Pharmacokinetics, Safety, and Tolerability of a 2-Month Dose Interval Regimen of the Long-Acting Injectable Antipsychotic Aripiprazole Lauroxil: Results From a 44-Week Phase I Study

Peter J. Weiden^{1,4} · Yangchun Du¹ · Lisa von Moltke¹ · Angela Wehr¹ · Marjie Hard^{1,5} · Morteza Marandi² · David P. Walling³

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Abstract

Background Aripiprazole lauroxil (AL) is a long-acting injectable antipsychotic approved for treatment of schizophrenia in adults. Approved AL doses and dosing regimens include 441 mg monthly, 662 mg monthly, and 882 mg monthly or every 6 weeks (q6wk), as well as the most recently approved dose, 1064 mg, administered every 2 months.

Objective Pharmacokinetics, safety, and tolerability of an AL regimen with a dose interval of every 2 months (1064 mg) were compared with two other regimens available as monthly and q6wk options.

Methods This study evaluated pharmacokinetics of AL given at a higher dosage strength (1064 mg) and at a longer dose interval (every 8 weeks [q8wk]) than previously studied. Patients with schizophrenia or schizoaffective disorder entering this 44-week, phase I, open-label, multicenter study had no recent exposure to aripiprazole and were maintained on other oral antipsychotics throughout the study. Patients were randomized to one of three AL dose regimens for 24 weeks (four 1064-mg injections [q8wk], five 882-mg injections [q6wk], or seven 441-mg injections [q4wk], with the last AL exposure at week 24). Oral aripiprazole was prohibited. Patients were followed for an additional 20 weeks to assess terminal aripiprazole plasma concentrations and ongoing safety. Plasma concentration samples were obtained at regular intervals to provide pharmacokinetic data for the duration of AL exposure and to measure persistence of plasma aripiprazole concentrations after AL discontinuation.

Results Eligible patients received AL 1064 mg q8wk ($n=35$), 882 mg q6wk ($n=34$), or 441 mg q4wk ($n=35$). Overall, 103/104 (99.0%) patients were taking concomitant non-aripiprazole oral antipsychotic medications during the study. All three AL dose regimens provided continuous exposure to aripiprazole. Mean aripiprazole concentrations from the 1064-mg q8wk regimen were comparable to the 882-mg q6wk regimen and higher than the 441-mg q4wk regimen. Overall incidence by group of any adverse events (AEs) throughout the study was 68.6% (1064 mg q8wk), 50.0% (882 mg q6wk), and 65.7% (441 mg q4wk). The most common AE across regimens was injection-site pain (range 8.6%–11.4%). Serious AEs were reported by eight patients (all but one [increased psychosis in one patient, 441-mg q4wk group] considered unrelated to study drug). Discontinuations due to AEs were reported for 2.9%, 11.8%, and 5.7% of patients receiving the 8-, 6-, and 4-week regimens, respectively. AEs of akathisia, dyskinesia, and dystonia occurred in 2.9%, 8.6%, and 5.7% of patients in the 1064-mg q8wk group, 8.8%, 0%, and 2.9% in the 882-mg q6wk group, and 8.6%, 0%, and 0% in the 441-mg q4wk group, respectively.

Study results have been presented as a poster at the American Psychiatric Association Annual Meeting, May 20–24, 2017, San Diego, CA, USA, and the American Society of Clinical Psychopharmacology Annual Meeting, May 29–June 2, 2017, Miami, FL, USA. Some pharmacokinetics results from this study were previously published in Hard ML, et al. 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):617–24.

Extended author information available on the last page of the article

Conclusions AL 1064 mg q8wk provided continuous exposure to aripiprazole throughout the 8-week dosing interval and had a safety profile consistent with the 4- and 6-week regimens. These findings were used to support FDA approval of the 1064-mg dose administered every 2 months.

Registration Clinicaltrials.gov: NCT02320032

Key Points

It is clinically important to have longer dose interval options for patients treated with long-acting injectable antipsychotics.

This study evaluated the pharmacokinetics and safety of a higher dosage strength of aripiprazole lauroxil (AL; 1064 mg) for suitability to extend the longest available dose interval of AL to 2 months.

The results of this study demonstrated that the 1064-mg dosage strength given every 2 months had plasma concentrations and a safety profile comparable to those of 441 mg monthly and 882 mg every 6 weeks.

1 Introduction

Long-acting injectable (LAI) atypical antipsychotics are an alternative to daily oral antipsychotics for treating schizophrenia [1, 2]. While long-acting treatment does not guarantee adherence, the nature of the fixed treatment schedule for injections given in clinical settings allows real-time assessment of a patient's ongoing adherence status and is often recommended for patients who struggle with taking daily oral antipsychotic medication. Nonetheless, long-acting regimens have their own set of challenges, including the need to provide staffing and logistical support to be able to administer the injection at a scheduled visit. Therefore, in some settings, the injection interval can be a factor that is relevant to the feasibility of administering LAIs. In addition, the injection interval may be a major determinant of LAI acceptability; for example, when the patient or family lives far away from the treatment facility. Taken together, staffing constraints, lengthy travel times, and patient preference can present 'real world' challenges that limit the use of LAIs for patients who otherwise might be excellent LAI candidates. Some of these constraints may be mitigated by having LAIs with longer dose intervals. Given the need to maintain therapeutic plasma levels for the entire interval between injections, the pharmacokinetics of some long-acting options may limit the maximal length of the dosing interval.

Aripiprazole lauroxil (AL) is a prodrug developed to provide sustained release of aripiprazole into the plasma circulation [3]. The efficacy of AL was demonstrated in a phase

III, 12-week, double-blind study comparing two dose regimens of AL (441 and 882 mg) given every 4 weeks (q4wk) with placebo for the treatment of acute symptoms of schizophrenia [4]. In that study, both dose regimens of AL were efficacious and well tolerated. In addition to the clinical data, pharmacokinetic modeling data for the 882-mg dose showed that steady-state plasma AL levels supported the feasibility of extending the dose interval of 882 mg to every 6 weeks (q6wk) [5]. Therefore, clinicians have the option of choosing the 882-mg dose for either a 4- or 6-week interval.

Based on an initial pharmacokinetic model [5], it was hypothesized that increasing the AL dosage strength to 1064 mg would achieve and sustain adequate aripiprazole plasma concentrations to extend the longest dose interval from 6 weeks to 2 months [3]. The phase I study described here was used to support the approval of the 1064-mg every 2 months AL regimen, which is the most recently approved AL dose regimen. Because the efficacy of the other AL regimens is established, the primary objective was to confirm that this higher dose strength would have a pharmacokinetic profile to support a 2-month interval with safety comparable to that of the other AL regimens. Therefore, this comprehensive study evaluated three AL dose regimens with different dosage strengths and dose intervals (1064 mg every 8 weeks [q8wk], 882 mg q6wk, and 441 mg q4wk). Another aspect of the safety and pharmacokinetic evaluation was to include a post-treatment evaluation period of 20 weeks, which is considerably longer than in most pharmacokinetics safety studies. Some pharmacokinetics results from this study were reported previously [6]; we provide additional analyses of pharmacokinetic data as well as full safety and tolerability results for each AL dose/dosing regimen.

This study also included a fourth treatment arm of a different formulation of AL 1064 mg known as 1064 mg (S). The particle size of the 1064 mg (S) formulation was larger and had a smaller surface-area-to-mass ratio compared with that of the commercially available AL formulations. The 1064 mg (S) formulation was included in the study in case the 1064-mg formulation did not meet the pharmacokinetic targets for a 2-month dose interval because, in theory, the larger particle size of 1064 mg (S) might decrease the rate of dissolution of the drug particles. Because the 1064-mg formulation met the criteria for a 2-month dose interval option, and the 1064 mg (S) did not offer any advantage over the 1064-mg formulation, its development was discontinued after study completion. Therefore, the 1064 mg (S) results are not included in this report.

2 Methods

This was a 44-week, phase I, open-label study to evaluate the pharmacokinetics, safety, and tolerability of different dose/dosing interval regimens of AL in patients with stable schizophrenia or schizoaffective disorder, and included a 24-week AL exposure period as well as a 20-week safety and pharmacokinetic post-treatment follow-up period. The study (Clinicaltrials.gov identifier: NCT02320032) was conducted from December 2014 to April 2016 in 15 centers in the United States in accordance with the ethical principles described in the Declaration of Helsinki and Good Clinical Practice Guidelines. Each eligible, consenting study participant provided written informed consent before study entry.

Because the primary outcomes of interest were the course of plasma aripiprazole concentrations and safety outcomes, patients continued on non-aripiprazole oral antipsychotics throughout the entire 44-week study period.

2.1 Study Design

After an initial 30-day screening period, the 44-week open-label study comprised a 24-week treatment period and a 20-week post-treatment follow-up period (Fig. 1). Eligible patients were randomized to one of four dosing regimens (1:1:1:1) using a randomization schedule developed by an independent biostatistician and applied through an Interactive Web Response System: AL 1064 mg q8wk, AL 1064 mg (S) formulation (the alternative AL formulation) q8wk, AL 882 mg q6wk, or AL 441 mg q4wk. As discussed above, the 1064 mg (S) formulation was not developed further, and the rest of the article will focus on the remaining three dose regimens. Of an initial study sample of 140 patients, 35 were randomized to the (S) formulation, leaving 105 patients randomized to the remaining three regimens. Hereafter, the methods and results reported focus only on the three AL regimens of interest ($n = 105$).

AL was administered in all regimens via intramuscular (IM) gluteal injections by study center personnel. Patients received their assigned open-label dose at different scheduled intervals (Fig. 1), corresponding to a total of four, five, or seven injections of 1064-, 882-, or 441-mg doses of AL, respectively, over 24 weeks. Study visits included safety assessments and plasma pharmacokinetics sampling and were conducted every 2 weeks throughout the 24 weeks of active AL exposure. The last dose was given at the week 24 visit (day 169) for all three AL regimens. Patients continued to be followed with additional safety and plasma pharmacokinetics sampling visits for another 20 weeks until the end of the follow-up period (Fig. 1).

Oral aripiprazole was prohibited for the duration of this study (except for two 5-mg test doses given during screening to assess tolerability in patients without prior aripiprazole exposure). Patients who were stable on any other oral antipsychotic treatment at screening were permitted to continue their medication for the duration of the study.

2.2 Patients

Eligible patients were adults between 18 and 65 years of age with a primary diagnosis of schizophrenia or schizoaffective disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [7], and were clinically stable at screening (defined as no psychiatric hospitalization for at least 3 months and a Clinical Global Improvement–Severity Subscale [CGI-S] score ≤ 3) [8]. Patients should also have been maintained on an antipsychotic medication regimen (apart from those mentioned in the exclusion criteria) for at least 2 months before screening.

Exclusion criteria included having a primary diagnosis other than schizophrenia or schizoaffective disorder, a history of intolerance to any form of aripiprazole, or any LAI exposure within 3 months before screening.

2.3 Concomitant Medications

Patients with ongoing or recent exposure to aripiprazole were excluded, as defined by exposure to any long-acting aripiprazole within 6 months of screening or oral aripiprazole within 28 days of randomization. Patients were also excluded if they had any known factor that would cause significant alterations in aripiprazole metabolism or plasma concentrations of aripiprazole (e.g., patients receiving potent oral inhibitors of the cytochrome P450 isoenzyme CYP2D6, such as fluoxetine, within 30 days before screening were excluded).

AL can be initiated with 21 days of oral aripiprazole. However, because of the nature of the phase I pharmacokinetics analysis, no initiation regimen was given. Almost all patients entering this study were maintained on a stable dose of a first-line (non-clozapine) oral antipsychotic that was continued throughout the 24 weeks of AL exposure and 20-week follow-up pharmacokinetics safety period.

2.4 Pharmacokinetics

Pharmacokinetic assessments were carried out as described previously [6]. Briefly, a total of up to 48 plasma samples were collected throughout the 44 weeks to measure plasma concentrations of aripiprazole over time using a validated analytical method.

Fig. 1 Study design. Arrows denote time of dosage. Breaks in the horizontal bars depict the three different dose intervals for the dose/dose interval groups. The double-line break on the right-hand side of the x-axis depicts the 20-week follow-up period after the last dose (not drawn to scale). In-clinic visits occurred approximately every 2 weeks for all patients (not shown). Patient screening period is not

shown here. It is important to note that, unlike in clinical treatment, 21-day oral aripiprazole lead-in treatment was not administered in this study. *Injection volume for indicated doses: 1064 mg q8wk, 3.9 mL; 882 mg q6wk, 3.2 mL; 441 mg q4wk, 1.6 mL. AL aripiprazole lauroxil, q4wk every 4 weeks, q6wk every 6 weeks, q8wk every 8 weeks, wk week

2.5 Safety

Key safety assessments included adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, and injection-site reactions (ISRs) at each study visit. Extrapyramidal symptoms (EPS), here broadly defined to encompass akathisia, dyskinesia, dystonia, and Parkinson-like events, were assessed as AEs. In addition, EPS were evaluated using Extrapyramidal Symptom Rating Scale (ESRS) scores ≥ 2 for parkinsonism, akathisia, dystonia, or dyskinesia at any postbaseline visit [9].

Because the dose and volume associated with the AL 1064-mg regimen are higher than those associated with the other dosing regimens, ISRs were carefully monitored throughout the study. All patients, regardless of injection interval, were assessed for ISRs every 2 weeks. Patients who completed the study received 13 ISR assessments over the 24 weeks of AL treatment and an additional 10 ISR assessments in the 20-week follow-up period.

2.6 Statistical Analysis

The pharmacokinetics population included all patients who received one or more dose of study drug and had at least one measurable concentration of aripiprazole. Pharmacokinetics parameters were calculated using noncompartmental techniques and summarized with descriptive statistics [6]. Calculated pharmacokinetics parameters reported here included area under the plasma drug concentration–time curve over the dosing interval (AUC_{τ}), AUC_{τ} normalized to dose (AUC_{τ}/D),

AUC from time zero until the last measurable plasma drug concentration time point (AUC_{last}), average concentration (C_{avg}), maximum concentration (C_{max}), time to C_{max} (t_{max}), and half-life ($t_{1/2}$). Additional pharmacokinetics results from this study have been reported previously [6]. The safety population included all randomized patients who received one or more dose of AL. Summary statistics were calculated for safety parameters, including mean, SD, median, minimum, and maximum values for continuous variables, and number and percentage of patients in each category for categorical variables.

Dose proportionality of aripiprazole was assessed using AUC_{last} and C_{max} over the studied dose range using the following power model: $\log(\text{pharmacokinetics parameter}) = \mu + \beta \times \log(\text{dose})$, where ‘ μ ’ was the intercept and ‘ β ’ was the slope. Estimates of slope and intercept with respective SEs and associated 90% CIs were calculated.

3 Results

3.1 Patient Disposition

The population in the analysis presented here included 104 patients who received at least one dose of the currently approved formulations of AL (1064 mg q8wk [$n=35$], 882 mg q6wk [$n=34$], and 441 mg q4wk [$n=35$]); one patient randomized to 882 mg q6wk did not receive study drug (Fig. 2). For the 1064-mg q8wk group, 29 (82.9%) received their complete course of four injections, compared with 24 (70.6%) in the 882-mg q6wk group completing five

injections and 29 (82.9%) in the 441-mg q4wk group completing seven injections. In total, 73.1% (76/104) of patients completed the study (i.e., received all of the injections associated with their dose/dosing interval assignment and completed the follow-up visit at study end).

Among the 28 (26.9%) patients in total who discontinued the study prematurely, the most common reasons by treatment arm were patient withdrawal of consent (11.4%) in the 1064-mg q8wk group and loss to follow-up in the 882-mg q6wk and 441-mg q4wk groups (17.6% and 8.6%, respectively).

3.2 Baseline Characteristics and Concomitant Medications

Patients entering this study were predominantly men (71.2%); mean age was 44.3 years (Table 1). Mean Clinical Global Impressions of Severity score was just under 3 (mildly ill) at study entry for all groups. Almost all patients (103/104 [99.0%]) were taking concomitant oral antipsychotic medications. As shown in Table 1, concomitant antipsychotics were prescribed at doses consistent with prescribing patterns in the United States, with risperidone being more frequent and at doses representative of outpatient maintenance treatment of schizophrenia.

3.3 Pharmacokinetics

Analysis of plasma aripiprazole concentration over time showed that all treatment regimens provided continuous exposure to aripiprazole; mean aripiprazole concentrations with 1064 mg q8wk were comparable to those with 882 mg q6wk and were higher than those with 441 mg q4wk for the

entire dosing interval (Fig. 3). During the 20-week follow-up period after the last injection of AL, plasma aripiprazole levels declined relatively slowly (Fig. 3).

A summary of key pharmacokinetics parameters for aripiprazole after the first dose and the last dose of AL is presented in Table 2. After the first injection, the exposure to aripiprazole, based on C_{max} and AUC, increased with increasing dose. A similar dose-related increase was noted after the last dose in AUC but was less apparent in C_{max} . On average, accumulation ratios for aripiprazole (AUC_{τ} [last dose]/ AUC_{τ} [first dose]) were 2.0, 2.6, and 9.7 for the 1064-mg q8wk, 882-mg q6wk, and 441-mg q4wk groups, respectively. Mean C_{avg} after the final dose was higher with AL 1064 mg q8wk (140.7 ng/mL) than with 882 mg q6wk (131.1 ng/mL) and 441 mg q4wk (125.8 ng/mL; Table 2). In the power model, the 90% confidence intervals (CIs) for the estimates of slope included 1, and dose-adjusted normalized AUC_{last} and C_{max} values across the doses overlapped, suggesting dose linearity in the pharmacokinetics parameters (Table 3). Furthermore, dose-related increases were observed for AUC_{τ} following the last dose (Fig. 4a), and values for dose-normalized AUC_{τ} (including medians) were similar and showed overlap across the regimens (Fig. 4b), indicating dose proportionality of AL. Values for C_{avg} at steady state showed that average aripiprazole concentrations with the 1064-mg q8wk regimen were similar to those with 882 mg q6wk and higher than those with 441 mg q4wk (Fig. 5).

3.4 Safety

The overall incidence of AEs over 44 weeks was 68.6%, 50.0%, and 65.7% in the 1064-mg q8wk, 882-mg q6wk, and

Fig. 2 Patient disposition (safety population). *q4wk* every 4 weeks, *q6wk* every 6 weeks, *q8wk* every 8 weeks

441-mg q4wk groups, respectively (Table 4); most AEs were of mild or moderate intensity. The most common AE across the three AL regimens was injection-site pain (8.6%–11.4%); weight increase, nasopharyngitis, and hypertension also occurred in > 5% of patients in each of the three dose/dosing interval groups.

Serious AEs were reported by 7.7% ($n=8$) of the total study population: 8.6% ($n=3$) of patients in the 1064-mg q8wk group (one patient each with knee injury, worsening of schizophrenia, and diabetic ketoacidosis), 8.6% ($n=3$) in the 441-mg q4wk group (one patient each with increased psychosis, exacerbation of schizophrenia, and agitation), and 5.9% ($n=2$) in the 882-mg q6wk group (one patient with worsening of osteoarthritis and one patient with cardiac arrest, acute respiratory failure, and acute myocardial infarction). With the exception of one event (increased psychosis in the 882-mg q6wk group, assessed as possibly related to study drug), SAEs were considered to be unrelated to AL.

AEs leading to study discontinuation occurred in 6.7% ($n=7$) of the study population: 2.9% ($n=1$) in the 1064-mg q8wk group (worsening schizophrenia), 11.8% ($n=4$) in the 882-mg q6wk group (osteoarthritis, musculoskeletal stiffness, disturbance of attention, and cardiac arrest), and 5.7% ($n=2$) in the 441-mg q4wk group (increased psychosis and epistaxis).

Overall, 11.5% ($n=12$) of patients reported ISRs; the 1064-mg q8wk group had an ISR frequency of 14.3%, compared with 8.8% for the 882-mg q6wk group and 11.4% for the 441-mg q4wk group (Table 5). None of the ISRs were severe, and no patient discontinued the study because of an ISR. Pain was the most commonly reported ISR (83.3% [10/12 ISR events]; Table 5), with a similar incidence across all dose/dosing interval groups (75% [3/4 ISR events], 100% [3/3 ISR events], and 80% [4/5 ISR events] in the 1064-mg q8wk, 882-mg q6wk, and 441-mg q4wk groups, respectively; Table 5).

For the overall patient population, the first injection was associated with the highest occurrence of ISRs relative to subsequent injections (Table 5). The reduction in incidence of ISR as a function of number of injections already received was seen for all three dose/dosing interval groups. The incidence of any ISR in the 1064-mg q8wk group decreased from 5.7% with the first injection to 3.4% with the fourth injection.

Overall, 11.4% ($n=4$), 17.6% ($n=6$), and 14.3% ($n=5$) of patients in the 1064-mg q8wk, 882-mg q6wk, and 441-mg q4wk groups, respectively, had AEs associated with EPS (Table 4). Akathisia was reported in 2.9% ($n=1$), 8.8% ($n=3$), and 8.6% ($n=3$) of patients in the 1064-mg q8wk, 882-mg q6wk, and 441-mg q4wk groups, respectively.

Table 1 Baseline characteristics and concomitant medications

Category	Aripiprazole lauroxil regimen		
	1064 mg q8wk ($n=35$)	882 mg q6wk ($n=34$)	441 mg q4wk ($n=35$)
Age, mean $\pm$ SD (years)	44.9 $\pm$ 10.7	44.8 $\pm$ 12.4	46.3 $\pm$ 11.0
Men, n (%)	29 (82.9)	25 (73.5)	20 (57.1)
Hispanic or Latino, n (%)	4 (11.4)	2 (5.9)	1 (2.9)
Race, n (%)			
Black or African American	26 (74.3)	25 (73.5)	26 (74.3)
White	9 (25.7)	8 (23.5)	9 (25.7)
American Indian or Alaska Native	0	1 (2.9)	0
Body mass index, mean $\pm$ SD (kg/m^2)	29.3 $\pm$ 4.4	29.3 $\pm$ 4.4	30.3 $\pm$ 4.3
Weight, mean $\pm$ SD (kg)	88.5 $\pm$ 18.3	88.6 $\pm$ 15.9	92.5 $\pm$ 16.4
CGI-S score, mean $\pm$ SD	2.9 $\pm$ 0.43	2.8 $\pm$ 0.46	2.9 $\pm$ 0.32
Patients taking concomitant antipsychotic medications, n (%)	35 (100)	33 (97.1)	35 (100)
Antipsychotic medications taken by $\geq 10\%$ of patients			
Risperidone, n (%)	12 (34.3)	9 (26.5)	16 (45.7)
Dose/day, mean $\pm$ SD (mg)	4.0 $\pm$ 1.9	3.8 $\pm$ 1.5	3.4 $\pm$ 1.9
Quetiapine, n (%)	9 (25.7)	10 (29.4)	6 (17.1)
Dose/day, mean $\pm$ SD (mg)	433.3 $\pm$ 173.2	430.0 $\pm$ 240.6	400.0 $\pm$ 209.8
Olanzapine, n (%)	6 (17.1)	8 (23.5)	6 (17.1)
Dose/day, mean $\pm$ SD (mg)	12.5 $\pm$ 6.1	15.0 $\pm$ 7.6	12.5 $\pm$ 5.2
Haloperidol, n (%)	4 (11.4)	3 (8.8)	4 (11.4)
Dose/day, mean $\pm$ SD (mg)	3.5 $\pm$ 1.7	7.3 $\pm$ 4.6	12.8 $\pm$ 9.1

CGI-S Clinical Global Impression – Severity, q4wk every 4 weeks, q6wk every 6 weeks, q8wk every 8 weeks

Fig. 3 Mean (SD) aripiprazole concentration over time. Reproduced 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; used with permission. *AL* aripiprazole lauroxil, *q4wk* every 4 weeks, *q6wk* every 6 weeks, *q8wk* every 8 weeks, *wk* week

Table 2 Summary of pharmacokinetic parameters for aripiprazole following the first and last dose of aripiprazole lauroxil by treatment group (PK population) [6]

Parameter	Aripiprazole lauroxil regimen					
	1064 mg q8wk		882 mg q6wk		441 mg q4wk	
	First dose	Last dose	First dose	Last dose	First dose	Last dose
$C_{\max}$ (ng/mL)						
Patients (<i>n</i>)	32	28	31	23	31	28
Mean (SD)	129.6 (62.7)	188.8 (79.8)	85.0 (63.0)	171.6 (81.1)	33.0 (29.6)	161.2 (109.2)
$t_{\max}$ (days)						
Patients (<i>n</i>)	32	28	31	23	31	28
Median (range)	43.4 (30–56)	34.4 (0–63)	41.8 (21–44)	20.0 (0–120)	27.9 (0–33)	28.0 (2–85)
AUC_{last} (day·ng/mL)						
Patients (<i>n</i>)	32	28	31	23	31	28
Mean (SD)	3692.4 (1900.0)	14,188.1 (6169.5)	1621.1 (1329.1)	13,222.3 (6976.8)	368.64 (359.4)	11,451.4 (6299.5)
AUC_{τ} (day·ng/mL)						
Patients (<i>n</i>)	19	28	11	23	5	28
Mean (SD)	3945.0 (2078.1)	7880.0 (3208.7)	2085.0 (1697.1)	5505.1 (2611.8)	363.5 (391.5)	3522.4 (2228.9)
$t_{1/2}$ (days)						
Patients (<i>n</i>)		26		19		22
Mean (SD)		53.9 (41.9)		55.1 (31.9)		57.2 (43.0)
C_{avg} (ng/mL)						
Patients (<i>n</i>)		28		23		28
Mean (SD)		140.7 (57.3)		131.1 (62.2)		125.8 (79.6)

Adapted from Hard et al. [6]; used with permission

AUC area under the plasma drug concentration–time curve, AUC_{last} AUC from time zero until the last measurable plasma drug concentration time point, AUC_{τ} AUC over the dosing interval, C_{avg} average plasma drug concentration, $C_{\max}$ maximum plasma drug concentration, PK pharmacokinetics, *q4wk* every 4 weeks, *q6wk* every 6 weeks, *q8wk* every 8 weeks, $t_{1/2}$ half-life, $t_{\max}$ time to $C_{\max}$

Table 3 Dose proportionality of aripiprazole following the last dose (PK population)

	Patients (n)	Intercept			Slope		
		Estimate	SE	90% CI	Estimate	SE	90% CI
AUC_{last} , (day·ng/mL)	79	7.70	1.26	5.60–9.80	0.249	1.04	–1.49 to 1.99
C_{max} , ng/mL	79	3.27	1.20	1.26–5.27	0.267	1.00	–1.39 to 1.93

PK parameters (Y) were analyzed using a power model: $\log(Y) = \text{intercept} + \text{slope} \times \log(\text{dose})$

AUC_{last} area under the plasma drug concentration–time curve from time zero until the last measurable plasma drug concentration time point, CI confidence interval, C_{max} maximum plasma drug concentration, PK pharmacokinetics, SE standard error

Fig. 4 Box plots of **a** area under the plasma aripiprazole concentration–time curve over the dosing interval (AUC_{τ}) and **b** AUC_{τ} normalized to dose by treatment group following the last dose. Boxes represent the 75th and 25th percentiles; the line within each box represents the median, and the '+' represents the mean. Whiskers indicate the minimum and maximum. AUC_{τ} area under the plasma drug concentration–time curve over the dosing interval, AUC_{τ}/D dose-normalized AUC_{τ} ; q4wk every 4 weeks, q6wk every 6 weeks, q8wk every 8 weeks

Fig. 5 Box plot of average concentration for aripiprazole following the last dose by treatment group. Boxes represent the 75th and 25th percentiles; the line within each box represents the median, and the '+' represents the mean. Whiskers indicate the minimum and maximum. C_{avg} mean plasma drug concentration, q4wk every 4 weeks, q6wk every 6 weeks, q8wk every 8 weeks

Dyskinesia was reported in three patients (8.6%) in the 1064-mg q8wk group but was not reported in any patients in the 882-mg q6wk or 441-mg q4wk groups.

Additional assessments also demonstrated minimal effects on movement disorders; mean changes from baseline in ESRS scores were generally small and not clinically meaningful. The proportions of patients with akathisia, dyskinesia, parkinsonism, and dystonia assessed using the ESRS (CGI-S item score ≥ 2 in ESRS at any postbaseline visit) in the 1064-mg q8wk group (5.7%, 5.7%, 8.6%, and 8.6%, respectively) were similar to those in the 441-mg q4wk (2.9%, 5.7%, 5.7%, 0%) and 882-mg q6wk groups (5.9%, 8.8%, 8.8%, 2.9%).

Table 4 Overview of AEs by treatment group^a

MedDRA preferred term	Aripiprazole lauroxil regimen ^b		
	1064 mg q8wk (n = 35)	882 mg q6wk (n = 34)	441 mg q4wk (n = 35)
Patients with ≥ 1 AE	24 (68.6)	17 (50.0)	23 (65.7)
AE by highest severity			
Mild	9 (25.7)	4 (11.8)	12 (40.0)
Moderate	13 (37.1)	11 (32.4)	8 (22.9)
Severe	2 (5.7)	2 (5.9)	3 (8.6)
Patients with any drug-related AE ^c	14 (40.0)	13 (38.2)	14 (40.0)
Patients with any SAE	3 (8.6)	2 (5.9)	3 (8.6)
Patients with any AE leading to discontinuation	1 (2.9)	4 (11.8)	2 (5.7)
AEs occurring in ≥ 5% of patients			
Injection-site pain	4 (11.4)	3 (8.8)	3 (8.6)
Dyskinesia	3 (8.6)	0	0
Weight increase	2 (5.7)	2 (5.9)	3 (8.6)
Nasopharyngitis	2 (5.7)	2 (5.9)	3 (8.6)
Hypertension	2 (5.7)	2 (5.9)	2 (5.7)
Vomiting	2 (5.7)	1 (2.9)	2 (5.7)
Upper respiratory tract infection	2 (5.7)	1 (2.9)	1 (2.9)
Dystonia	2 (5.7)	1 (2.9)	0
Back pain	2 (5.7)	1 (2.9)	0
Neck pain	2 (5.7)	1 (2.9)	0
Akathisia	1 (2.9)	3 (8.8)	3 (8.6)
Insomnia	1 (2.9)	3 (8.8)	0
Psychotic disorder	1 (2.9)	1 (2.9)	2 (5.7)
Arthralgia	1 (2.9)	0	2 (5.7)
Headache	1 (2.9)	0	2 (5.7)
Dizziness	0	2 (5.9)	0
Laceration	0	2 (5.9)	0
Musculoskeletal stiffness	0	2 (5.9)	0
Anxiety	0	0	2 (5.7)
Sluggishness	0	0	2 (5.7)
AEs associated with EPS			
Any	4 (11.4)	6 (17.6)	5 (14.3)
Dyskinesia	3 (8.6)	0	0
Dystonia	2 (5.7)	1 (2.9)	0
Akathisia	1 (2.9)	3 (8.8)	3 (8.6)
Restlessness	1 (2.9)	1 (2.9)	1 (2.9)
Tremor	0	1 (2.9)	0
Oromandibular dystonia	0	0	1 (2.9)

Data reported as patients, *n* (%)

AE adverse event, EPS extrapyramidal symptoms, MedDRA Medical Dictionary for Regulatory Activities, Version 18.0, *q4wk* every 4 weeks, *q6wk* every 6 weeks, *q8wk* every 8 weeks, SAE serious adverse event

^aAEs listed in order of incidence for the aripiprazole lauroxil 1064-mg q8wk dosage

Table 4 (continued)

^bPatients in each of the aripiprazole lauroxil treatment arms were, in almost all cases, taking a concomitant therapeutic dose of an oral antipsychotic (most commonly risperidone, quetiapine, olanzapine, or haloperidol)

^cIncludes two patients who reported severe AEs considered possibly related to the study drug (one patient on 1064 mg q8wk with elevated creatinine phosphokinase and one patient on 441 mg q4wk with increased psychosis)

4 Discussion

In this study, the pharmacokinetics, safety, and tolerability of the 1064-mg q8wk regimen were compared with those of two other approved AL regimens. Pharmacokinetics data from the study presented in this article as well as another publication [6] show that plasma aripiprazole concentrations achieved with the AL 1064-mg q8wk regimen were found to be within the upper and lower limits of the range associated with clinically effective and well tolerated doses of AL, as determined in a phase III efficacy study of two AL doses, 441 mg q4wk and 882 mg q4wk [4], and aripiprazole exposure increased with increasing AL dose. In addition, administration of AL 1064 mg q8wk resulted in plasma aripiprazole concentrations comparable to that observed with administration of 882 mg q6wk for the entire dosing interval. Although some patients were receiving concomitant antipsychotics metabolized by CYP2D6 (i.e., risperidone or haloperidol), given the in vivo CYP2D6 inhibitory profile of these antipsychotics [10–12], it is not anticipated that these or any of the other non-aripiprazole concomitant oral antipsychotics would affect the pharmacokinetics of aripiprazole. The overall safety profile of the AL 1064-mg q8wk regimen was similar to that of the other two AL regimens in this population of patients with stable schizophrenia. The safety profile of the 1064-mg q8wk regimen was also consistent with that of oral aripiprazole as well as the known safety profile of AL [4, 13–17].

The incidence of ISRs was comparable for each dosage group. Given that the frequency of ISRs for the 882-mg q6wk group (8.8%) was lower than that for both the 441-mg q4wk (11.4%) and 1064-mg q8wk (14.3%) groups, the frequency of ISRs reported did not demonstrate an association with the dose or volume of AL. The incidence of injection-site pain in this phase I study was higher than the incidence previously reported for AL 441-mg q4wk and 882-mg q4wk regimens [4, 18]. We hypothesize that these differences may be related to the study design of the current phase I study, which focused primarily on safety. Higher ISR (pain) rates associated with phase I studies for another long-acting formulation of aripiprazole (compared with later-phase/open-label studies) have also been noted [19, 20].

Table 5 Total injection-site reactions by treatment group

	Aripiprazole lauroxil regimen			All patients (<i>n</i> = 104)
	1064 mg q8wk (<i>n</i> = 35)	882 mg q6wk (<i>n</i> = 34)	441 mg q4wk (<i>n</i> = 35)	
ISRs by injection number				
First injection				
Any ISR	2/35 (5.7) ^a	2/34 (5.9) ^b	3/35 (8.6) ^c	7/104 (6.7)
Second injection ^d				
Any ISR	2/31 (6.5)	1/32 (3.1)	1/33 (3)	4/96 (4.2)
Third injection				
Any ISR	1/29 (3.4)	1/31 (3.2)	0/33 (0)	2/94 (2.1)
Any ISR reported	5/35 (14.3) ^e	3/34 (8.8)	4/35 (11.4)	12/104 (11.5)
Injection-site pain ^f	4/5 (80)	3/3 (100)	3/4 (75)	10/12 (83.3)

Data shown as *n*/*m* (%), where *m* is number of evaluable patients, unless otherwise stated

ISR injection-site reaction, *q4wk* every 4 weeks, *q6wk* every 6 weeks, *q8wk* every 8 weeks

^aThe 1064-mg q8wk group includes any report of ISR at study visits for weeks 2, 4, 6, and 8 (if reported prior to second injection at week 8)

^bThe 882-mg q6wk group includes any report of ISR at study visits for weeks 2, 4, and 6 (if reported prior to second injection at week 6)

^cThe 441-mg q4wk group includes any report of ISR at study visits for weeks 2 and 4 (if reported prior to second injection at week 4)

^dSee ISR first injection footnotes for information on differences in ISR assessments according to dose/dose interval assignment

^eUsing report of ISR at any safety visit

^fOther reports of induration (1064 mg q8wk, *n* = 1; 441 mg q4wk, *n* = 1)

The overall incidence of EPS-related AEs was consistent with earlier results. There were no obvious differences in akathisia incidence between the 1064-mg q8wk group and the 882-mg q6wk or 441-mg q4wk groups. The incidence of akathisia events (2.9%–8.8%) in this study was consistent with that reported in the 52-week long-term study in patients who had not previously received AL (0.9%–4.6%) [18]. Higher frequencies of dystonia and dyskinesia as AEs were observed in the 1064-mg q8wk group in the current study compared with the 441-mg q4wk and 882-mg q4wk groups evaluated in the 52-week study (dystonia: 5.7% vs 1.4%–2.7%; dyskinesia: 8.6% vs 0%–0.5%) [18].

Results from this study demonstrate that the 1064-mg q8wk dosage regimen offers similar safety and tolerability to that of the 4- or 6-week dosage regimens of AL and comparable or higher aripiprazole plasma concentrations with the option of dosing only six times per year. Having a range of dosing interval options allows for greater flexibility in treatment planning. A 2-month dosing interval option may expand the range of ways to individualize the LAI regimen into the patient's treatment plan, taking into account factors such as patient preferences, logistical barriers, or aligning injection regimen with other psychosocial interventions.

Limitations of the study included the lack of a placebo group or active control and the relatively small patient populations in each treatment group; therefore, no conclusions on dose-related effects could be drawn. The use of concomitant antipsychotic drugs makes it harder to attribute any new-onset AE to the prior oral antipsychotic, the AL exposure,

or the combination of these. Presumably, the baseline AE assessment would capture any pre-existing AE associated with the ongoing oral antipsychotic; in addition, as part of ongoing AE monitoring, investigators were asked their assessment of the likelihood of any given AE as being attributable to study medication exposure. However, the primary goal of this analysis was to determine the relative safety of the 1064-mg dosage strength. Because all patients across the AL dose regimens were on other oral antipsychotics, presumably any impact of ongoing oral antipsychotic use would be equivalent across the randomized groups. The lack of serious AEs associated with dopamine antagonism (e.g., severe antipsychotic-induced parkinsonism) provides some additional information on the safety of AL with some other antipsychotics. We strongly caution the reader to use other sources of safety data from short-term and long-term phase III and phase IIIb studies as being a more accurate source of safety information for AL as a treatment for schizophrenia [4, 18, 21]. Nonetheless, the overall results of this safety analysis demonstrated a low incidence of EPS with AL even at higher doses and during prolonged treatment (together with concomitant oral antipsychotic medication).

5 Conclusions

The results of this study provide an overview of the pharmacokinetics and long-term safety profile associated with the administration of different dose/dosing interval regimens of

AL in a variety of patient populations that might be encountered in the real-world clinical setting. Overall, the results from the current study show that AL 1064-mg q8wk, 882-mg q6wk, and 441-mg q4wk regimens provide continuous exposure to aripiprazole within the previously established clinically relevant range. Taking into consideration the limitations of the data derived from this study, including the fact that most patients were taking concomitant oral antipsychotic medications, AL across dosing groups appeared to be well tolerated and had a safety profile similar to the established safety profile of oral aripiprazole.

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Compliance with Ethical Standards

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Conflict of Interest P.J. Weiden, L. von Moltke, A. Wehr, and M. Hard are former employees of Alkermes, Inc., and may own stock/options in the company; Y. Du is currently an employee of Alkermes, Inc., and may own stock/options in the company; M. Hard is currently an employee of Moderna, Inc.; M. Marandi has received advisory and speaking fees from Alkermes, Inc.; D.P. Walling has received grants from Alkermes, Inc., Janssen, Otsuka, Forum, Lundbeck, Sunvion, Acadia, Allergan, Intracellular, Noven, Merck, AbbVie, and Roche.

Research Involving Human Participants The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki and Good Clinical Practice Guidelines.

Informed Consent Each eligible, consenting study participant provided written informed consent before study entry.

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Affiliations

Peter J. Weiden^{1,4} · Yangchun Du¹ · Lisa von Moltke¹ · Angela Wehr¹ · Marjie Hard^{1,5} · Morteza Marandi² · David P. Walling³

✉ Peter J. Weiden
pjweiden@gmail.com

¹ Alkermes, Inc., Waltham, MA, USA

² Radiant Clinical Research, Cerritos, CA, USA

³ CNS Network, LLC, Garden Grove, CA, USA

⁴ Present Address: Karuna Therapeutics, 33 Arch Street, Suite 3110, Boston, MA 02110, USA

⁵ Present Address: Moderna, Inc., Cambridge, MA, USA