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REVIEW

Aripiprazole Lauroxil: Development and Evidence-Based Review of a Long-Acting Injectable Atypical Antipsychotic for the Treatment of Schizophrenia

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Video abstract

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Abstract: This review article describes why and how aripiprazole was formulated as aripiprazole lauroxil (AL), an extended-release antipsychotic agent that is delivered via a long-acting injectable formulation, and the clinical trials investigating its use. AL was formulated as an inactive prodrug of aripiprazole using LinkeRx® technology to provide a prolonged-release antipsychotic with predictable dissolution over time. The resulting AL pharmacokinetic profile is characterized by a long half-life and little peak-to-trough aripiprazole concentration variability across dosing intervals of every 1 month, every 6 weeks, and every 2 months. The prodrug technology was further refined to develop an AL initiation formulation with a somewhat faster release of aripiprazole, eliminating the need for a 21-day oral aripiprazole supplementation period. With this initiation formulation, AL treatment can be started in 1 day. Key AL characteristics, including pharmacokinetic profile and efficacy, safety, and tolerability data, are presented. In addition to the efficacy and safety established in clinical trials of oral aripiprazole, a placebo-controlled 12-week pivotal study investigated AL 441 mg and 882 mg monthly regimens in patients with acutely exacerbated schizophrenia and provided efficacy and safety information that led to US Food and Drug Administration approval in 2015. Thereafter, studies established the long-term safety profile and durability of the AL treatment effect. The 25-week, active-controlled ALPINE study evaluated the feasibility and effectiveness of AL 1064 mg every 2 months, initiated using the 1-day AL initiation regimen, without further oral supplementation beyond day 1, in patients hospitalized for acutely exacerbated schizophrenia with subsequent transition to outpatient care. In short-term and long-term studies, AL was generally well tolerated at initiation and during acute and maintenance treatment. Pharmacokinetic, efficacy, and safety characteristics support the use of AL across inpatient and outpatient treatment settings.

Plain Language Summary: Treatment of schizophrenia with continuous antipsychotic medication has been shown to improve symptoms, daily functioning, and quality of life. One important option for antipsychotic treatment is a long-acting injectable medication. Antipsychotic injections can be administered weeks or months apart in place of daily oral medication. Aripiprazole lauroxil is a long-acting injectable antipsychotic for adults with schizophrenia that has several important features; it provides continuous, stable medication after monthly, every-6-week, or every-2-month injections, and multiple dose options are available (see video abstract). In addition, patients can start treatment with aripiprazole lauroxil using either a 1-day or 21-day initiation regimen

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with their first dose. The 1-day initiation regimen allows people with schizophrenia to start treatment during a doctor's office visit or during a brief stay in the hospital. In short-term studies, aripiprazole lauroxil significantly reduced symptoms of acute schizophrenia. In longer-term studies, side effects were similar to those expected when using oral aripiprazole, and symptoms improved over extended durations of treatment lasting up to 3.5 years. Aripiprazole lauroxil's safety and efficacy profile and multiple dosing and initiation options make it a treatment option for schizophrenia in inpatient and outpatient settings.

Keywords: dosing, pharmacokinetics, phase 3 clinical trials, safety, treatment efficacy, treatment initiation

Introduction

Long-acting injectable (LAI) antipsychotic medications have long been considered an option for long-term treatment of adults with schizophrenia.[1] However, LAIs have been used primarily as a practical treatment method for addressing nonadherence to oral medication in patients with a history of poor adherence and relapse.[2–7] Beyond that role, however, they can be used as a preferred antipsychotic formulation at any stage of schizophrenia treatment,[8] in agreement with an evidence-based, patient-centered approach to the treatment of serious mental illness.[1,9,10] LAIs offer reliable efficacy for the management of acute exacerbations of schizophrenia,[8] reduce the risk of relapse and hospitalization,[11–14] and provide consistent medication coverage during maintenance therapy.[15] Moreover, LAI antipsychotic formulations have been associated with positive patient-reported outcomes, improved quality of life (QoL), and enhanced medication satisfaction.[12,16–19] LAI antipsychotics can help strengthen the therapeutic alliance by supporting regular patient–clinician contact and removing the uncertainty regarding adherence to antipsychotic medication treatment.[2,20]

Several available atypical oral antipsychotics, including risperidone, paliperidone, olanzapine, and aripiprazole, are available as LAI formulations and are approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia in adults.[21–27] When selecting an LAI antipsychotic, clinicians can match the unique features of current LAI options with the patient's specific values and preferences.[1] As with oral formulations, LAI antipsychotic selection is based in part on its efficacy and safety profile and the patient's previous response to medications.[1] Additional considerations for LAI choice include patient and physician familiarity with—and acceptance of—a particular option, pharmacokinetics and associated dosing considerations, site of administration, ease of use when preparing and injecting, and dosing interval, as well as other features inherent to particular formulations.[3,28–30] In 2003, risperidone microspheres administered every 2 weeks became the first atypical LAI antipsychotic that received FDA approval.[24] Since that time, additional LAIs that are differentiated according to active moiety and formulation characteristics have been developed, enabling tailored treatment approaches for individual patients.[3,28,29]

Aripiprazole lauroxil (AL [Aristada®, Alkermes, Inc., Waltham, MA]) was developed to offer an LAI treatment option differentiated from those available at the time of its FDA approval (2015).[21] Aripiprazole was chosen for this new LAI formulation because of its known efficacy in treating symptoms of schizophrenia[31–33] and its favorable safety and tolerability profile.[34] AL was developed as a prodrug of aripiprazole, taking advantage of a proprietary technology to produce an LAI antipsychotic with specific pharmacokinetic characteristics,[35] including having a long, slow, and predictable dissolution over time. In addition, the new prodrug formulation could be administered in a range of dosage strengths with 3 distinct injection interval options, could be placed in prefilled syringes,[28,35,36] and had the potential to be further refined and developed as an initiation formulation, obviating the need for an extended period of oral aripiprazole supplementation at AL initiation.[37]

The aims of this article are to describe the development of AL and present the evidence base for its efficacy and safety in adults with schizophrenia from phase 3 and 4 clinical trials.

Development of Aripiprazole Lauroxil

Aripiprazole

Aripiprazole is an atypical antipsychotic with partial agonist activity at serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[38–41] It also has partial agonist activity at dopamine D2 receptors, differentiating it from earlier antipsychotics.[40–43] Oral aripiprazole has a relatively long elimination half-life (approximately 75 hours),[44] with

steady state achieved by day 14.[45] It has an established history of efficacy in treating schizophrenia.[31–33] Treatment with oral aripiprazole is associated with a low risk of late-emerging adverse events (AEs) during long-term continuous exposure[46,47] and with few dose-related AEs.[34] Akathisia is among the most common AEs experienced by patients treated with aripiprazole;[48,49] it generally occurs early in treatment and is mild or moderate in severity.[48,50] Rates of other drug-induced movement disorders with aripiprazole are similar to those with other atypical antipsychotics.[33,48] Aripiprazole has minimal or modest effects on metabolic parameters and weight gain[33,51] and is not associated with elevated prolactin plasma concentrations.[43]

Prodrug Technology

Development of an LAI formulation of aripiprazole that would be an advance in drug-delivery technology required optimizing its pharmacokinetic profile so that it would enter the bloodstream gradually and consistently over weeks to months after injection.[35] This advance was achieved via development of a prodrug of aripiprazole.[35] Prodrugs are inactive agents that are converted by physiologic processes into the desired active agent. Use of a prodrug can result in improved pharmacokinetics, which can increase a medication's effective half-life from hours to days or weeks, thus lengthening the interval during which plasma drug concentrations remain at a relevant level for clinical efficacy.[15] AL was formulated as a prodrug of aripiprazole in which a fatty acid (lauric acid) "tail" is attached to the active aripiprazole molecule,[52] forming stable crystalline particles in an aqueous suspension that can be injected into muscle tissue.[35–37,52] The tail itself is attached reversibly using a proprietary linker technology (LinkeRx®, Alkermes, Inc., Waltham, MA).[52,53] Once AL is administered, the fatty acid tail is cleaved from the linker by esterases, and then the linker dissociates from the aripiprazole molecule[52,53] via hydrolysis (Figure 1), completing the 2-step bioconversion and releasing aripiprazole molecules into the bloodstream.[52–54]

The solubility and dissolution rates of AL, however, are further governed by the size of its crystalline particles, not just by the rate of enzymatic conversion of the prodrug into active aripiprazole.[52] Larger particles dissolve more slowly than smaller particles because of their lower surface-to-volume ratio (Figure 2).[55] The micrometer-sized particles of AL facilitate controlled and extended release over time as the prodrug molecules within the particles are initially protected from bioconversion, while only the outermost molecules are exposed to esterases and thus convert to active aripiprazole.[52] The AL particle size allows for dosing intervals that can occur monthly, every 6 weeks, or every 2 months.[52] At the time of its initial approval, AL treatment was initiated using 21 days of oral aripiprazole supplementation to increase plasma aripiprazole concentrations to relevant levels more rapidly during the initial 6 weeks of treatment.[37]

To reduce the need for an extended period of oral aripiprazole supplementation at initiation, a second formulation of the AL prodrug molecule was developed (Aristada Initio®; Alkermes, Inc., Waltham, MA) with pharmacokinetics suited to deliver relevant plasma aripiprazole concentrations more rapidly after injection.[37,56] This product was formulated

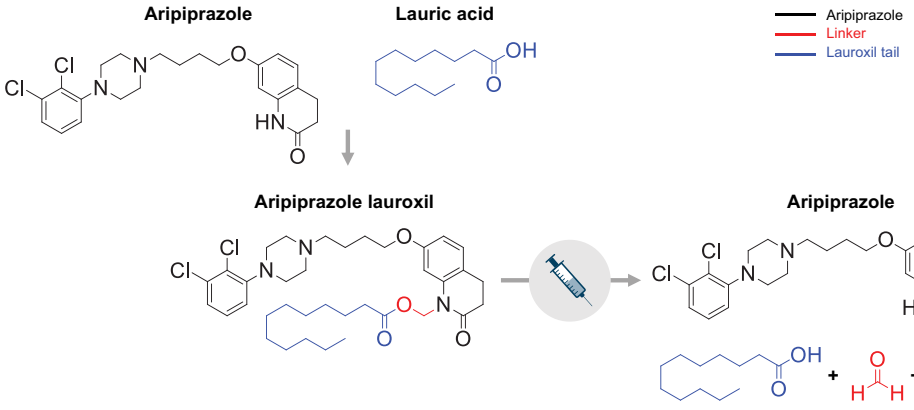

Figure 1 Aripiprazole lauroxil is a prodrug of aripiprazole.[a]
Notes: [a]The lauroxil tail (fatty acid chain; blue) is reversibly attached to aripiprazole (black) via a linker (red) using LinkeRx technology.[35] After the prodrug in aqueous solution is injected, the fatty acid tail is cleaved from the linker by esterase activity, and then the linker dissociates from the active aripiprazole molecule[52,53] by hydrolysis.[52,53] The release of active aripiprazole is governed by the size of its crystalline particles, not by the rate of enzymatic conversion of the prodrug into active aripiprazole.[52]

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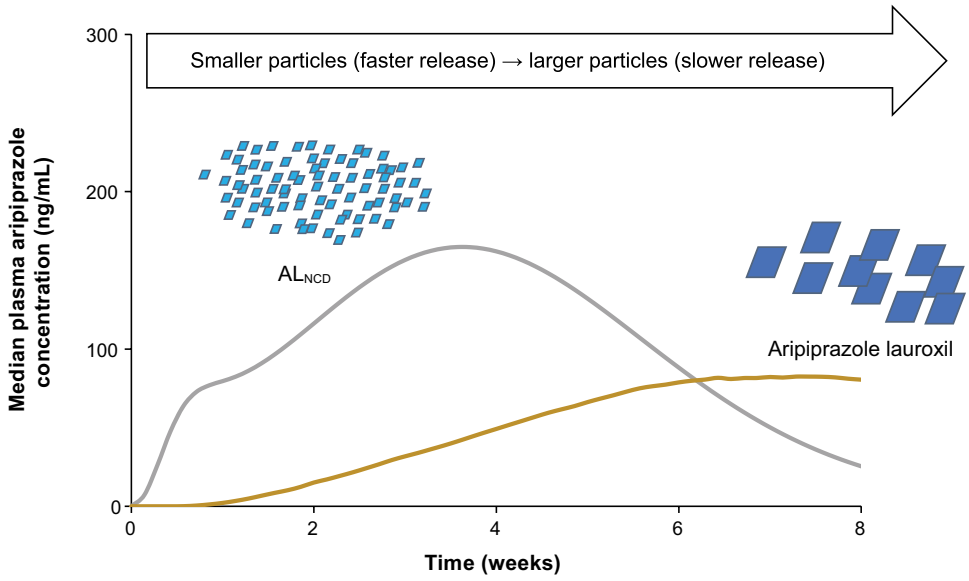

Figure 2 Kinetics of AL_{NCD} and aripiprazole lauroxil.[a]
Notes: Adapted from Jain R, Meyer J, Wehr A, Rege B, von Moltke L, Weiden PJ. Size matters: the importance of particle size in a newly developed injectable formulation for the treatment of schizophrenia. *CNS Spectrums*. 2020;25(3):323–330. *Copyright © 2019, Cambridge University Press*. Creative Commons CC BY license.[37] [a]Schematic of plasma aripiprazole levels over time of the nanomolar particle-sized AL_{NCD} versus the micromolar particle-sized aripiprazole lauroxil. Plasma levels are based on model simulations of aripiprazole levels achieved after administration of AL_{NCD} or aripiprazole lauroxil.
Abbreviation: AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion.

using a NanoCrystal Dispersion technology to generate crystals smaller than those present in the maintenance AL formulation, enabling faster dissolution.[52,57] The smaller nanometer-sized crystals in the AL NanoCrystal Dispersion formulation (AL_{NCD}) dissolve faster than the larger micrometer-sized crystals in AL, resulting in a shorter delay in achieving relevant plasma concentrations (Figure 2).[37] The short remaining lag time for reaching relevant aripiprazole concentrations after a 675 mg AL_{NCD} injection can be addressed with a single 30 mg oral dose of aripiprazole administered on the same day as AL_{NCD} for a 1-day initiation regimen.[37] The AL maintenance dose (which can be any available dose level) can be administered the same day as the 1-day initiation regimen or up to 10 days later.[21] Thus, on day 1, patients can receive an injection of AL, AL_{NCD}, and a single dose of oral aripiprazole. The plasma aripiprazole levels of the 3 components separately and together are illustrated in Figure 3.

Pharmacokinetic Profile of Aripiprazole Lauroxil

The terminal half-life of AL ranges from approximately 54 to 57 days across dosage strengths (Supplementary Table 1),[58,59] compared with approximately 75 hours for oral aripiprazole.[44] AL_{NCD} was designed to have a half-life of approximately 15 days, substantially shorter than that of AL. Figure 4 shows the slow rise in plasma aripiprazole concentrations after administration of the AL 441 mg monthly, AL 882 mg every-6-week, and AL 1064 mg every-2-month regimens (started without AL_{NCD} or supplemental oral aripiprazole) and the extended aripiprazole exposure that occurs after an AL injection at steady state.[60] As a consequence of this long, slow change in aripiprazole concentrations, little variation is observed across the dosing interval.[35] The modest peak-to-trough ratio (1.1 for monthly regimens; 1.3 for 882 mg every 6 weeks[35]) indicates that AL dissolution results in consistent aripiprazole concentrations over the injection interval, with little variability around the average concentration at steady state.[35] By comparison, a long-acting injectable aripiprazole formulated without a prodrug technology (aripiprazole monohydrate)[61] has a shorter mean half-life (300 mg, 29.9 days; 400 mg, 46.5 days) and a greater peak-to-trough ratio (300 mg, 1.7; 400 mg, 1.5) for monthly dosing intervals.[62,63]

Aripiprazole Lauroxil Initiation and Dosing Options

The pharmacokinetic characteristics of the AL prodrug formulation leads to tailored options that may facilitate individualized treatment for adult patients with schizophrenia (as described in the video abstract). AL's dissolution

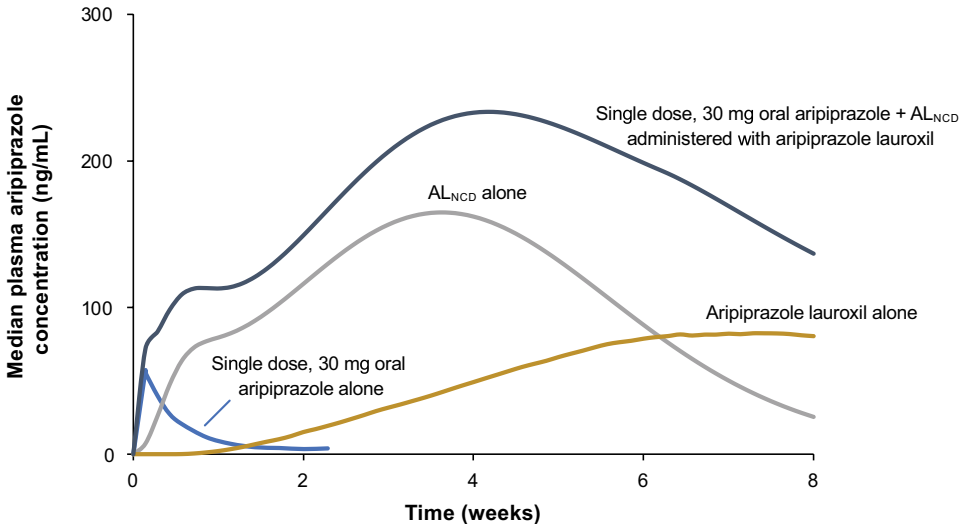

Figure 3 Pharmacokinetics of aripiprazole lauroxil and 1-day initiation regimen components.[a]
Notes: Adapted from Jain R, Meyer J, Wehr A, Rege B, von Moltke L, Weiden PJ. Size matters: the importance of particle size in a newly developed injectable formulation for the treatment of schizophrenia. *CNS Spectrums*. 2020;25(3):323–330. *Copyright © 2019, Cambridge University Press*. Creative Commons CC BY license.[37] Plasma concentrations based on model simulations of aripiprazole levels after administration of AL_{NCD}, AL 1064 mg, one 30 mg dose of oral aripiprazole, or AL_{NCD} + AL 1064 mg + 30 mg oral aripiprazole. Concentrations for oral aripiprazole are based on observed data.
Abbreviations: AL, aripiprazole lauroxil; AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion.

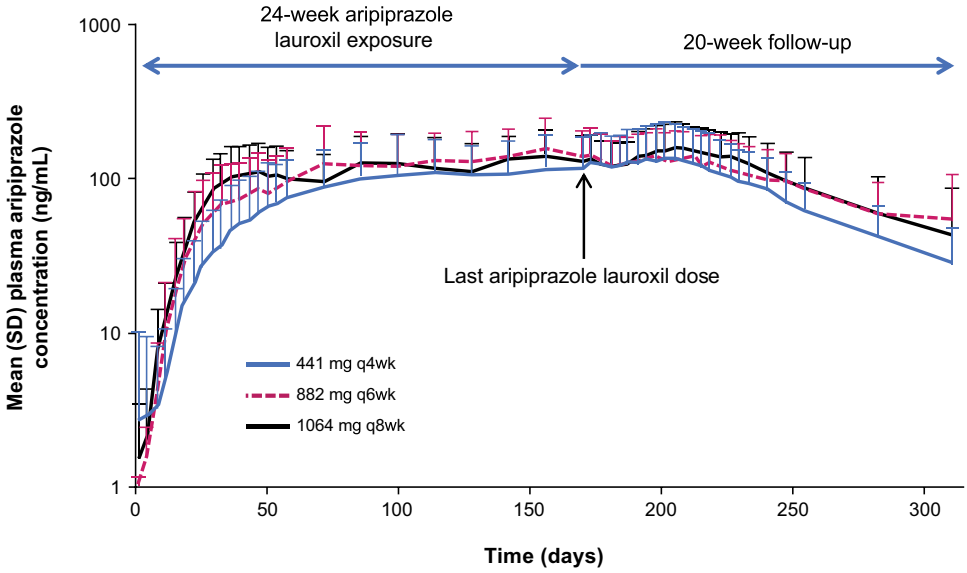

Figure 4 Plasma aripiprazole concentrations with multiple-dose exposure to aripiprazole lauroxil.[a]
Notes: Adapted with permission from Hard ML, Mills RJ, Sadler BM, Wehr AY, Weiden PJ, von Moltke L. Pharmacokinetic Profile of a 2-Month Dose Regimen of Aripiprazole Lauroxil: A Phase I Study and a Population Pharmacokinetic Model. *CNS Drugs*. 2017 Jul;31(7):617–624. © *The Author(s) 2017*. Creative Commons Attribution-NonCommercial 4.0 International License.[60] [a]Aripiprazole lauroxil was administered in a phase 1 study using 3 dosing regimens; no initiation regimen was used in this study.
Abbreviation: qxwk, every x weeks.

rate enabled the development of multiple dosing regimens with a range of injection intervals, including the first FDA-approved every-2-month LAI antipsychotic regimen.[60] Altogether, 5 AL dosing regimens are available: AL 441 mg monthly, 662 mg monthly, and 882 mg monthly; AL 882 mg every 6 weeks; and AL 1064 mg every 2 months.[21] Each of these dosing regimens provides predictable plasma aripiprazole levels that are generally stable over the dosing interval, whether 4, 6, or 8 weeks in duration.[28,35,60]

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Aripiprazole dose exposures resulting from the 5 AL regimens fall within the range of approved oral aripiprazole dosages, from 10 to 20 mg or higher per day.[21,44] Among the AL regimens, the 441 mg monthly regimen results in the lowest possible dose exposure, equivalent to oral aripiprazole 10 mg/day, while the AL 882 mg monthly regimen yields the highest possible dose exposure (Figure 5), equivalent to oral aripiprazole 20 mg or higher per day. The remaining 3 AL regimen options provide an intermediate dose exposure (equivalent to oral aripiprazole 15 mg/day), each based on a different dosing interval:[35,60] AL 662 mg monthly, AL 882 mg every 6 weeks, and AL 1064 mg every 2 months. The range of AL dose-level and injection-interval options allows clinicians to select a regimen suited to an individual's treatment needs[64,65] and facilitates dose conversion when switching to LAI treatment with AL.[21] The availability of higher dose strengths also allows AL to be used when co-prescribed with medications that act as a CYP 3A4 inducer, as described in the AL FDA prescribing information.[21,66]

A 12-week pivotal AL study (NCT01469039) established the efficacy of the 441 mg and 882 mg monthly regimens versus placebo[67] and thus the lower and upper relevant plasma aripiprazole concentrations, respectively (ie, concentrations that were associated with clinical efficacy for those 2 doses).[28] Based on data from a phase 1 study and population pharmacokinetic modelling, AL 662 mg monthly, 882 mg every-6-week, and 1064 mg every-2-month regimens each produced plasma aripiprazole concentrations that were intermediate between those upper and lower concentrations[28,60,68] (Figure 5). Consequently, clinicians can select an AL regimen that yields lower, intermediate, or higher plasma aripiprazole concentrations,[28] depending on patient needs and history of response to antipsychotic treatment. Further, the 3 regimens yielding comparable intermediate plasma aripiprazole concentrations over 3 different dosing interval options—monthly, every 6 weeks, and every 2 months—enable flexibility and personalization of the dosing interval for those patients prescribed an intermediate regimen[28] (Figure 5).

Since the development of AL_{NCD}, AL treatment can be initiated using either of 2 strategies: the 1-day regimen of one AL_{NCD} injection and a single 30 mg oral dose of aripiprazole, or a 21-day regimen of oral aripiprazole

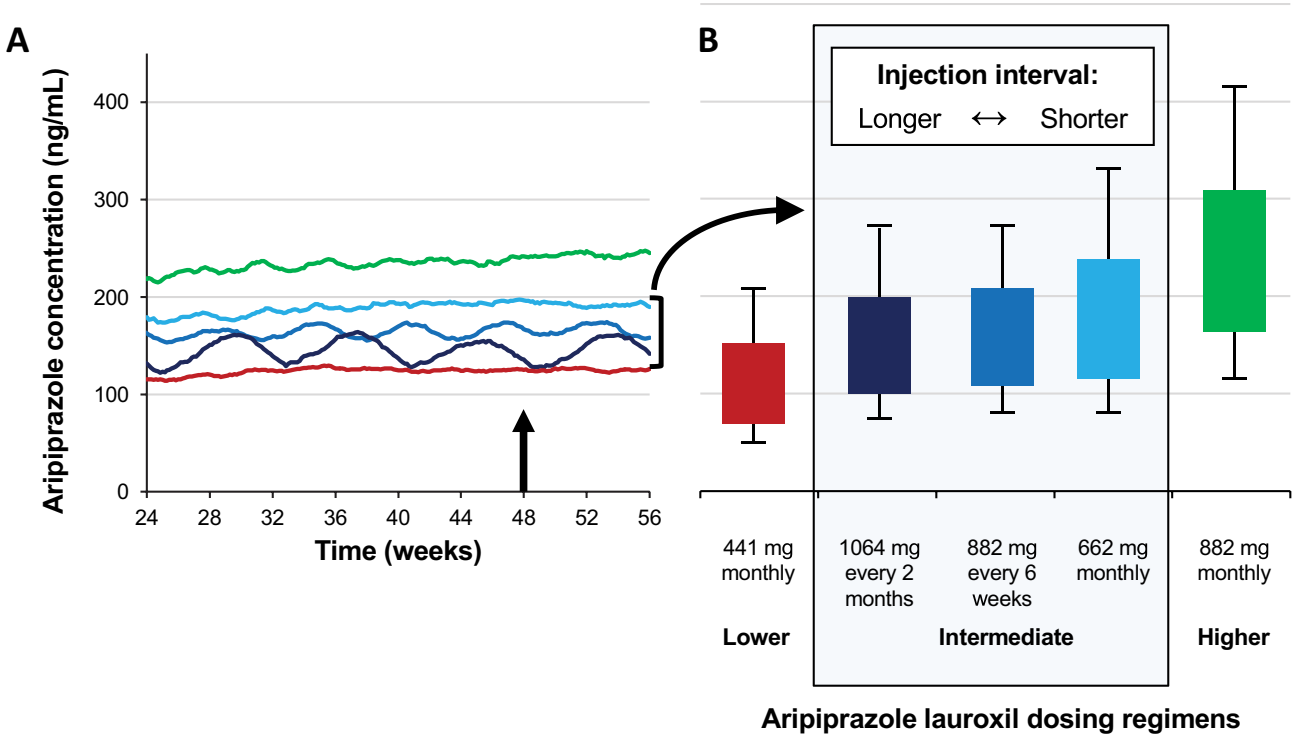

Figure 5 Steady-state plasma aripiprazole concentrations for the 5 aripiprazole lauroxil dosing regimens.[a]

Notes: Adapted with permission from Hard ML, Mills RJ, Sadler BM, Wehr AY, Weiden PJ, von Moltke L. Pharmacokinetic Profile of a 2-Month Dose Regimen of Aripiprazole Lauroxil: A Phase I Study and a Population Pharmacokinetic Model. *CNS Drugs*. 2017;31(7):617-624. Creative Commons CC BY license.[60] [a]Panel (**A**) Median simulated steady-state plasma aripiprazole concentrations for weeks 24–56 after initiation of each AL regimen using 21-day oral aripiprazole supplementation. Panel (**B**) Average simulated steady-state aripiprazole concentrations for the same AL regimens calculated for the injection interval starting at week 48 (arrow in panel [**A**]). The AL 441 mg monthly and 882 mg monthly regimens provide plasma aripiprazole exposure in the lower (equivalent to oral aripiprazole 10 mg/day) and higher (equivalent to oral aripiprazole 20 mg or higher per day) ranges, respectively, of aripiprazole concentrations associated with efficacy. The AL 662 mg monthly, 882 mg every-6-week, and 1064 mg every-2-month regimens provide intermediate-range aripiprazole concentrations (equivalent to oral aripiprazole 15 mg/day). Boxes, 25th to 75th percentiles; whiskers, 10th and 90th percentiles.

Abbreviation: AL, aripiprazole lauroxil.

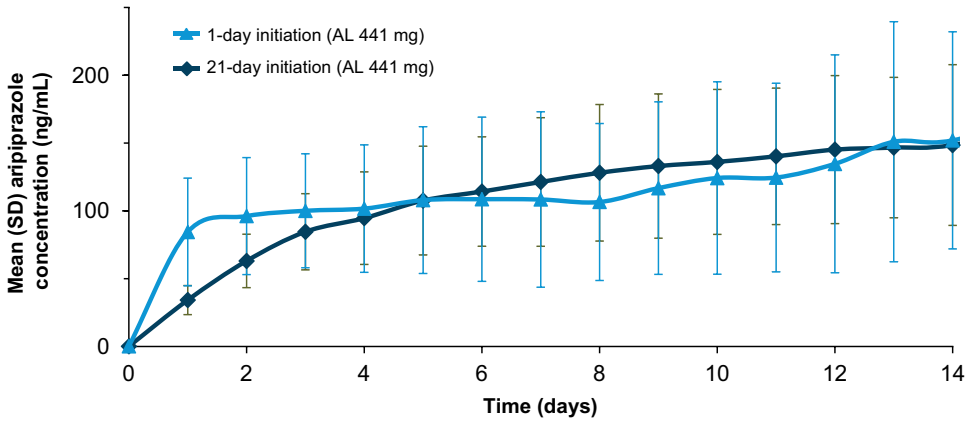

Figure 6 Plasma aripiprazole concentrations resulting from 1-day or 21-day initiation of aripiprazole lauroxil.[a]
Notes: [a]The 1-day regimen, like the 21-day initiation regimen, results in aripiprazole concentrations that are in the relevant range within 4 days of initiation. Mean (+SD) aripiprazole concentrations over time (28 days) after 21-day initiation (21 days of 15 mg oral aripiprazole) or 1-day initiation (AL_{NCD} plus one 30 mg dose of oral aripiprazole) administered with one AL dose on day 1.
Abbreviations: AL, aripiprazole lauroxil; AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion.

supplementation.[37,52,56] The 2 initiation strategies, while providing comparable aripiprazole exposures (Figure 6),[56] are suitable in different settings of care and allow for flexibility to align with patients' clinical needs. Oral supplementation for starting LAI treatment may be preferable in certain circumstances;[6,37] for example, patients who are stabilized on oral aripiprazole can continue treatment with oral aripiprazole for 21 days when starting AL.[21] Initiating AL treatment with AL_{NCD} should be avoided in patients requiring dosage adjustments due to drug interactions.[21] Alternatively, the 1-day regimen can be used to initiate AL treatment in one office visit or during an inpatient stay;[69] once administered, along with 30 mg of oral aripiprazole, initiation dosing is complete and continuous plasma aripiprazole exposure is ensured from day 1.[56] Further, the AL_{NCD} injection (and the AL 441 mg dose) can be administered via either the deltoid or gluteal muscle,[21,70] which both patients and clinicians consider valuable options.[3,71,72]

Importantly, the prolonged-release characteristics of AL are advantageous if doses are missed or delayed.[35] A population pharmacokinetic analysis indicated that when AL concentrations are at steady state, delays in the scheduled injection interval of up to 4 weeks resulted in minimal decreases in median aripiprazole plasma concentrations; injection delays of 4 and 6 weeks resulted in 10% and 25% decreases in median aripiprazole plasma concentrations, respectively, for each AL dose assessed.[35] These findings are the basis of guidance on missed doses, according to which AL dosing can be resumed without the use of an initiation regimen up to 6 weeks after a 441 mg dose, up to 8 weeks after a 662 mg or 882 mg dose, or up to 10 weeks after a 1064 mg dose.[21] After longer gaps (6–7 weeks for 441 mg, 8–12 weeks for 662 mg or 882 mg, and 10–12 weeks for 1064 mg), AL can be reinitiated using either 7 days of oral aripiprazole supplementation or AL_{NCD} alone without oral supplementation.[21,35]

Aripiprazole Lauroxil Outcomes

The efficacy, safety, and tolerability of AL have been assessed in multiple phase 3 or Phase 4 clinical studies for the treatment of adults with schizophrenia.[46,47,67,69,73] Study characteristics are summarized in Table 1; additional details associated with each study are discussed within the respective publications cited.

The 12-week pivotal study examined outcomes in patients with an acute exacerbation of schizophrenia treated with AL 441 mg or 882 mg monthly, initiated with the 21-day regimen, versus placebo.[67] Safety and tolerability of the AL 441 mg or 882 mg monthly regimens were also examined in 3 open-label studies: a 52-week safety study[46] (NCT01626456) with a 1- to 2.5-year extension[47] (NCT01895452) and a 6-month open-label study of patients switched from another LAI antipsychotic[73] (NCT02634320).

Following the FDA approval of the AL monthly and every-6-weeks regimens, the AL 1064 mg every-2-month regimen and AL_{NCD} received FDA approval on the basis of pharmacokinetic and safety studies in which they were

Table 1 Summary of Phase 3 and 4 Studies of Aripiprazole Lauroxil in Patients with Schizophrenia

ClinicalTrials.Gov Identifier	Primary Publication (year)	Study Design	Treatment Groups (n)	Primary Endpoint
NCT01469039 (phase 3)	Meltzer et al (2015)[67]	12-week randomized, DB, placebo-controlled trial in patients with acute exacerbation of schizophrenia	AL 441 mg q4wk with 21-day oral aripiprazole initiation (207) AL 882 mg q4wk with 21-day oral aripiprazole initiation (208) Placebo (207)	Change from baseline to day 85 in PANSS total score vs placebo
NCT03345979 (phase 3b)	Weiden et al (2020)[69]	25-week randomized, DB, active-controlled trial in patients with acute exacerbation of schizophrenia	AL 1064 mg q8wk initiated with AL_{NCD} + 1 dose of 30 mg oral aripiprazole (99) Paliperidone palmitate (101)	Within-group change from baseline to week 4 in PANSS total score
NCT01626456 (phase 3)	Nasrallah et al (2019)[46]	52-week OL safety study	AL 441 mg q4wk (110) AL 882 mg q4wk (368)	Safety and tolerability from baseline to week 52
NCT01895452 (phase 3)	Lauriello et al (2020)[47]	1- to 2.5-year OL extension to the long-term safety study	AL 441 mg q4wk (65) AL 882 mg q4wk (226)	Safety and tolerability over ≤128 weeks, starting from week 52 of the long-term safety study
NCT02634320 (phase 4)	Miller et al (2019)[73]	6-month OL switching study	AL 441/661/882 mg q4wk or 882 mg q6wk, flexibly dosed (51[a])	Change from baseline to last treatment visit in CGI-S score

Notes: [a]Overall N=51. In an analysis of those who switched from paliperidone palmitate, efficacy in 50 patients was reported (1 patient switched from risperidone LAI).
Abbreviations: AL, aripiprazole lauroxil; AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion; CGI-S, Clinical Global Impression–Severity scale; DB, double-blind; LAI, long-acting injectable; OL, open-label; PANSS, Positive and Negative Syndrome Scale; qxwk, every x weeks.

comparable with the AL monthly regimens and 21-day oral supplementation, respectively.[56,60,74] The ALPINE (Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; NCT03345979) study provided additional efficacy data supporting the use of the AL_{NCD} initiation regimen and the AL 1064 mg every-2-month regimen in patients with acute schizophrenia without any oral aripiprazole dosing beyond day 1. ALPINE was a 25-week effectiveness and safety study assessing AL 1064 mg every 2 months using the AL_{NCD} initiation regimen or paliperidone palmitate 156 mg monthly, included as an active control with known efficacy,[75–77] in adult patients hospitalized for acute schizophrenia through the transition to outpatient treatment and during continued care in the community setting.[69]

Efficacy for Acute Symptoms

AL significantly reduced acute symptoms of schizophrenia on the primary endpoint in both of the phase 3 double-blind studies (Table 2). In the placebo-controlled 12-week pivotal study, change from baseline in Positive and Negative Syndrome Scale[78] (PANSS) total score was statistically significant versus placebo at week 12,[67] and comparable efficacies were observed for the 2 dose groups (AL 441 mg every 4 weeks and AL 882 mg every 4 weeks; Figure 7). Cohen's *d* for the pooled AL doses was 0.61 (95% CI: 0.44–0.79); number needed to treat based on ≥30% improvement from baseline in PANSS total score at day 85 was 6 (95% CI: 5–11).[79] In exploratory post hoc subgroup analyses, significant improvements in PANSS total score were observed in the AL 441 mg and 882 mg dose groups versus placebo regardless of sex and across patient age groups, including in those under 30 years of age.[80] AL 441 mg and 882 mg also were associated with efficacy in patients with the most severe symptoms (PANSS total score >92) at baseline.[81]

Secondary efficacy analysis findings were consistent with those in the primary 12-week pivotal study results (Table 2). AL was associated with significant improvement in illness severity based on Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I) scores at week 12 in the 12-week pivotal study.[67,82]

Table 2 Summary of Efficacy Findings From Phase 3 and 4 Studies of Aripiprazole Lauroxil

Study and Treatment Groups (n)	Efficacy Findings
12-week pivotal study[67,82–84] Efficacy and safety vs placebo • AL 441 mg q4wk (207) • AL 882 mg q4wk (208) • Placebo (207)	Primary • PANSS total score change from baseline to day 85 vs placebo; both dose groups $P<0.001$ Secondary and exploratory • CGI-I score at day 85 vs placebo; both $P<0.001$ • CGI-S score at day 85 vs placebo; both $P<0.001$ • PANSS Positive, Negative, and General Psychopathology subscale score changes from baseline to day 85 vs placebo; all $P<0.001$ • PANSS Prosocial subscale score change from baseline to day 85 vs placebo; both $P<0.0001$ • PANSS 5 factor (Marder) score changes from baseline to day 85 vs placebo; all $P<0.001$ • PANSS hostility item score change (in patients scoring >1 at baseline) from baseline to day 85 vs placebo; both $P<0.05$ • PANSS response rates[a] at day 85 vs placebo; all $P<0.01$ • PSP total score change from baseline to day 85 vs placebo; both $P<0.0001$ • PSP excited component score change from baseline to day 85 vs placebo; both $P<0.001$ • PSP disturbing and aggressive behavior domain score change from baseline to day 85 vs placebo; both $P<0.01$
ALPINE Study[69,85] Efficacy and safety, active control • AL 1064 mg q8wk initiated with AL_{NCD} + 1 dose of 30 mg oral aripiprazole (99) • Active control[b] (paliperidone palmitate) (101)	Primary • PANSS total score change from baseline to week 4 (within-treatment group); both AL and PP groups, $P<0.001$ Secondary and exploratory • PANSS total score change from baseline to weeks 4, 9, and 25 (within-treatment group); AL and PP groups $P<0.001$ • PANSS Positive, Negative, and General Psychopathology subscale score[c] changes from baseline to week 25 • CGI-S score[c] change from baseline to week 25 Patient and caregiver perspectives[c] • Burden Assessment Scale total score and change from baseline to week 9 • Q-LES-Q-SF total score at weeks 5, 13, and 25 • Medication Satisfaction Questionnaire scores at weeks 5, 13, and 25
Long-term (52-week) safety and extension[47,86,87] • AL 441 mg q4wk (110) • AL 882 mg q4wk (368) Extension • AL 441 mg q4wk (65) • AL 882 mg q4wk (226)	Exploratory (post hoc analyses) • 52-week safety study (change from baseline to week 64) • PANSS total score; $P<0.0001$ • CGI-S score; $P<0.0001$ • Time to remission (baseline to week 64)[c] • Combined studies, stabilized patients (change from week 12 to week 124) • PANSS total score; $P<0.0001$ • PANSS Positive and Negative subscale scores[c] • CGI-S score[c] • Patient perspectives (change from baseline to week 124) ○ SF-36v2 MCS ($P<0.05$) and PCS
Open-label switch[73] • AL[d] (50[e])	Primary • CGI-S score change from baseline to month 6; $P<0.01$ Secondary • BPRS change from baseline to month 6; $P=0.01$

Notes: [a]Response defined as ≥30% improvement from baseline in PANSS total score. [b]The study was not powered to test between-group difference; no between-group comparisons were made. [c]Statistical comparison was not performed. [d]AL 441/661/882 mg q4wk flexibly dosed or AL 882 mg q6wk. [e]Overall N=51. In an analysis of those who switched from paliperidone palmitate, efficacy in 50 patients was reported (1 patient switched from risperidone LAI).

Abbreviations: AL, aripiprazole lauroxil; AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression–Improvement scale; CGI-S, Clinical Global Impression–Severity scale; LAI, long-acting injectable; MCS, mental component summary; PANSS, Positive and Negative Syndrome Scale; PCS, physical component summary; PSP, Personal and Social Performance; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; qxwk, every x weeks; SF-36v2, 36-Item Short Form Survey version 2.

Results from ALPINE supported the efficacy of both the 1-day AL_{NCD} plus 30 mg oral aripiprazole initiation regimen and treatment over 25 weeks with AL 1064 mg administered every 2 months.[69] In ALPINE, treatment with AL was associated with a significant reduction in PANSS total score versus baseline at the week 4 primary endpoint (Figure 8).[69] Significant improvements from baseline in PANSS total score were also observed after transition to outpatient care at the 9- and 25-week key secondary endpoints. Statistically significant reductions from baseline in CGI-S[88] and in PANSS Positive, Negative, and General Psychopathology subscale scores at week 25 were observed with AL treatment.[85] Statistically significant reductions were observed also during active control treatment with paliperidone palmitate;[69,85] the study was not powered to test between-group differences.[69]

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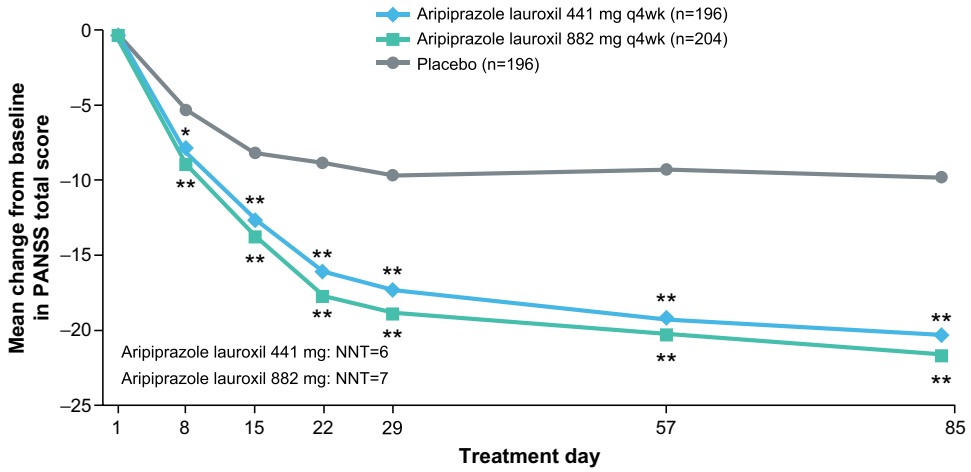

Figure 7 Efficacy results from the phase 3 aripiprazole lauroxil 12-week pivotal study.

Notes: Adapted with permission from Meltzer HY, Risinger R, Nasrallah HA, Du Y, Zummo J, Corey L, Bose A, Stankovic S, Silverman BL, Ehrich EW. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015 Aug;76(8):1085–90. © *Copyright 2015 Physicians Postgraduate Press, Inc.*[67] [a]Change from baseline in PANSS total score during 12 weeks of double-blind treatment with AL 441 mg or 882 mg monthly, initiated using the 21-day regimen, versus placebo for acutely exacerbated schizophrenia (LOCF). NNT versus placebo was calculated based on a ≥30% reduction from baseline PANSS total score at day 85.[79] **P*=0.004, ***P*<0.001 versus placebo.

Abbreviations: AL, aripiprazole lauroxil; LOCF, last observation carried forward; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale; q4wk, every 4 weeks.

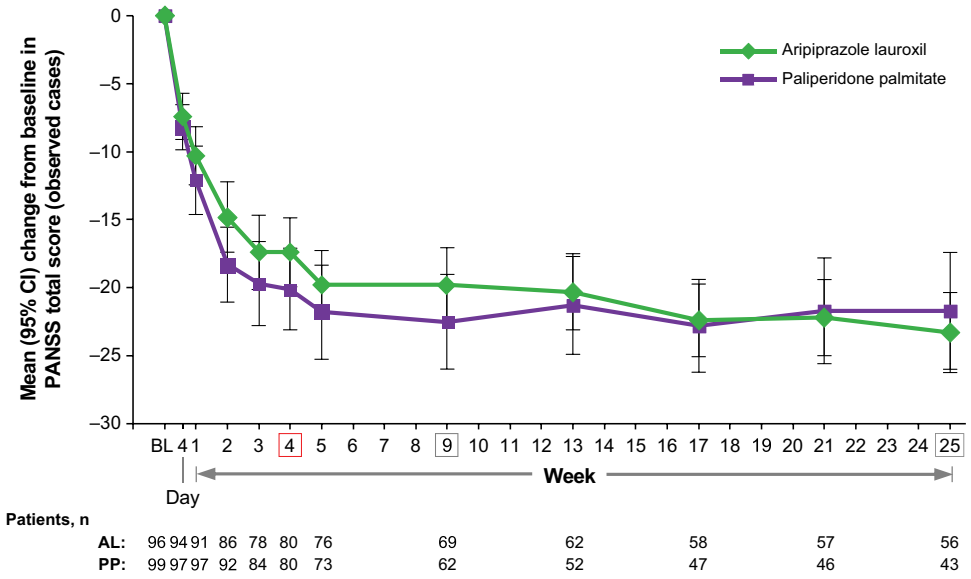

Figure 8 Efficacy results from the phase 3 ALPINE study.

Notes: Adapted with permission from Weiden PJ, Claxton A, Kunovac J, Walling DP, Du Y, Yao B, Yagoda S, Bidollari I, Keane E, Cash E. 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 May 19;81(3):19m13207. © *Copyright 2020 Physicians Postgraduate Press, Inc.*[69] [a]Mean (95% CI) change in PANSS total score from baseline to week 4 (primary endpoint, red box) and weeks 9 and 25 (secondary endpoints, gray boxes) during 25 weeks of double-blind treatment with aripiprazole lauroxil 1064 mg every 2 months, initiated using the 1-day regimen; paliperidone palmitate 156 mg monthly was included as an active control. ALPINE was not powered for between-group comparison with paliperidone palmitate.

Abbreviations: AL, aripiprazole lauroxil; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; BL, baseline; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate.

Durability of Long-Term Aripiprazole Lauroxil Therapy

Longer-term, open-label AL treatment was associated with continued therapeutic efficacy over treatment durations of up to 3.5 years (Figure 9).[47,86] Patients who completed the 12-week pivotal study and continued into the 52-week safety study had sustained improvements in PANSS total and CGI-S scores over 1 year of continuous AL exposure.[86] In a post

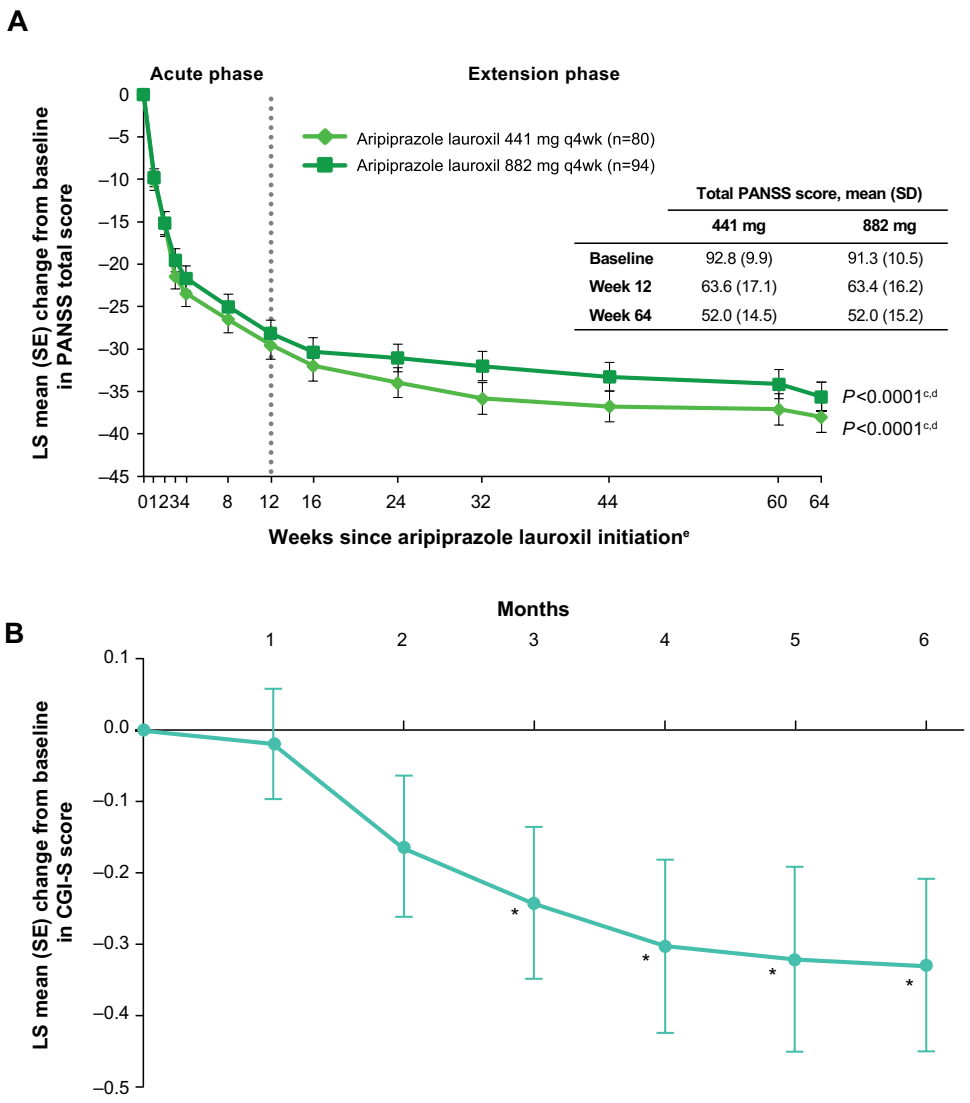

Figure 9 Efficacy results for phase 3, open-label aripiprazole lauroxil studies.[a,b]

Notes: [a]Panel (**A**) Therapeutic durability of AL 441 mg or 882 mg monthly in a post hoc analysis of data from the 12-week pivotal study[67] and a 52-week open-label safety study.[85] Change from baseline in PANSS total score (MMRM) is shown for patients who had at least 1 PANSS/CGI-S assessment after drug administration in the extension study. Adapted with permission from McEvoy JP, Risinger R, Mykhnyak S, Du Y, Liu CC, Stanford AD, Weiden PJ. Durability of Therapeutic Response With Long-Term Aripiprazole Lauroxil Treatment Following Successful Resolution of an Acute Episode of Schizophrenia. *J Clin Psychiatry*. 2017 Sep-Oct;78(8):1103–1109. © *Copyright 2017 Physicians Postgraduate Press, Inc.*[85] [b]Panel (**B**) Change from baseline in CGI-S scores (MMRM) during 6-month open-label treatment with AL 441, 662, or 882 mg q4wk (flexible dosing) or AL 882 mg q6wk in 50 patients switched from paliperidone palmitate (1 patient who switched from risperidone LAI was excluded); mean (SD) CGI-S score at baseline: 3.9 (0.6). Adapted with permission from Miller BJ, Claxton A, Du Y, Weiden PJ, Potkin SG. Switching patients with schizophrenia from paliperidone palmitate to aripiprazole lauroxil: a 6-month, prospective, open-label study. *Schizophr Res*. Feb 7 2019;208:44–48. © *2019 The Authors. Published by Elsevier B.V.* Creative Commons CC-BY-NC-ND license.[73] [c]*P* values reported for change in mean PANSS total score from week 0 to week 64. [d]A separate analysis comparing changes in mean PANSS total score from week 12 (beginning of extension study) to week 64 showed significant reductions in PANSS total score (*P*<0.0001). [e]Indicated weeks denote assessment time points. *$P<0.05$ versus baseline.

Abbreviations: AL, aripiprazole lauroxil; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; CGI-S, Clinical Global Impressions–Severity; LAI, long-acting injectable; LS, least squares; MMRM, mixed-effects model for repeated measurement; PANSS, Positive and Negative Syndrome Scale; qxwk, every x weeks.

hoc analysis of 112 weeks of continuous data (including the 52-week study and long-term open-label extension), symptoms (PANSS total score) and severity of illness (CGI-S) improved over the course of the analysis period. Consistent with findings for oral aripiprazole for schizophrenia,[89] no dose effect between groups was observed (Table 2).[47] In addition, clinically stable patients with schizophrenia (n=51) who initiated AL because of lack of efficacy or tolerability concerns with their previous LAI antipsychotic achieved statistically significant improvement in CGI-S (Figure 9) and Brief Psychiatric Rating Scale[90] scores in the 6 months after the switch.[73]

Exploratory Efficacy and Patient- and Caregiver-Reported Outcomes

In secondary and post hoc analyses, 12-week pivotal study patients administered the AL 441 mg or 882 mg monthly regimen had significantly higher rates of response (≥30% improvement from baseline in PANSS total score) compared with patients administered placebo and significantly greater improvements from baseline versus placebo on PANSS Positive, Negative, and General Psychopathology subscale scores, as well as PANSS 5-factor scores (positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression[91]) at day 85 (Table 2).[82] Treatment with the AL 441 mg or 882 mg monthly regimen was also associated with significant improvements in social functioning, based on PANSS Prosocial Subscale scores, and in amelioration of agitation/hostility with reductions in PANSS excited component and hostility item scores compared with placebo at day 85.[83,84] Functional outcomes were also assessed in the 12-week pivotal study using the Personal and Social Performance (PSP) scale,[92] and significant improvements were observed versus placebo in the PSP total score and disturbing and aggressive behavior domain score at day 85.[83,84]

Treatment with AL had a positive effect on functional and health-related QoL outcomes in additional short- and longer-term assessments (Table 2). In ALPINE, patients reported stable QoL on the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form[93] through the outpatient period (weeks 5, 13, and 25).[85] The majority of ALPINE patients remained satisfied or very satisfied with AL throughout treatment, and their caregivers reported an improvement in burden of care from baseline to weeks 9 and 25.[85] Active control treatment (paliperidone palmitate) also was associated with improvements in patient and caregiver outcomes.[85] Significant improvement in mental health–related QoL was observed over 124 weeks in the combined 52-week and long-term extension studies[87] based on SF-36v2 health Survey[94] mental component summary scores.

Safety and Tolerability

The safety and tolerability profile of AL was consistent with that of the oral aripiprazole formulation in inpatients and outpatients with an acute exacerbation of schizophrenia,[67,69] in clinically stable patients with schizophrenia initiating AL after a switch from another LAI,[73] and during long-term continuous exposure[47] (Table 3).[47,67,69,73] The prodrug technology would not be likely to influence the safety or tolerability of AL. Lauric acid (the fatty acid tail) is a major component of coconut and palm kernel oils,[95] and the linker molecule is hydrolyzed to a normal metabolic intermediary in fatty acid metabolism.[52,96] Indeed, no new or unexpected safety findings emerged during long-term AL safety studies, either overall or with respect to AEs of clinical interest that may occur during atypical antipsychotic treatment.[46,47] Among patients switching from oral antipsychotics, the safety profile of AL did not appear to be influenced by previous treatment.[97]

Table 3 Summary of Key Safety Findings From Aripiprazole Lauroxil Phase 3 and 4 Studies

Endpoint	12-Week Pivotal Study[67]			ALPINE Study[69]				Combined Long-term OL Safety Studies[a,47]		OL Switching Study[73]
	AL 441 mg q4wk[b] (n=207)	AL 882 mg q4wk[b] (n=208)	Placebo (n=207)	AL 1064 mg q8wk, 1-day Initiation Regimen (n=99)		Paliperidone Palmitate[c] (n=101)		AL 441 mg q4wk (n=110)	AL 882 mg q4wk (n=368)	AL 441, 662, or 882 mg q4wk or 882 mg q6wk[d] (N=51)
				Weeks 0–4	Weeks 0–25	Weeks 0–4	Weeks 0–25			
SAEs, n (%)	3 (1.4)	4 (1.9)	4 (1.9)	2 (2.0)	8 (8.1)	3 (3.0)	7 (6.9)	0	18 (4.9)	5 (9.8)
SAEs leading to death, n (%)	0	0	1 (0)[e]	0	0	0	1 (1.0)[f]	0	2 (0.5)	0
AEs leading to discontinuation, n (%)	14 (6.8)	6 (2.9)	36 (17.4)	4 (4.0)	10 (10.1)	8 (7.9)	11 (10.9)	3 (2.7)	31 (8.4)	2 (3.9)
Any AE, n (%)	122 (58.9)	119 (57.2)	129 (62.3)	57 (57.6)	69 (69.7)	60 (59.4)	72 (71.3)	58 (52.7)	217 (59.0)	21 (41.2)

(*Continued*)

Table 3 (Continued).

Endpoint	12-Week Pivotal Study[67]			ALPINE Study[69]				Combined Long-term OL Safety Studies[a,47]		OL Switching Study[73]
	AL 441 mg q4wk[b] (n=207)	AL 882 mg q4wk[b] (n=208)	Placebo (n=207)	AL 1064 mg q8wk, 1-day Initiation Regimen (n=99)		Paliperidone Palmitate[c] (n=101)		AL 441 mg q4wk (n=110)	AL 882 mg q4wk (n=368)	AL 441, 662, or 882 mg q4wk or 882 mg q6wk[d] (N=51)
				Weeks 0–4	Weeks 0–25	Weeks 0–4	Weeks 0–25			
AEs occurring in ≥5%[g] of patients, %										
Akathisia	11.6	11.5	4.3	9.1	9.1	10.9	10.9	4.5	4.9	2.0
Anxiety	2.9	5.3	6.8	—	—	—	—	3.6	6.3	5.9
Diarrhea	2.4	2.4	3.4	—	—	—	—	5.5	3.0	3.9
Dystonia	—	—	—	4.0	4.0	6.9	7.9	—	—	—
Headache	8.2	8.7	8.2	6.1	8.1	6.9	7.9	10.9	5.4	—
Injection site pain	3.4	4.8	1.9	16.2	17.2	24.8	24.8	0.9	4.9	—
Insomnia	9.7	12.0	11.6	—	—	—	—	7.3	14.4	3.9
Nasopharyngitis	—	—	—	—	—	—	—	7.3	4.6	—
Psychotic disorder	—	—	—	—	—	—	—	—	—	7.8
Schizophrenia worsening/ exacerbation	5.8	2.4	10.6	1.0	5.1	2.0	2.0	5.5	4.6	—
Somnolence	—	—	—	4.0	4.0	6.9	6.9	—	—	—
Suicidal ideation	—	—	—	—	—	—	—	—	—	5.9
Weight increased	2.9	2.4	0.5	2.0	9.1	11.9	16.8	9.1	5.2	3.9

Notes: [a]From the analysis of combined 52-week safety study and long-term extension data reported by Lauriello et al in 2020[47]; the long-term extension data are not reported separately elsewhere. Patients entered the 52-week study after completing the 12-week pivotal study or entered as stable outpatients receiving an oral antipsychotic. [b]AL initiated with the 21-day oral aripiprazole regimen. [c]PP was included as an active control of known efficacy; the ALPINE study was not designed to compare the 2 treatment groups. [d]Administration of 21-day oral aripiprazole supplementation with the initial dose of AL was at the discretion of the investigator.[73] [e]One patient in the placebo group died as a result of homicide;[67] percentage rounded to 0. [f]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. [g]Publications did not include values for all AEs listed here. Reported AEs that did not meet the threshold percentage in published tables (≥2%,[47,67] ≥3%,[73] or ≥5%[69]) are marked "—".

Abbreviations: AE, adverse event; AL, aripiprazole lauroxil; DB, double-blind; NCD, NanoCrystal Dispersion; OL, open-label; qxwk, every x weeks; SAE, serious adverse event.

In the 12-week pivotal study, 14/207 (6.8%) patients assigned to AL 441 mg every 4 weeks and 6/208 (2.9%) patients assigned to AL 882 mg every 4 weeks discontinued treatment because of AEs, compared with 36/207 (17.4%) patients assigned to placebo.[67] The higher rate in the placebo arm was attributable primarily to exacerbations of schizophrenia.[67] Rates of discontinuation due to AEs during up to 180 weeks of continuous open-label treatment were 2.7% (3/110) and 8.4% (31/368) for the AL 441 mg and 882 mg monthly regimens, respectively.[47] The most common AEs leading to discontinuation in the combined long-term studies were exacerbation/worsening of schizophrenia (14/368 [2.9%]), exacerbation of psychotic disorder (2/368 [0.4%]), and akathisia (2/368 [0.4%]).[47] Among patients assigned to AL 1064 mg every 8 weeks in ALPINE, 10/99 (10.1%) discontinued because of AEs, the most common of which were exacerbation/worsening of schizophrenia (5 [5.1%]), injection site pain (2 [2.0%]; 1 associated with placebo injection), and psychotic disorders (2 [2.0%]).[69]

Akathisia was the only AE reported by greater than 5% of and at least twice the rate observed with placebo in patients administered AL 441 mg every 4 weeks or AL 882 mg every 4 weeks in the 12-week pivotal study (Table 3).[67] As

observed with oral aripiprazole,[50] akathisia was generally reported early in AL treatment; first occurrences of akathisia were reported mostly within 4 weeks of AL initiation in the 12-week pivotal study and in ALPINE,[67,69] and higher rates were not observed with longer-term exposure.[47,69] Few patients discontinued AL treatment because of akathisia (2/478 during up to 180 weeks of open-label AL treatment; 0/99 AL-treated patients in the 25-week ALPINE study [2/101 paliperidone palmitate–treated patients in ALPINE]).[47,69] Other drug-induced movement disorder AEs (dystonia, dyskinesia, Parkinson-like events) were reported in 9 (9%) patients in ALPINE (paliperidone palmitate: 12%); of those 9 AL-treated patients, 8 (8%) reported the AEs during the first 4 weeks of treatment.[98] No drug-induced movement disorder AEs were reported by >2% of patients in the 12-week pivotal study.[67] Among 478 patients who received up to 1 year of open-label AL exposure, 18 (3.8%) patients reported AEs of akathisia, and 45 (9.4%) patients reported any drug-induced movement disorder AEs (dyskinesia, dystonia, Parkinson-like events, restlessness, or akathisia), including those who reported akathisia.[46]

With extended antipsychotic exposure, the potential for clinically significant weight gain is a particular concern.[99–104] Two to 3% of patients treated with AL in the 12-week pivotal study and 9% of those who received AL in the 25-week ALPINE study reported weight gain as an AE (Table 3).[67,69] Figure 10 presents change in weight over time in ALPINE study patients. In an analysis of metabolic and endocrine profiles of patients enrolled in the 52-week safety study, AL (441 mg or 882 mg every 4 weeks) was associated with mean (SD) weight change of +0.8 (5.9) kg (body mass index: +0.3 [2.0]); 18.4% of patients had a ≥7% increase in body weight from baseline at any assessment.[46] Among patients with up to 3.5 years of AL treatment in the combined 52-week safety and long-term extension studies, 6.1% reported an AE of weight gain.[47] Patients in those combined long-term studies gained a mean of 1.2 (6.6) kg from baseline to last assessment; no discontinuations because of weight gain were reported.[47]

No clinically meaningful changes were observed for any glycemic-control or lipid parameters in the 52-week safety study.[46] Consistent with the known effects of aripiprazole,[105] little change in plasma prolactin concentrations was observed with AL treatment in male and female patients in ALPINE (Figure 11).[98] Mean (SD) prolactin concentrations decreased from baseline to the last assessment in the 52-week study (males: −8.7 [14.7] ng/mL; females: −14.9 [43.4] ng/mL)[46] and in

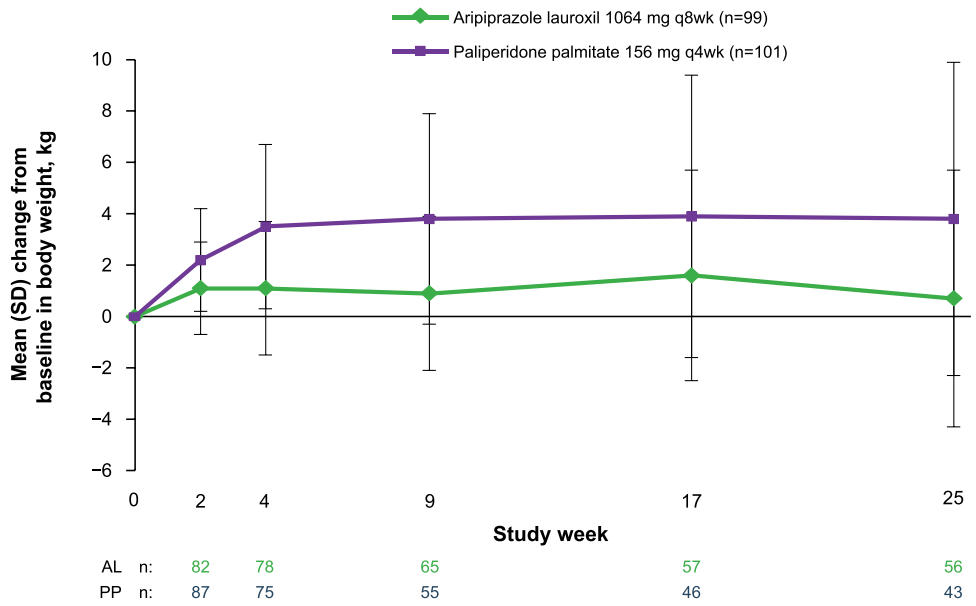

Figure 10 Weight change in ALPINE.[a]

Notes: Reprinted with permission from 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 Feb 28;85(1):23m15095. © *Copyright 2024 Physicians Postgraduate Press, Inc.*[98]

[a]Weight change during 25 weeks of double-blind treatment with aripiprazole lauroxil 1064 mg every 2 months, initiated using the 1-day regimen; paliperidone palmitate 156 mg monthly was included as an active control. ALPINE was not powered for between-group comparison with paliperidone palmitate.

Abbreviations: AL, aripiprazole lauroxil; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; PP, paliperidone palmitate; qxwk, every x weeks.

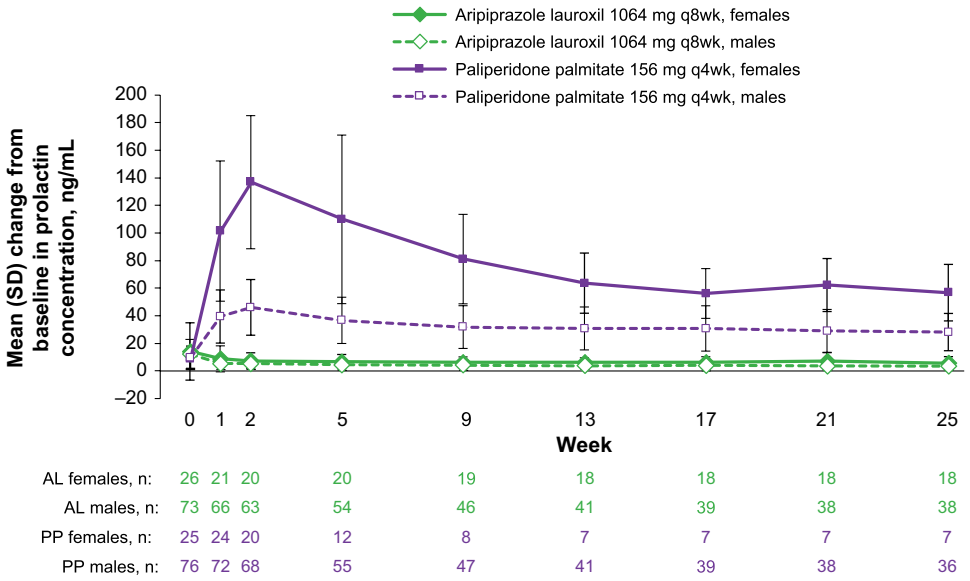

Figure 11 Change in plasma prolactin concentrations in ALPINE.[a]

Notes: Reprinted with permission from 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 Feb 28;85(1):23m15095. © *Copyright 2024 Physicians Postgraduate Press, Inc.*[98]

[a]Change in plasma prolactin concentrations during 25 weeks of double-blind treatment with aripiprazole lauroxil 1064 mg every 2 months, initiated using the 1-day regimen; paliperidone palmitate 156 mg monthly was included as an active control. ALPINE was not powered for between-group comparison with paliperidone palmitate.

Abbreviations: AL, aripiprazole lauroxil; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; PP, paliperidone palmitate; qxwk, every x weeks.

the combined long-term studies (males: −6.7 [16.5] ng/mL; females: −16.5 [45.2] ng/mL).[47] In a post hoc analysis of a 6-month open-label switching study where 50 patients were switched from prior treatment with paliperidone palmitate to AL, mean (SD) serum prolactin reductions of 23.0 (11.7) ng/mL for males and 49.8 (54.1) ng/mL for females were observed in patients who had data after 6 months of AL treatment (n=32); proportions of patients with elevated prolactin levels fell from 90.0% at baseline to 6.3% at month 6.[106]

Incidence of injection site pain was generally low in phase 3 or phase 4 AL clinical studies, with fewer than 5% of patients reporting AEs of injection site pain in the 12-week pivotal study, in patients switched from other LAIs, and in the combined long-term studies (Table 3).[47,67,73] Injection site pain was reported in 17.2% of AL-treated patients in ALPINE, which included an additional injection (AL_{NCD}) at initiation and placebo injections to maintain the blind (ALPINE patients received twice as many intramuscular injections as would be administered in clinical practice, including both deltoid and gluteal injections on the first and eighth days of treatment).[69] Injection site pain occurred most commonly early in treatment, associated with the AL_{NCD} and/or the first AL injection.[67,69,107] Few AEs of injection site pain were reported after week 4.[67,69]

Overall, the long-term safety and tolerability profile of AL is consistent with that of oral aripiprazole and with short-term observations from the 12-week pivotal study.[46,47] During up to 3.5 years of continuous open-label treatment with AL 441 mg or 882 mg monthly regimens in the 52-week safety study and long-term extension, no clinically meaningful findings in physical examinations, vital signs, laboratory tests, or electrocardiography values were observed.[46,47] Further, primary and post hoc analyses from the ALPINE study indicated that the initiation of AL using a 1-day initiation regimen (AL_{NCD} plus a single 30 mg oral dose of aripiprazole) was not associated with the emergence of additional safety risks compared with the known risks of oral aripiprazole.[69,98]

Real-World Outcomes and Costs

Real-world data on the use of AL in clinical practice are increasingly available, and healthcare utilization and costs associated with AL have now been examined.[108] In a retrospective analysis of Medicaid claims data (April 2015 to

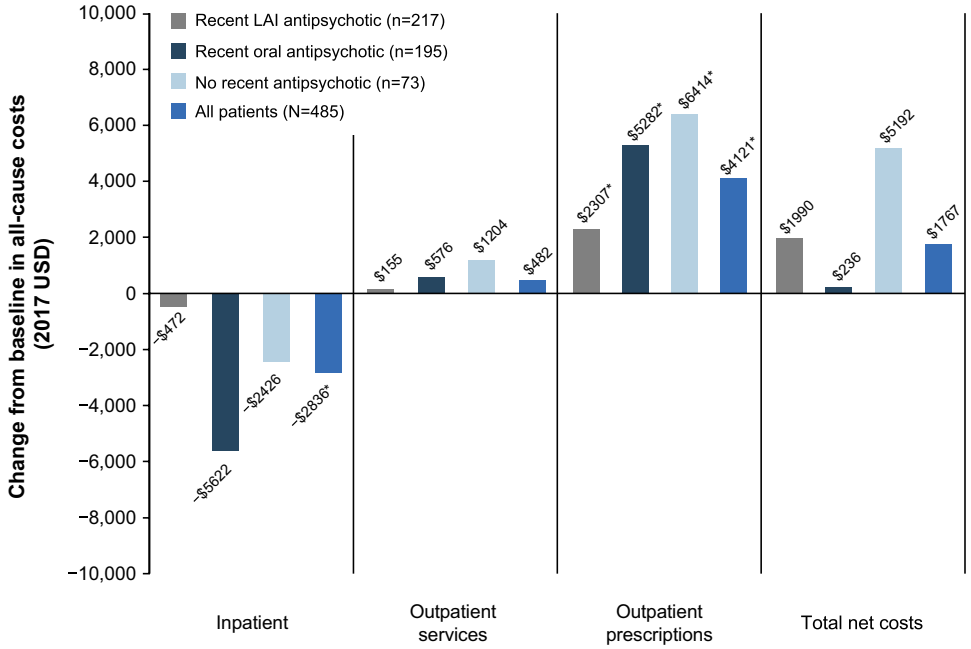

Figure 12 Real-world all-cause costs during treatment with aripiprazole lauroxil.[a]
Notes: Reprinted with permission from Lauriello J, Weiden PJ, Gleeson CD, Shah A, Boulanger L, Jariwala-Parikh K, Hedgeman E, O'Sullivan AK. Real-World Outcomes and Costs Following 6 Months of Treatment with the Long-Acting Injectable (LAI) Aripiprazole Lauroxil for the Treatment of Schizophrenia. *CNS Drugs*. 2021 Oct;35(10):1123–1135. © *The Author(s) 2021*. Creative Commons Attribution-NonCommercial 4.0 International License.[108] [a]Mean differences in all-cause healthcare costs were calculated for the 6-month period before (baseline) versus after (follow-up) initiation of treatment with aripiprazole lauroxil. *$P<0.05$ versus baseline period.
Abbreviations: LAI, long-acting injectable antipsychotic; USD, US dollars.

December 2017) for patients with a diagnosis code for schizophrenia, there was no significant change in overall all-cause total costs from the 6-month period before first claim for AL (baseline) to the 6-month follow-up period (Figure 12).[108] A significant increase in pharmacy costs from baseline to follow-up was offset by reductions in inpatient utilization and costs and mental health–related emergency department utilization. Mean number of all-cause inpatient admissions per patient decreased significantly between the baseline and follow-up periods.[108] The greatest reductions in inpatient costs, as well as in all-cause and mental health–related inpatient admissions and emergency department visits, were observed among patients who had been prescribed an oral antipsychotic (rather than an LAI or no antipsychotic) before starting AL.[108] Reductions in inpatient and mental health–related emergency department utilization are consistent with the evidence that LAIs are effective in preventing psychotic relapse and hospitalization.[11–14]

Conclusions

AL was developed using a prodrug technology for slow dissolution to provide an LAI antipsychotic with several dosage strengths (lower, intermediate, and higher, equivalent to oral aripiprazole doses of 10, 15, and 20 mg or higher per day, respectively) for use over a range of dosing intervals (4, 6, or 8 weeks) to meet individualized patient medical and quality-of-care needs. The placebo-controlled 12-week pivotal study, the 25-week active-controlled ALPINE study, and the additional open-label studies[67,69,82,85] provide safety and efficacy data on the use of AL for acutely exacerbated schizophrenia in adults, and as an ongoing maintenance treatment during inpatient-to-outpatient transitions, after a switch from another LAI antipsychotic, and for long-term maintenance treatment. Furthermore, based on the ALPINE study results, AL can be initiated in 1 day (AL_{NCD} + 30 mg oral aripiprazole)[70] without any oral supplementation beyond day 1 and this first every-2-month LAI formulation of aripiprazole provides effective maintenance treatment over time.

Abbreviations

AE, adverse event; AL, aripiprazole lauroxil; AL_{NCD}, AL NanoCrystal Dispersion formulation; ALPINE, Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness; CGI-I, Clinical Global Impression–Improvement; CGI-S,

Clinical Global Impression–Severity; FDA, US Food and Drug Administration; LAI, long-acting injectable; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; QoL, quality of life.

Data Sharing Statement

The data used in the preparation of this manuscript are proprietary to Alkermes, Inc. Alkermes, Inc., is committed to public sharing of data in accordance with applicable regulations and laws, and requests can be submitted to the corresponding author.

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MD, CH, JAM, BR, and DM are or were employees of Alkermes, Inc., and may own stock/options in the company.

ARH has served on advisory boards for Acadia, Alkermes, Biogen, BioXcel, Intra-Cellular, and Teva and on speaker's bureaus for Acadia, Alkermes, Axsome, BioXcel, Bristol Myers Squibb, Intra-Cellular, Neurocrine, and Teva.

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PJW is a former employee of Alkermes and has been a consultant for Alkermes, Lyndra, MapLight, and Teva.

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