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

Peter J. Weiden, MD[a,*]; Amy Claxton, PhD[a]; Jelena Kunovac, MD[b]; David P. Walling, PhD[c]; Yangchun Du, PhD[a]; Baiyun Yao, PhD[a]; Sergey Yagoda, MD, PhD[a]; Ilda Bidollari, MD, MBA[a]; Elizabeth Keane, BA[a]; and Ethan Cash, BS[a]

ABSTRACT

Objective: Evaluate efficacy and safety of a 2-month formulation of aripiprazole lauroxil (AL) with 1-day initiation during hospitalization for acute exacerbation of schizophrenia followed by transition to outpatient care.

Methods: The phase 3b double-blind Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness (ALPINE) study was conducted from November 2017 to March 2019. Adults with acute schizophrenia according to *DSM-5* criteria were randomized (1:1) to AL (AL NanoCrystal Dispersion + oral aripiprazole 30 mg, day 1; AL 1,064 mg, day 8 and every 8 weeks [q8wk]) or paliperidone palmitate (PP 234 mg, day 1; PP 156 mg, day 8 and then q4wk) for 25 weeks. Patients remained hospitalized ≥ 2 weeks after randomization per protocol. Primary endpoint was within-group change in Positive and Negative Syndrome Scale total score ($PANSS_T$) from baseline to week 4. Secondary analyses included within- and between-group changes from baseline at various time points. Adverse events (AEs) and laboratory data were monitored.

Results: A total of 200 patients were randomized (AL, n = 99; PP, n = 101); 56.6% and 42.6%, respectively, completed the study. For AL, the mean baseline $PANSS_T$ was 94.1; scores were significantly reduced from baseline at week 4 (−17.4; $P < .001$) and were also reduced at weeks 9 (−19.8) and 25 (−23.3). With PP, $PANSS_T$ also improved significantly from baseline (94.6) at week 4 (−20.1; $P < .001$) and also improved at weeks 9 (−22.5) and 25 (−21.7). The 3 most common AEs over 25 weeks in the AL group were injection site pain (17.2%), increased weight (9.1%), and akathisia (9.1%). The same AEs were the most common in the PP group (injection site pain [24.8%], increased weight [16.8%], and akathisia [10.9%]).

Conclusions: AL and PP were efficacious and well-tolerated for initiating treatment of schizophrenia in the hospital and continuing outpatient treatment.

Trial Registration: ClinicalTrials.gov identifier: NCT03345979

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[a]Alkermes, Inc, Waltham, Massachusetts

[b]Altea Research, Las Vegas, Nevada

[c]CNS Network, LLC, Garden Grove, California

**Corresponding author:* Peter J. Weiden, MD, Karuna Therapeutics, 33 Arch Street, Suite 3110, Boston, MA 02110 (pjweiden@gmail.com).

Long-acting injectable (LAI) antipsychotics provide continuous antipsychotic exposure over periods of weeks to months. It is believed that LAIs are an underused treatment option for schizophrenia.[1–3] For inpatient services, starting an LAI rather than its oral counterpart may have several advantages for patients' long-term treatment plans. Once efficacy and tolerability of the LAI are established during hospitalization, the discharge plan can include continuation of the LAI during transition to outpatient treatment.[1,2,4,5] One barrier to more frequent use of LAIs could be fragmentation of psychiatric services, especially between inpatient and outpatient care.[6–8] Although hospitalization is an opportune time to start an LAI, other competing priorities may preclude implementation.[3] Inpatient services must prioritize stabilization of acute symptoms in a relatively short time frame. These immediate concerns might distract inpatient teams from recommending or starting LAIs during this time.[3] Despite these challenges, placebo-controlled studies[9–11] of LAIs initiated in the hospital have shown safety and efficacy of LAIs for treatment of acute symptoms of schizophrenia.

Another challenge facing inpatient services is whether there is adequate time to fully initiate the LAI before discharge, given that the duration of short-term hospitalizations for schizophrenia treatment averages 10.5 days in the United States.[12] A common initiation strategy to achieve therapeutic plasma concentrations is to use the oral antipsychotic counterpart for a prescribed period of time after the first LAI injection. However, the time needed to complete oral regimens ranges from 2 to 3 weeks and therefore extends beyond most inpatient stays.[9,13,14] As a result, using oral supplementation when starting an LAI during an acute hospital stay will often result in a need to continue an oral antipsychotic after discharge, which, in turn, poses a risk of premature cessation of the oral antipsychotic before the full initiation regimen is completed. Some LAI formulations can be initiated without continued oral supplementation. Aripiprazole lauroxil (AL; Aristada; Alkermes, Inc.; Waltham,

Clinical Points

- It is widely believed that long-acting injectable (LAI) antipsychotics remain underused for the treatment of schizophrenia. One potential barrier to treatment is that starting an LAI can be a challenge in acute inpatient settings given very short lengths of stay.
- The LAI aripiprazole lauroxil (AL) has a 2-month dose interval option with the 1-day initiation option. Patients started on this regimen can be discharged without a need for antipsychotic dosing for 2 months.
- In this study, efficacy and safety of using 1-day initiation to start and continue patients on the AL 2-month dose interval option into outpatient treatment (total treatment time, 25 weeks) were consistent with results from previous studies of starting other AL monthly regimens using 3-week oral aripiprazole supplementation. No additional safety issues were observed, and symptoms continued to improve over 25 weeks.

Massachusetts) and paliperidone palmitate (PP; Invega Sustenna; Janssen Pharmaceuticals, Inc.; Titusville, New Jersey) are LAIs indicated for treatment of schizophrenia in adults and can be started without need for continued oral supplementation following the first LAI injection.[15,16] Both LAIs may reduce the time required to fully complete LAI initiation before discharge.

The Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness (ALPINE) study was designed to examine efficacy and tolerability of starting either AL or PP in patients with acute exacerbation of schizophrenia during hospitalization for acute phase treatment (through week 4) as well as transition to outpatient care for ongoing continuation phase therapy (through week 25). The primary objective was to evaluate efficacy of starting a 2-month AL regimen using the 1-day initiation regimen in acutely symptomatic patients at 4 weeks after initiation, with secondary efficacy endpoints at 9 weeks (corresponding with a single dose interval of the initial 2-month AL injection) and at 25 weeks (corresponding with 3 AL injections at 8-week intervals). The study included a PP arm to provide an active control for AL while avoiding use of a placebo in patients with schizophrenia in need of active medication. Secondary efficacy objectives used the same time points (weeks 4, 9, and 25) for the PP arm.

METHODS

This phase 3b, randomized, double-blind, active-controlled study (Clinicaltrials.gov identifier: NCT03345979) was conducted from November 2017 to March 2019 at 16 US sites. 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.

Patients

Eligible patients were adults (aged 18–65 years) diagnosed with schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), criteria[17] (confirmed by Mini-International Neuropsychiatric Interview 7.0.2 for Schizophrenia and Psychotic Disorder Studies[18]) with an acute exacerbation or relapse of symptoms that began ≤ 2 months before screening and warranted hospitalization. Additional key eligibility criteria included prior history of hospitalization for schizophrenia and Positive and Negative Syndrome Scale total score ($PANSS_T$)[19] of 80–120 (inclusive) with a score of ≥ 4 on ≥ 2 of any of the following for PANSS positive symptoms items: delusions (item 1), conceptual disorganization (item 2), hallucinations (item 3), and suspiciousness/persecution (item 6). Clinical Global Impression–Severity of Illness scale (CGI-S)[20] scores ≥ 4 (moderately ill or worse) were also required.

Key exclusion criteria included current primary *DSM-5* diagnosis other than schizophrenia; currently deemed to be at imminent risk of suicide; first antipsychotic treatment within the past 12 months; history of recent LAI treatment; history of treatment resistance; or history of hypersensitivity, intolerance, or inadequate response to aripiprazole, risperidone, or paliperidone.

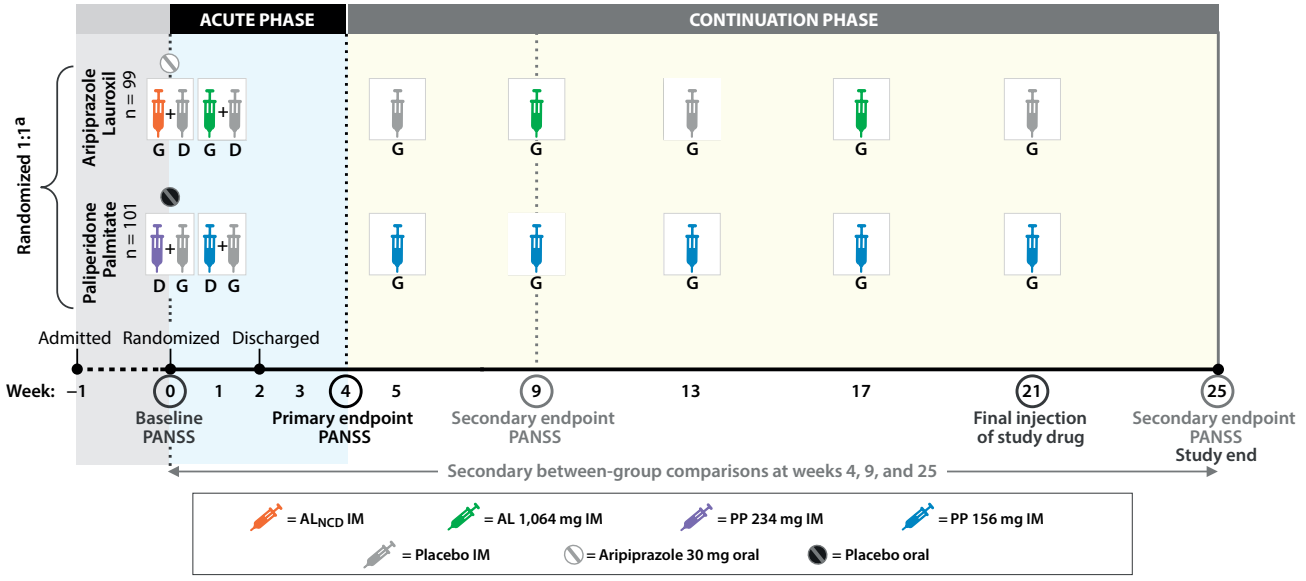
Study Design and Treatments

The ALPINE study duration was approximately 26 weeks, with a 1-week screening period and a 25-week double-blind LAI treatment period (Figure 1). The study included an initial inpatient stay during the screening period and at least the first 2 weeks of double-blind treatment. Patients were required to stay in the hospital for ≥ 2 weeks. If doing so was clinically appropriate, patients were discharged 2 weeks after randomization but could delay discharge 1 week if needed. Post-discharge follow-up schedule began with outpatient visits at weeks 3, 4, and 5 and then changed to an every-4-weeks visit schedule until the last visit at week 25 (weeks 9, 13, 17, 21, and 25).

Inpatient LAI Initiation

Patients were randomized 1:1 to AL or PP on day 1 by interactive web response system. Before randomization (at screening), patients were stratified by prior history of exposure to aripiprazole and/or risperidone/paliperidone (stratification level 1: prior exposure to both aripiprazole and risperidone/paliperidone or exposure to none of these medications; level 2: prior exposure to either aripiprazole or risperidone/paliperidone). Those patients who had reliable histories of having received (and tolerated) both did not have any further oral antipsychotic exposure before their randomization injection visit. Those with a history of only risperidone/paliperidone exposure received oral aripiprazole 5 mg as a test dose to establish tolerability during the first 2 days of inpatient screening. Those exposed to only aripiprazole received 2 days of oral risperidone 1 mg, and those with no exposure to either received the 2 agents,

Figure 1. ALPINE Study Timeline



[a]Patients were randomized 1:1 using an interactive web response system to AL or PP on day 1, stratified by prior history of exposure to aripiprazole or risperidone/paliperidone.

Abbreviations: AL = aripiprazole lauroxil, AL_{NCD} = AL NanoCrystal Dispersion, D = deltoid, G = gluteal, IM = intramuscular, PANSS = Positive and Negative Syndrome Scale, PP = paliperidone palmitate.

8 hours apart over 2 days. Prior antipsychotic medications were discontinued upon inpatient admission, with a washout period of 2 to 5 days.

Patients randomized to AL received the 1-day AL initiation regimen (AL NanoCrystal Dispersion [AL_{NCD}] gluteal injection + single 30-mg dose of oral aripiprazole) with placebo deltoid injection on study day 1. The first AL 1,064-mg injection (gluteal) was administered on day 8 with a placebo deltoid injection to reflect timing of the PP initiation regimen to preserve the blind (Figure 1). The 1,064-mg AL dose was chosen because it was approved after the pivotal efficacy study[9] and has the longest dose interval available among AL regimens.

Patients randomized to PP received a single PP 234-mg deltoid injection with a placebo gluteal injection and oral placebo tablet on day 1 and a PP 156-mg injection (deltoid) with placebo injection (gluteal) on day 8. After day 1, no oral antipsychotic was permitted with either treatment arm.

Outpatient LAI Treatment

After the AL 1,064-mg (gluteal) injection on day 8, AL was administered every 8 weeks (q8wk; weeks 9 and 17), with placebo injections (gluteal) administered at weeks 5, 13, and 21 to match the timing of PP injections (Figure 1) to maintain the blind.

PP 156-mg injections (gluteal) were administered q4wk after the day 8 injection (weeks 5, 9, 13, 17, and 21).

Assessments

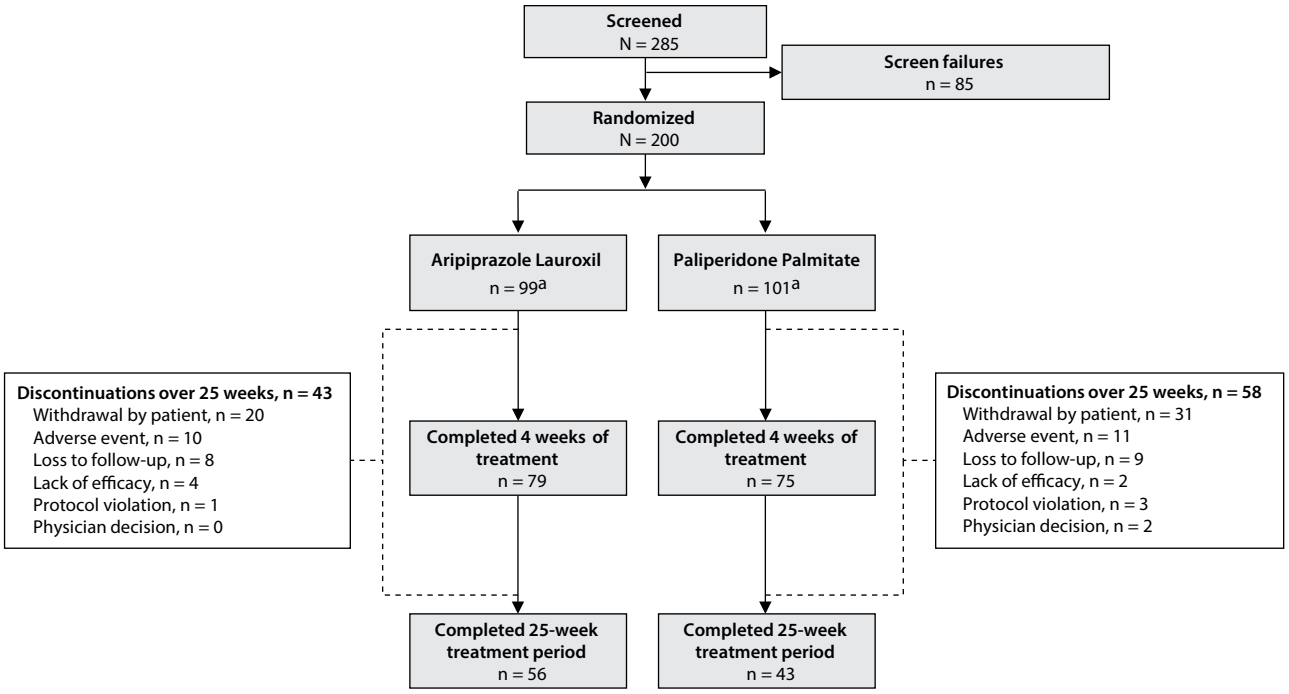
Efficacy was assessed using the PANSS at screening, randomization (day 1), day 4, weeks 1 and 2 (inpatient), and each outpatient visit. Baseline was defined as the last nonmissing assessment before the first dose of study drug on day 1. The primary efficacy endpoint was change in $PANSS_T$ from baseline to week 4 within each treatment group. Secondary analyses included within–treatment group changes in $PANSS_T$ from baseline to weeks 9 and 25 and between-group comparisons at weeks 4, 9, and 25. Safety and tolerability endpoints included incidence of adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation. Additional standard safety assessments included laboratory parameters (eg, hematology, chemistry, metabolic parameters, prolactin, urinalysis), vital signs, body weight, injection site reactions, abnormal movement scales,[21–23] Columbia-Suicide Severity Rating Scale,[24] and side effects scales.[25,26]

Statistical Analysis

The safety population included all patients who received ≥ 1 dose of study drug. Efficacy was assessed for all patients in the safety population with ≥ 1 post baseline PANSS assessment. No formal sample size calculations were performed. Study sites were pooled to ensure ≥ 10 patients per treatment group within each pooled site to improve estimation precision; 7 pooled sites resulted.

Change in $PANSS_T$ from baseline to weeks 4, 9, and 25 was tested for AL and PP separately using 1-sample *t* tests (observed cases). Changes in $PANSS_T$ from baseline to weeks 4, 9, and 25 were compared between treatment groups using mixed model for repeated measures (MMRM). Models included treatment, visit, treatment-by-visit interaction, baseline $PANSS_T$, stratification factor, and pooled study site as covariates and an unstructured variance-covariance matrix for within-subject variability. AEs were summarized

Figure 2. Patient Disposition in ALPINE



[a]Includes all patients with ≥ 1 dose of study drug. Five patients (aripiprazole lauroxil, n = 3; paliperidone palmitate, n = 2) were not included in the efficacy analysis because they did not receive any postbaseline PANSS assessment.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

descriptively for the first 4 weeks of treatment and cumulatively for the full treatment period (from week 0 to week 25).

RESULTS

In total, 200 patients were randomized and received their respective LAI initiation regimen on day 1 (AL, n = 99; PP, n = 101; Figure 2). All 200 patients were included in the safety analyses, and 195 were included in the efficacy analysis (AL, n = 96; PP, n = 99). Seventy-seven percent of patients completed the 4-week acute phase (AL, 79.8%; PP, 74.3%); 25-week completion rates were 56.6% for AL and 42.6% for PP.

The most common reasons for discontinuation in both treatment groups were withdrawal by patient, AEs, and loss to follow-up, both throughout the study (Figure 2) and among patients who discontinued during the first 4 weeks of treatment (Supplementary Table 1).

Demographic and baseline clinical characteristics were similar in both groups (Supplementary Table 2). Of the 200 patients, 162 (81.0%) had a history of prior exposure to risperidone/paliperidone, 112 (56.0%) had prior exposure to aripiprazole, and 26 (13.0%) had no prior exposure to any of these antipsychotics. Of the 99 patients randomized to the AL treatment arm, 43 were given the test dose of oral aripiprazole for 2 days and 17 were given oral risperidone for 2 days, with 12 of these patients receiving both aripiprazole and risperidone test doses. Of the 101 patients randomized to the PP arm, 45 were given the test dose of oral aripiprazole for 2 days and 21 were given oral risperidone for 2 days, with 14 of these patients receiving both aripiprazole and risperidone test doses.

A total of 138 (69.0%) of the 200 patients reported having antipsychotic exposure in the 30 days prior to the screening visit; the last antipsychotic received prior to screening is listed by treatment group in Supplementary Table 3. Overall, quetiapine was reported most commonly (18.5%), followed by olanzapine (17.0%), risperidone/paliperidone (15.0%), and aripiprazole (10.5%), with the remaining patients split between another atypical antipsychotic (4.0%) or a conventional antipsychotic (also 4.0%). Patients without any identified antipsychotic (n = 62 [31.0%]) presumably had no known exposure in the 30 days prior to screening.

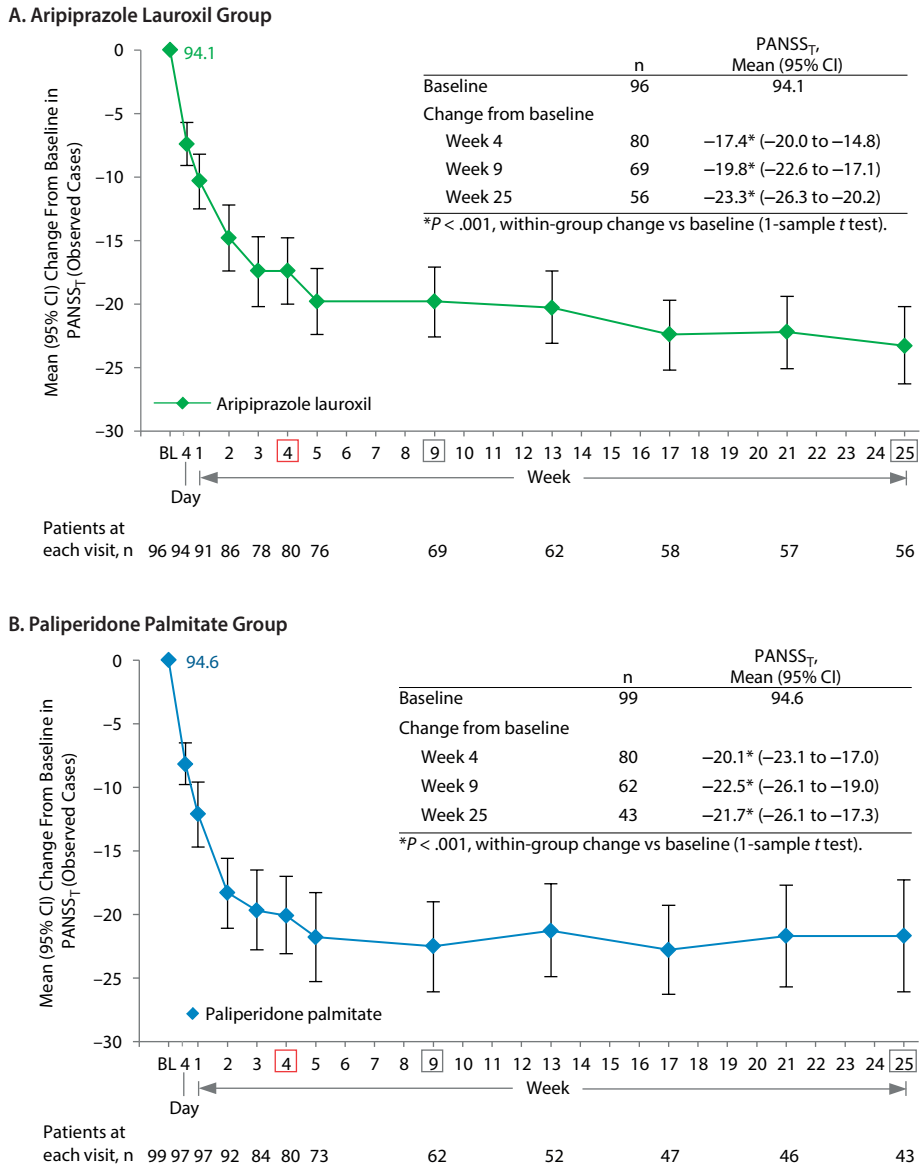
Efficacy

Patients in the AL group achieved statistically significant improvement in $PANSS_T$ from baseline to week 4, with a mean change of −17.4 based on observed cases ($P < .001$; Figure 3A). Continued improvement in $PANSS_T$ from baseline with AL treatment was observed at weeks 9 (−19.8) and 25 (−23.3; both $P < .001$).

With PP, improvement in $PANSS_T$ from baseline was also statistically significant at weeks 4 (−20.1), 9 (−22.5), and 25 (−21.7; all $P < .001$; Figure 3B).

The study was not powered to formally test between-group differences. The 95% CIs for LS mean changes in $PANSS_T$ over time from the MMRM analysis overlap at each

Figure 3. PANSS Total Score Changes Over Time[a] Throughout the Study With (A) Aripiprazole Lauroxil and (B) Paliperidone Palmitate



[a]Mean (95% CI) PANSS$_T$ changes from baseline to week 4 (primary endpoint) and weeks 9 and 25 (secondary endpoints) using observed cases. Error bars represent 95% CIs. Mean baseline PANSS$_T$ is indicated at the first time point. Red box indicates primary endpoint; gray boxes indicate secondary endpoints.
Abbreviations: BL = baseline, PANSS$_T$ = Positive and Negative Syndrome Scale total score.

time point for AL and PP (Supplementary Figure 1). LS mean (95% CI) difference in change from baseline in PANSS$_T$ with AL versus PP was 2.0 (−1.5 to 5.5) at week 4, 2.7 (−1.0 to 6.4) at week 9, and −0.9 (−5.0 to 3.2) at week 25. The 95% CIs for differences with AL versus PP all included zero.

Safety and Tolerability

Aripiprazole lauroxil adverse events. During 25 weeks of treatment, 69 (69.7%) of 99 AL-treated patients experienced ≥ 1 AE; AEs were largely mild or moderate in severity (94.2%). Most patients (57/99 [57.6%]) experienced AEs during the first 4 weeks of treatment (Table 1). AEs reported by ≥ 5% of AL-treated patients through week 25 were injection site pain, increased weight, akathisia, headache, and schizophrenia. The 3 most frequently reported AEs with AL through week 25 included injection site pain (17/99 [17.2%]), which was predominantly mild (16/17) and occurred with active and placebo injections; akathisia (9/99 [9.1%]), which was also predominantly mild (8/9); and increased weight (9/99 [9.1%]), which was mild or moderate.

SAEs occurred in 8 AL-treated patients (8.1%) (Table 1 and Supplementary Table 4), and there was no trend in

Table 1. Summary of Adverse Events With Aripiprazole Lauroxil up to Weeks 4 and 25[a]

	Aripiprazole Lauroxil (n = 99)	
Patients	Week 0 to Week 4	Cumulative AEs, Week 0 to Week 25[b]
Any AE	57 (57.6)	69 (69.7)
Mild	45 (45.5)	45 (45.5)
Moderate	10 (10.1)	20 (20.2)
Severe	2 (2.0)	4 (4.0)
AEs occurring in ≥ 5% of patients in either treatment group[c]		
Injection site pain[d]	16 (16.2)	17 (17.2)
Increased weight	2 (2.0)	9 (9.1)
Akathisia	9 (9.1)	9 (9.1)
Headache	6 (6.1)	8 (8.1)
Schizophrenia	1 (1.0)	5 (5.1)
Somnolence	4 (4.0)	4 (4.0)
Dystonia[e]	4 (4.0)	4 (4.0)
AEs leading to study discontinuation	4 (4.0)	10 (10.1)
Schizophrenia	1 (1.0)	5 (5.1)
Injection site pain[f]	2 (2.0)	2 (2.0)
Psychotic disorder	0	2 (2.0)
Suicide attempt	0	1 (1.0)
Suicidal ideation	0	1 (1.0)
Generalized tonic-clonic seizure	1 (1.0)	1 (1.0)
Akathisia	0	0
Dystonia[e]	0	0
Upper abdominal pain	0	0
Increased blood prolactin	0	0
Dizziness	0	0
Galactorrhea	0	0
Overdose	0	0
Road traffic accident	0	0
SAEs	2 (2.0)	8 (8.1)
SAEs leading to death	0	0

[a]Values are shown as n (%). For each time period, if a patient experienced ≥ 1 AE in a category, the patient is counted only once according to the greatest severity.
[b]AEs listed in the "week 0 to week 4" column are also included in this column.
[c]Includes AEs reported in ≥ 5% of patients treated with aripiprazole lauroxil or paliperidone palmitate.
[d]Includes placebo injections.
[e]Includes Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 preferred terms of dystonia and oromandibular dystonia.
[f]1 patient assigned to aripiprazole lauroxil discontinued due to injection site pain associated with a placebo injection.
Abbreviations: AE = adverse event, SAE = serious adverse event.

Table 2. Summary of Adverse Events With Paliperidone Palmitate up to Weeks 4 and 25[a]

	Paliperidone Palmitate (n = 101)	
Patients	Week 0 to Week 4	Cumulative AEs, Week 0 to Week 25[b]
Any AEs	60 (59.4)	72 (71.3)
Mild	34 (33.7)	33 (32.7)
Moderate	24 (23.8)	34 (33.7)
Severe	2 (2.0)	5 (5.0)
AEs occurring in ≥ 5% of patients in either treatment group[c]		
Injection site pain[d]	25 (24.8)	25 (24.8)
Increased weight	12 (11.9)	17 (16.8)
Akathisia	11 (10.9)	11 (10.9)
Headache	7 (6.9)	8 (7.9)
Dystonia[e]	7 (6.9)	8 (7.9)
Somnolence	7 (6.9)	7 (6.9)
Schizophrenia	2 (2.0)	2 (2.0)
AEs leading to study discontinuation	8 (7.9)	11 (10.9)
Akathisia	2 (2.0)	2 (2.0)
Dystonia[e]	1 (1.0)	2 (2.0)
Schizophrenia	1 (1.0)	1 (1.0)
Injection site pain	1 (1.0)	1 (1.0)
Upper abdominal pain	1 (1.0)	1 (1.0)
Increased blood prolactin	1 (1.0)	1 (1.0)
Dizziness	1 (1.0)	1 (1.0)
Galactorrhea	1 (1.0)	1 (1.0)
Suicide attempt	0	1 (1.0)
Overdose	0	1 (1.0)
Road traffic accident	0	1 (1.0)
Psychotic disorder	0	0
Suicidal ideation	0	0
Generalized tonic-clonic seizure	0	0
SAEs	3 (3.0)	7 (6.9)
SAEs leading to death	0	1 (1.0)[f]

[a]Values are shown as n (%). For each time period, if a patient experienced ≥ 1 AE in a category, the patient is counted only once according to the greatest severity.
[b]AEs listed in the "week 0 to week 4" column are also included in this column.
[c]Includes AEs reported in ≥ 5% of patients treated with aripiprazole lauroxil or paliperidone palmitate.
[d]Includes placebo injections.
[e]Includes Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 preferred terms of dystonia and oromandibular dystonia.
[f]1 SAE leading to death (road traffic accident) occurred in the paliperidone palmitate group; the event was assessed by the investigator as definitely not related to treatment.
Abbreviations: AE = adverse event, SAE = serious adverse event.

time on treatment to occurrence of SAEs. Ten AL-treated patients (10.1%) discontinued because of AEs. AEs leading to discontinuation in ≥ 2 patients receiving AL were schizophrenia, injection site pain (1 associated with placebo injection), and psychotic disorders.

Paliperidone palmitate adverse events. During 25 weeks of treatment, 72 (71.3%) of 101 PP-treated patients experienced ≥ 1 AE; most AEs were mild or moderate in severity (93.1%). Most patients (60/101 [59.4%]) experienced AEs during the first 4 weeks of treatment (Table 2). AEs reported by ≥ 5% of patients through week 25 with PP were injection site pain, increased weight, akathisia, headache, dystonia, and somnolence. The 3 most frequently reported AEs with PP through week 25 included injection site pain (25/101 [24.8%]), which was predominantly mild (22/25) and occurred with active and placebo injections; akathisia (11/101 [10.9%]), which was also predominantly mild (8/11); and increased weight (17/101 [16.8%]), which was mild or moderate.

Seven PP-treated patients (6.9%) experienced SAEs (Table 2 and Supplementary Table 5), and there was no trend in time on treatment to occurrence of SAEs. There was 1 SAE with fatal outcome (road traffic accident) in the PP group that was assessed as unrelated to treatment. Eleven patients (10.9%) discontinued because of AEs. AEs leading to discontinuation in ≥ 2 patients receiving PP were akathisia and dystonia (including 1 event each of dystonia and oromandibular dystonia).

DISCUSSION

Transition from inpatient to outpatient care after acute hospitalization for schizophrenia is a critical time. One in 11 schizophrenia patients discharged from a short hospital

stay in the United States is readmitted within 1 week.[27] This 1-week readmission rate for schizophrenia is the highest among 20 medical and mental health conditions reported[27] and speaks to the need to have prospective data evaluating interventions that start in the hospital and to assess outcomes during and after transitions of care for schizophrenia.

The ALPINE study was designed to provide prospective data on efficacy and safety of LAIs for treatment of an acute exacerbation of schizophrenia, started in the hospital and continued through transition of care, well into outpatient continuation treatment. Both LAIs used in ALPINE—aripiprazole lauroxil and paliperidone palmitate—have initiation regimens that can be completed within approximately 1 week or less of treatment initiation, well within the window of most short-term acute hospitalizations for schizophrenia.[12] The 4-week retention rate of up to approximately 80% indicates that both AL and PP initiated in the acute setting were efficacious and well-tolerated for most ALPINE patients and provided support through the stressful experience of transition to outpatient care. Results from ALPINE can inform inpatient and outpatient services evaluating feasibility of starting LAI antipsychotics in hospitalized patients, where acute efficacy is required but relatively little time is available to fully initiate LAIs before transition to outpatient care.

The ALPINE study provided the first efficacy data for both the 1-day AL initiation regimen and the 2-month dose interval AL option, which were approved by the US Food and Drug Administration based on pharmacokinetic and safety studies.[28–30] Acute symptom improvement in ALPINE patients who initiated AL with the 1-day initiation regimen was comparable to that previously observed in a pivotal study[9] using 21-day oral aripiprazole supplementation. Turning to efficacy of the 2-month AL regimen, the trajectory of $PANSS_T$ for the 1,064-mg dose continued every 8 weeks over the 25-week study was consistent with that reported with AL 441 mg and 882 mg q4wk in a previously published 12-week efficacy study[9] followed by a 52-week safety study[31] in which patients started on either of these AL q4wk regimens continued that regimen for up to 64 weeks. Similarly, the PP initiation regimen also effectively reduced symptoms of schizophrenia acutely, with durability of effect during continuation treatment consistent with that reported in previous studies.[32–34]

Concerns about safety of discharging patients on treatment with an LAI, or about potential safety issues developing after discharge, may be factors in clinicians' hesitation to prescribe LAIs in acute hospital settings.[3,35] In ALPINE, safety findings for AL and PP throughout the study were consistent with the known profiles of each of these LAIs and the respective oral formulations, indicating tolerability through transitions of care.[9,11,36–40] The most frequent AEs (≥ 5%) in the AL group (injection site pain, increased weight, akathisia, headache, and schizophrenia) were among those previously reported for acute treatment with monthly AL 441-mg and 882-mg regimens.[9,15,36] Similarly, the most common AEs (≥ 5%) for patients in the PP group (injection site pain, increased weight, akathisia, headache, dystonia, and somnolence) were in line with other published PP trials.[32–34] For both treatment arms, most AEs (including injection site pain and first instances of akathisia) occurred during the first 4 weeks after LAI initiation. These results support published findings[41–43] that tolerability of atypical LAIs is consistent with that of the respective oral formulations and indicate that starting an LAI in the hospital does not seem to pose any additional safety risks after discharge for either AL or PP above and beyond their oral counterparts.

There are several important limitations of the ALPINE study. The study was not designed as or powered for a direct comparison between AL and PP. The purpose of the blinded PP arm was to provide an active control with known efficacy; the primary efficacy outcome was therefore within-group changes from baseline. The absence of a placebo arm limits interpretation of efficacy findings. The nature of a phase 3b clinical trial limits generalizability of the findings to the broader hospitalized schizophrenia population starting LAIs; enrolling patients who consent to participate in research and excluding those with major comorbidities may introduce bias. Also, rates of successful transition and continuation of LAI after discharge in ALPINE may be higher than that observed in routine clinical care and might have been driven in part by clinical trial incentives or characteristics of enrolled patients.

As is common for long-term clinical trials in schizophrenia, there was a substantial rate of early withdrawal from ALPINE: approximately 50% of the patients discontinued before the end of the study at week 25. Despite limitations of comparing across studies, we note that the discontinuation rate of about 25% at week 4 and about 50% at week 25 in ALPINE is within the expected range for LAI antipsychotic studies.[38,44–47] The nature of clinical trials is such that the persistence of treatment in clinical practice might differ—in either direction—from these retention rates. The study design was limited to only 2 LAI treatments, and the particular LAIs used are alike in not requiring oral antipsychotic supplementation beyond the first day of treatment initiation. Therefore, post-discharge results may not generalize to use of the AL 21-day oral aripiprazole supplementation option or the initiation of other LAIs requiring oral supplementation.

In addition, tolerability to oral aripiprazole and/or risperidone for those patients without prior exposure was assessed using oral test doses consisting of 5 mg/d of aripiprazole and/or 1 mg/d of risperidone during the first 2 days before randomization. This method is consistent with methods used in previous phase 3 studies with LAIs[9,32]; however, while this approach will allow for assessment of immediate hypersensitivity, full evaluation of tolerability can take up to 2 weeks.[15,16] Further, because the fixed-dose design did not allow for dose adjustments, results may not reflect safety or efficacy results for optimized dosing. Finally, the q4wk visits and LAI/placebo injection schedule was driven by considerations regarding blinding; therefore, ALPINE results do not address potential impact of starting hospitalized patients on a 2-month AL dose interval.

CONCLUSIONS

In the phase 3b, randomized, double-blind ALPINE study, starting acutely symptomatic patients with schizophrenia on a 2-month dose regimen of AL with the 1-day initiation regimen demonstrated safety and efficacy consistent with that seen in prior AL studies. These findings support clinical effectiveness of the 1-day initiation regimen. Also, this study demonstrated AL efficacy and tolerability in patients discharged on the AL 2-month regimen for continuation treatment. The inclusion of PP provided an active control with known safety and efficacy that can also be rapidly initiated. Both regimens can be effectively used in patients with schizophrenia through the often challenging transition from acute hospitalization to outpatient continuation treatment.

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Supplementary Material

Article Title: 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

Author(s): Peter J. Weiden, MD; Amy Claxton, PhD; Jelena Kunovac, MD; David P. Walling, PhD; Yangchun Du, PhD; Baiyun Yao, PhD; Sergey Yagoda, MD, PhD; Ilda Bidollari, MD, MBA; Elizabeth Keane, BA; and Ethan Cash, BS

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List of Supplementary Material for the article

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Supplementary Table 1. Patient Disposition Up to Week 4

	Aripiprazole Lauroxil (n=99)	Paliperidone Palmitate (n=101)	Total (N=200)
Completed first 4 weeks of treatment, n (%)	79 (79.8)	75 (74.3)	154 (77.0)
Discontinued during first 4 weeks, n (%)	20 (20.2)	25 (24.8)	45 (22.5)
Reasons for discontinuation, n (%)			
Withdrawal by patient	10 (10.1)	16 (15.8)	26 (13.0)
Adverse event	4 (4.0)	5 (5.0)	9 (4.5)
Lost to follow-up	3 (3.0)	3 (3.0)	6 (3.0)
Lack of efficacy	2 (2.0)	1 (1.0)	3 (1.5)
Protocol violation	1 (1.0)	0	1 (0.5)

Supplementary Table 2. Demographics and Baseline Characteristics[a]

	Aripiprazole Lauroxil (n=99)	Paliperidone Palmitate (n=101)	Total (N=200)
Age, mean (SD), years	43.5 (9.7)	43.4 (10.8)	43.4 (10.3)
Men, n (%)	73 (73.7)	76 (75.2)	149 (74.5)
Race, n (%)			
Black or African American	72 (72.7)	78 (77.2)	150 (75.0)
White	25 (25.3)	17 (16.8)	42 (21.0)
Asian	2 (2.0)	4 (4.0)	6 (3.0)
Multiple races[b]	0	2 (2.0)	2 (1.0)
Ethnicity, n (%)			
Hispanic or Latino	8 (8.1)	11 (10.9)	19 (9.5)
Weight, mean (SD), kg	84.8 (19.8)	85.0 (18.8)	84.9 (19.2)
BMI, mean (SD), kg/m^2	28.2 (5.5)	27.9 (5.1)	28.0 (5.3)
Prior antipsychotic exposure, n (%)			
Aripiprazole	5 (5.1)	7 (6.9)	12 (6.0)
Risperidone[c]	31 (31.3)	31 (30.7)	62 (31.0)
Both aripiprazole and risperidone[c]	51 (51.5)	49 (48.5)	100 (50.0)
Neither aripiprazole nor risperidone[c]	12 (12.1)	14 (13.9)	26 (13.0)
$PANSS_T$, mean (SD)[d]	94.1 (9.0)	94.6 (8.4)	94.4 (8.7)

[a]Safety population (patients who received ≥1 dose of study drug).
[b]A patient who reported ≥1 race is counted once under this category.
[c]"Risperidone" includes risperidone or paliperidone (oral or LAI).
[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.
Abbreviations: BMI, body mass index; LAI, long-acting injectable; $PANSS_T$, Positive and Negative Syndrome Scale total score.

Supplementary Table 3. Last Known Antipsychotic Prior to Study Entry

Patients, n (%)	Aripiprazole Lauroxil (n=99)	Paliperidone Palmitate (n=101)	Total (N=200)
Patients with antipsychotic exposure in the 30 days before screening	69 (69.7)	69 (68.3)	138 (69.0)
Quetiapine	17 (17.2)	20 (19.8)	37 (18.5)[a]
Olanzapine	21 (21.2)	13 (12.9)	34 (17.0)
Risperidone/paliperidone	16 (16.2)	14 (13.9)	30 (15.0)[b]
Aripiprazole	8 (8.1)	13 (12.9)	21 (10.5)
Other atypical antipsychotic	4 (4.0)	4 (4.0)	8 (4.0)[c]
Other conventional antipsychotic	3 (3.0)	5 (5.0)	8 (4.0)[d]
Patients without antipsychotic exposure in the 30 days before screening	30 (30.3)	32 (31.7)	62 (31.0)

[a]Includes quetiapine (n=4) and quetiapine fumerate (n=33).
[b]Includes risperidone (n=25) and paliperidone (n=5).
[c]Asenapine (n=1), brexpiprazole (n=1), iloperidone (n=1), lurasidone (n=2), and ziprasidone (n=3).
[d]Fluphenazine (n=3), haloperidol (n=4), and thiothixene (n=1).

Supplementary Table 4. Serious Adverse Events with Aripiprazole Lauroxil

	Aripiprazole Lauroxil (n=99)	
Patients, n (%)	**Week 0 to Week 4**	**Cumulative AEs, Week 0 to Week 25[a]**
Serious AEs	2 (2.0)	8 (8.1)
Schizophrenia	1 (1.0)	5 (5.1)
Psychotic disorder	0	2 (2.0)
Generalized tonic-clonic seizure	1 (1.0)	1 (1.0)
Leukocytosis	0	1 (1.0)
Hypercalcemia	0	1 (1.0)
Renal failure	0	1 (1.0)
Suicidal ideation	0	1 (1.0)
Suicide attempt	0	1 (1.0)

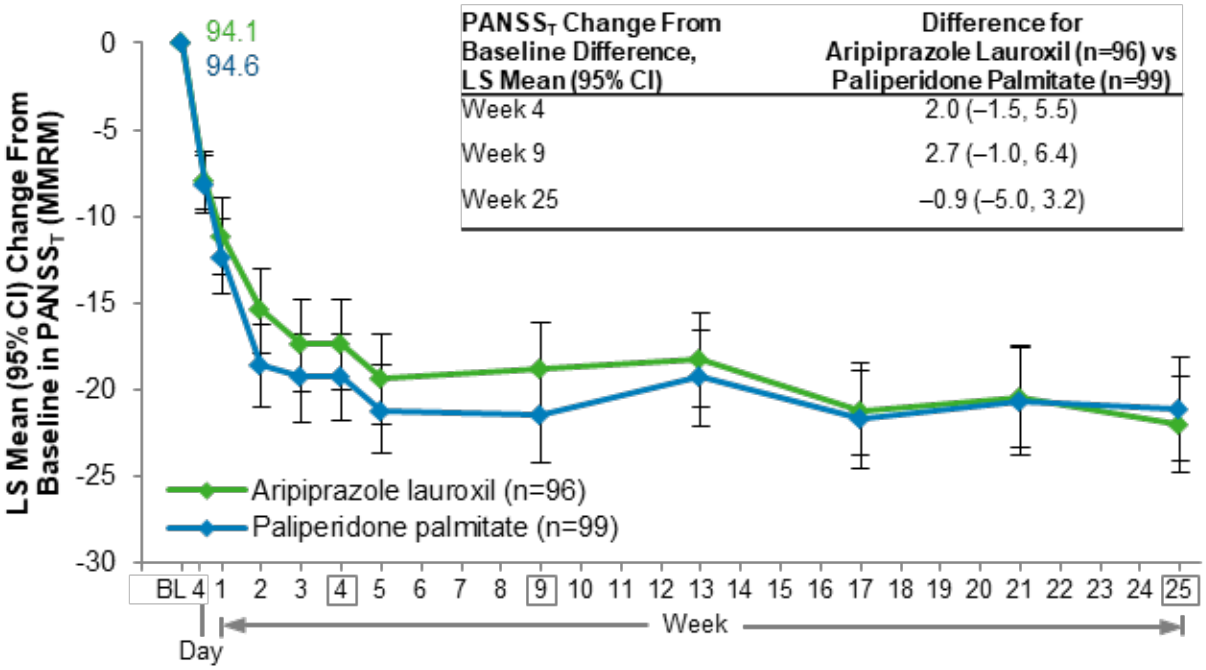
[a]AEs listed in the “week 0 to week 4” column are also included in this column.
Abbreviation: AE, adverse event.

Supplementary Table 5. Serious Adverse Events with Paliperidone Palmitate

	Paliperidone Palmitate (n=101)	
Patients, n (%)	**Week 0 to Week 4**	**Cumulative AEs, Week 0 to Week 25[a]**
Serious AEs	3 (3.0)	7 (6.9)
Schizophrenia	2 (2.0)	2 (2.0)
Alcohol poisoning	1 (1.0)	1 (1.0)
Psychotic symptom	1 (1.0)	1 (1.0)
Suicide attempt	0	1 (1.0)
Overdose	0	1 (1.0)
Road traffic accident	0	1 (1.0)[b]
Bone deformity	0	1 (1.0)
Dystonia	0	1 (1.0)
Depression	0	1 (1.0)

[a]AEs listed in the "week 0 to week 4" column are also included in this column.
[b]1 serious AE leading to death (road traffic accident) occurred in the paliperidone palmitate group; the event was assessed by the investigator as definitely not related to treatment.
Abbreviation: AEs, adverse events.

Supplementary Figure 1. PANSS Total Score Between-Group Analysis Using MMRM.[a]



[a]LS mean (95% CI) PANSS$_T$ changes from baseline using MMRM (secondary endpoint). Error bars represent 95% CIs. Mean baseline PANSS$_T$ is indicated at the first time point (aripiprazole lauroxil, green; paliperidone palmitate, blue). Gray boxes indicate secondary endpoints.
Abbreviations: BL, baseline; LS, least squares; MMRM, mixed-model repeated measures; PANSS$_T$, Positive and Negative Syndrome Scale total score.