsychopharmacology*. 2019;44(9):1589–1596. doi:10.1038/s41386-019-0363-2
21. Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet*. 2017;389(10074):1103–1113. doi:10.1016/s0140-6736(17)30060-0