Key Words: antipsychotic agents, aripiprazole, aripiprazole lauroxil, prodrugs, psychomotor agitation, psychopharmacology, schizophrenia, weight gain

A Phase-1 Study Comparing Pharmacokinetic and Safety Profiles of Three Different Dose Intervals of Aripiprazole Lauroxil

By Robert Risinger, Marjie Hard, Peter J. Weiden

ABSTRACT ~ Background: *Aripiprazole lauroxil (AL) is an FDA-approved treatment for schizophrenia. AL is a non-ester prodrug of aripiprazole that results in extended systemic release of aripiprazole after intramuscular (IM) administration. This Phase-1 study evaluated the pharmacokinetics (PK) and safety of a new AL dose (1064 mg)* for 2-month dose intervals. The study also evaluated 4- and 6-week dose intervals of AL at the 441 mg and 882 mg doses, respectively.* ***Methods:*** *A total of 139 patients diagnosed with schizophrenia and stabilized on a first-line antipsychotic (other than aripiprazole) were randomized to one of 3 dose/dose-interval groups: a 4-week interval of AL 441 mg (n = 35), a 6-week interval of AL 882 mg (n = 34), and an 8-week interval of AL 1064 mg IM injection (n = 70). After randomization, AL assignment was open label and administered as gluteal injections over 24 weeks. The total number of injections over this time period was related to the interval: 7 injections for the 441 mg group, 5 for the 882 mg group, and 4 for the 1064 mg group. PK and safety assessments occurred every 2 weeks and extended for an additional 20 weeks after the last injection. Patients continued their prior antipsychotic throughout, such that the safety (but not the PK) findings also reflect a second antipsychotic co-prescribed with AL.* ***Results:*** *PK findings: administration of AL 1064 mg every 8 weeks and AL 882 mg every 6 weeks provided continuous exposure to aripiprazole. Compared with the AL 441 mg every 4 weeks group, the longer dose-interval groups had consistently higher plasma concentrations for the entirety of the 6- and 8-week dose intervals for the 882 mg and 1064 mg dose groups. Safety findings: the overall safety profile of the group randomized to the 8 week/1064 mg combination was comparable to the 6 week/882 mg and 4 week/441 mg groups. The most common adverse event (AE) for all groups was injection-site reaction (pain). There was no apparent dose-AE signal for extrapyramidal symptoms, akathisia, sedation, or weight gain. In particular, there was no other safety signal identified with the longest interval/*

Presented at the American Psychiatric Association Annual Meeting, May 20–24, 2017, San Diego, CA.

Dr. Risinger, previously at Alkermes, Inc., Waltham, MA, USA; Drs. Hard, Weiden, Alkermes, Inc, Waltham, MA, USA; Dr. Hard, currently at Nuventra Pharma Sciences, Durham, NC, USA. Dr. Risinger, currently at NeuroRxPharmaceuticals, Wilmington, DE, USA.

To whom correspondence should be addressed: James Fratantonio, Manager, Medical Information, Alkermes Inc., 852 Winter Street, Waltham, MA 02451-1420. Phone: 781.609.6466; E-mail: james.fratantonio@alkermes.com

highest-dose AL group of 8 weeks/1064 mg. ***Conclusion:*** *AL allows for a range of dose/dose-interval combinations. The PK results from this study show that a dosing interval of every 8 weeks for the 1064 mg dose resulted in aripiprazole concentrations within the established therapeutic window for AL. There was no safety signal directing any particular concern to any of the three doses/dose intervals studied. All patients continued their primary antipsychotics without any apparent tolerability issue arising from the addition of the AL injections. The results of this study show that 1064 mg AL may be suitable for a 2-month dose interval. The three doses/dose intervals studied have the potential to help clinicians and patients expand their choice of AL treatment to best meet the needs of the individual patient.* Psychopharmacol Bull. *2017;47(3):26–34.*

*The following information concerns the use of a dose of AL that has not been approved by the US Food and Drug Administration.

Background

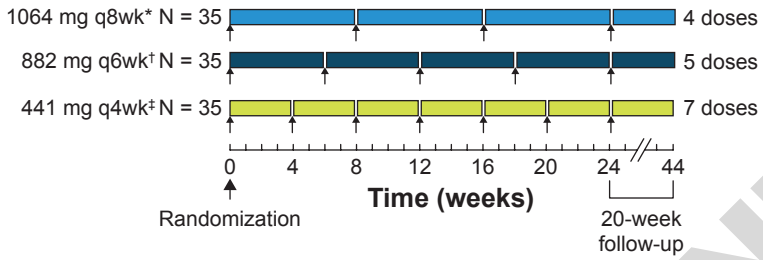
- Extending the number of dose intervals for long-acting atypical injectable antipsychotic therapy may offer clinicians and patients greater flexibility and options to recommend a dose and dose interval that best meets the needs of the individual patient
- Aripiprazole lauroxil (AL) is an atypical antipsychotic approved in the US for the treatment of schizophrenia, at doses administered every 4 weeks (q4wk), 441 mg, 662 mg, and 882 mg, and every 6 weeks (q6wk), 882 mg[1]
- This phase-1, randomized, open-label, parallel study evaluated the safety, tolerability, and pharmacokinetics (PK) of various doses and dose intervals of AL, including a new AL dose assessed for potential use every 2 months

Methods

- Data presented here are based on data from a 48-week, phase-1, open-label study of AL in patients with chronic schizophrenia or schizoaffective disorder (Clinicaltrials.gov: NCT02320032)
- The primary goal was to evaluate the safety, tolerability, and PK of a new AL dose and dose interval (1064 mg every 8 weeks [q8wk])
- The study included a 30-day screening period, a 24-week treatment period, and a 20-week follow-up period (Figure 1)
- Patients were randomized 1:1:1:1 to one of four dose/interval groups:
  - AL 441 mg q4wk
  - AL 882 mg q6wk
  - AL 1064 mg q8wk
  - AL 1064 (S) mg q8wk (an alternative AL formulation)
- Patients continued their prior antipsychotic throughout

FIGURE 1

Study Design



Notes: *Injection volume: 3.9 mL; †Injection volume: 3.2 mL; ‡Injection volume: 1.6 mL. All injections were gluteal. Please note that the AL 1064 (S) mg dose is not included in this schema.
Abbreviations: AL, aripiprazole lauroxil; PK, pharmacokinetics; q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks.

- Study clinical visits and safety assessments occurred every 2 weeks, and further safety assessments extended for an additional 20 weeks after the last injection

Patients

- Patients aged 18–65 years with demonstrated tolerability to aripiprazole, on stable antipsychotic medication without regimen changes for at least 2 months prior to screening, *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-V) diagnosis of schizophrenia or schizoaffective disorder who were clinically stable
- The main exclusion criteria comprised prior AL or intramuscular (IM) aripiprazole within 6 months or other long-acting injectable antipsychotic medication within 3 months prior to screening, had received oral aripiprazole within 28 days prior to randomization, or were medically or psychiatrically unstable

Clinical Assessments and Statistical Analysis

Pharmacokinetics

- PK analyses were based on the PK population (all patients in the safety population who had ⩾1 measurable concentration of AL)
- PK parameters were summarized by treatment group by descriptive statistics. Concentration data were summarized according to nominal (protocol-specified) sampling times
- PK parameters were calculated using noncompartmental techniques using actual elapsed time from dosing to estimate individual plasma PK parameters (Table 2)

Safety

- Safety analyses were carried out in all randomized patients who received ⩾1 dose of AL
- Safety was assessed on the basis of adverse events (AEs), injection-site reactions (ISRs), body weight, vital signs, electrocardiogram (ECG) parameters, and laboratory parameters
- Summary statistics were obtained for each treatment group

RESULTS

Patient Disposition, Demographics, and Baseline Characteristics

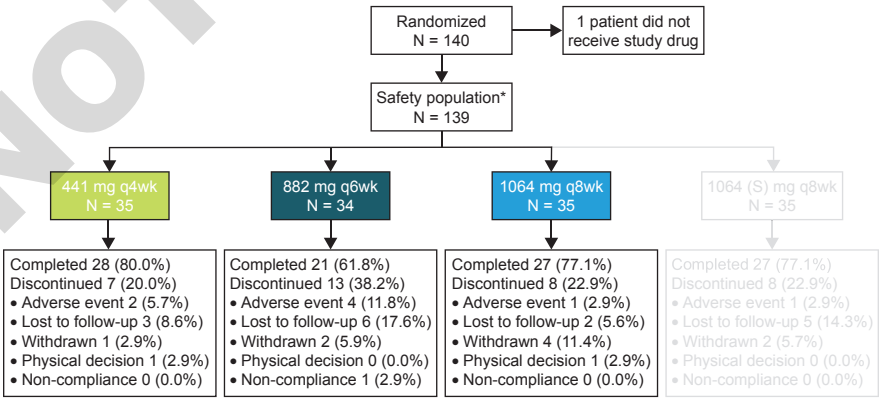
- In total, 139 patients received at least one dose of AL (Figure 2)
- Of the 139 patients, 74.1% of patients completed the study and 25.9% discontinued prematurely
  - Most commonly due to lost to follow-up (11.5%), withdrawal by patient (6.5%), and AE (5.8%)
- Baseline patient demographics and characteristics are shown in Table 1

Pharmacokinetics

- In the 20-week period following the final dose of AL, sampling of multiple plasma concentrations was carried out and used to calculate the half-life of AL
- Compared with the AL 441 mg q4wk group, the longer dose interval (882 mg and 1064 mg) groups had consistently higher plasma

FIGURE 2

Patient Disposition



Notes: *The safety profile of both 1064 mg formulations was generally consistent. As the S formulation of AL is not being developed further, data from this cohort will not be presented in the rest of the poster, subsequent results focus on all other cohorts.

TABLE 1

Patient Baseline Demographics and Characteristics

CATEGORY	ARIPIPRAZOLE LAUROXIL 1064 MG Q8WK (N = 35)	882 MG Q6WK (N = 34)	441 MG Q4WK (N = 35)
Age (years), mean ± SD	44.9 ± 10>	44.8 ± 12.4	46.3 ± 11.0
Male, n (%)	29 (82.9)	25 (73.5)	20 (57.1)
Hispanic or Latino, n (%)	4 (11.4)	2 (5.9)	1 (2.9)
Primary 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
BMI (kg/m^2), mean ± SD	29.3 ± 4.4	29.3 ± 4.4	30.3 ± 4.3

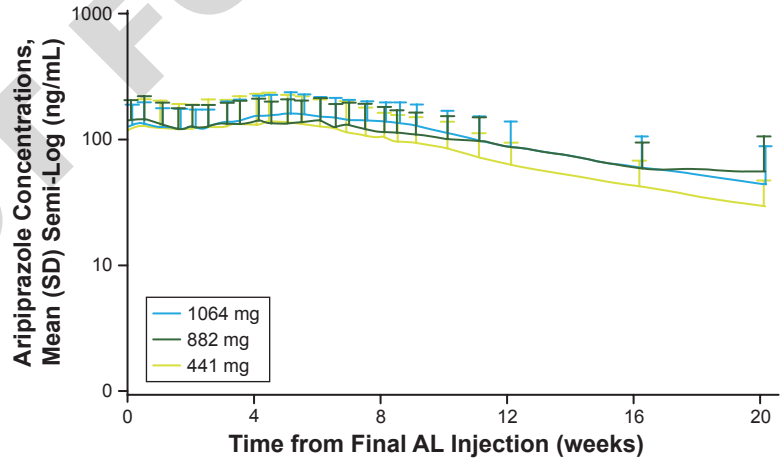
Abbreviations: BMI, body mass index; q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks; SD, standard deviation.

concentrations for the entirety of the 6- and 8-week dose intervals for the dose groups

- Following the final injection of AL in the phase study, maximum aripiprazole concentrations were achieved 20–34 days after the last dose and persisted for the duration of the study (Figure 3)

FIGURE 3

Observed Steady-State Aripiprazole Plasma Concentrations Following Last Dose of Each Aripiprazole Lauroxil Regimen with 20 Weeks Follow-Up



Notes: After the first injection, patients received assigned AL regimen for up to 24 weeks, corresponding to a total of 4, 5, or 7 injections of 1064 mg, 882 mg, or 441 mg, respectively. The final injection for all AL regimens was administered on Day 169 (week 0 on the above). All patients were followed for 20 weeks after the last injection to monitor safety and for PK assessments.
Abbreviations: AL, aripiprazole lauroxil; q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks; SD, standard deviation.

TABLE 2

Observed PK Parameters for Aripiprazole Following the Last Dose of AL by Treatment Group

	ARIPIPRAZOLE LAUROXIL TREATMENT GROUP, MEAN (%CV)		
PARAMETER STATISTICS	1064 MG Q8WK	882 MG Q6WK	441 MG Q4WK
C_{max}, ng/mL	188.8 (42.3)	171.6 (47.3)	161.2 (67.8)
C_{avg}, ng/mL	140.7 (40.7)	131.1 (47.4)	125.8 (63.3)
AUC_T, day*ng/mL	7880.0 (40.7)	5505.1 (47.4)	3522.4 (63.3)
$t_{1/2}$, days	53.9 (77.9)	55.1 (58.0)	57.2 (75.2)

Abbreviations: %CV, percent coefficient of variation; AL, aripiprazole lauroxil; AUC_T, area under the plasma concentration-time curve calculated using the trapezoidal method over dosing interval; C_{avg}, average concentration; C_{max}, maximum observed concentration; q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks; $t_{1/2}$, terminal half-life.

- PK parameters for aripiprazole following the last dose of AL by treatment group are shown in Table 2
  - The mean $t_{1/2}$ of aripiprazole following the last AL dose was independent of dose and ranged from 54–57 days
- Comparison of $C_{avg,ss}$ at steady state across the tested dose regimens demonstrated that the 882 mg q6wk and the 1064 mg q8wk regimens result in average aripiprazole concentrations that are within the approved AL dose regimens

Safety

- In total, 82.9% (n = 29) of patients in the AL 1064 mg group received all 4 IM injections of AL, 70.6% (n = 24) of patients in the 882 mg group received all 5 injections, and 82.9% (n = 29) of patients in the 441 mg group received all 7 injections

Adverse Events

- The overall incidence of treatment-emergent AEs (TEAEs) are shown in Table 3; most were of mild or moderate intensity
- The most common TEAE for all groups was injection-site pain, which ranged from 8.6%–11.4% across the dose/interval groups (Table 3)
- Drug-related TEAEs were seen in 40%, 38.2%, and 40% of patients in the 1064 mg, 882 mg, and 441 mg groups, respectively
- Serious AEs were reported in 8.6% of patients in the 1064 mg and 441 mg groups and 5.9% of patients in the 882 mg group
- In total, 2.9%, 11.8%, and 5.7% of patients in the 1064 mg, 882 mg, and 441 mg groups, respectively, experienced a TEAE that led to discontinuation

TABLE 3

Treatment-Emergent Adverse Events in ⩾5% of Patients in the 1064 mg Group

	ARIPIPRAZOLE LAUROXIL		
	1064 MG Q8WK (N = 35)	882 MG Q6WK (N = 34)	441 MG Q4WK (N = 35)
Patients with ⩾1 TEAE	24 (68.6)	17 (50.0)	23 (65.7)
TEAEs occurring in ⩾5% of patients in the 1064 mg group			
Injection-site pain	4 (11.4)	3 (8.8)	3 (8.6)
Dyskinesia	3 (8.6)	0	0
Back pain	2 (5.7)	1 (2.9)	0
Neck pain	2 (5.7)	1 (2.9)	0
Hypertension	2 (5.7)	2 (5.9)	2 (5.7)
Nasopharyngitis	2 (5.7)	2 (5.9)	3 (8.6)
Upper respiratory tract infection	2 (5.7)	1 (2.9)	1 (2.9)
Vomiting	2 (5.7)	1 (2.9)	2 (5.7)
Weight increased	2 (5.7)	2 (5.9)	3 (8.6)
Cough	2 (5.7)	0	0
Dystonia	2 (5.7)	1 (2.9)	0

Note: TEAEs listed in order of incidence for the 1064 mg dose.
Abbreviations: q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks; TEAE, treatment-emergent adverse event.

Injection-site Reactions

- A total of 12 out of 104 (11.5%) patients reported ISRs, with pain being the most common (10 of 12, or 83.3% of all reported ISRs)
- Incidences of ISRs (reported as TEAEs) were similar across treatment groups: 14.3% in the 1064 mg group, 8.8% in the 882 mg group, and 11.4% in the AL 441 mg; none were severe
- The incidence of any ISR in the 1064 mg group decreased from 5.7% with the first injection to 3.4% at the fourth injection

Extrapyramidal Symptoms, Akathisia, and Dyskinesia

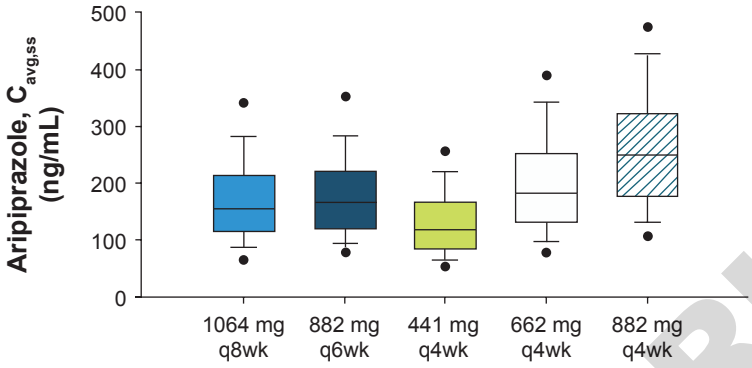
- The proportion of patients with treatment-emergent extrapyramidal symptoms based on extrapyramidal rating scale criteria (ESRS) of CGI-S item score ⩾2 at any post-baseline visit was similar across dose groups 1064 mg, 882 mg, and 441 mg and are listed below
  - Akathisia: 5.7%, 5.9%, and 2.9%
  - Dyskinesia: 5.7%, 8.8%, and 5.7%
  - Parkinsonism: 8.6%, 8.8%, and 5.7%
  - Dystonia: 8.6%, 2.9%, and 0%

Body Weight and Metabolic Effects

- The mean change in body weight from baseline to the last AL injection given at week 24 was 0.8 kg, 3.3 kg, and 0.7 kg for the 1064 mg q8wk, 882 mg q6wk, and 441 mg q4wk regimens, respectively

FIGURE 4

Simulated Steady State Average Plasma Aripiprazole Concentrations: 1064 mg q8wk Vs Other AL Regimens



Notes: The average steady state plasma concentration ($C_{avg,ss}$) was determined after 48 weeks of dosing for all regimens. The box represents the 75th and 25th percentiles, the line within each box marks the median, the whiskers indicate the 10th and 90th percentiles, and the dots represent the 5th and 95th percentiles.
Abbreviations: q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks.

- Weight increase (≥7% increase from baseline) at any point up to and including Day 225 was reported in 20.6% of the 1064 mg group, compared with 11.4% and 27.3% of patients in the 441 mg and 882 mg groups, respectively
- No clinically meaningful changes from baseline were observed for mean fasting glucose, glycated hemoglobin, or lipid parameters
- No clinically relevant changes from baseline chemistry, hematology, vital signs, or ECGs were observed

2-Month Population Pharmacokinetic Model

- A 2-month population PK model (2MPopPK) included data from Study A105[2] and showed that $C_{avg,ss}$ for the 1064 mg q8wk regimen was within the 441 mg q4wk and 882 mg q6wk ranges (Figure 4)
- The 2MPopPK data support a dosing regimen of 1064 mg every 2 months, providing aripiprazole concentrations that are within the established range of efficacy for AL determined in the phase-3 study[3]

Conclusions

- All 3 dose arms were within the therapeutic range as determined in a phase-3 efficacy study[3]
- Administration of AL 1064 mg q8wk and 882 mg q6wk provided continuous exposure to aripiprazole at concentrations above that

observed for the lowest therapeutic dose of AL (441 mg q4wk) for the entirety of the dose interval

- Overall, the safety profile of AL 1064 mg q8wk was similar to those of the 441 mg and 882 mg treatment groups and consistent with the safety profile of AL
  - All TEAEs were consistent with those previously reported[3,4]
- All patients continued their primary antipsychotics without any apparent tolerability issue arising from the addition of the AL injections
- Both the PK and the safety results support the feasibility of using an AL dose of 1064 mg as a 2-month dose interval ✤

Disclosures

This study was funded by Alkermes, Inc. Medical writing support was provided by Mia Cahill of ApotheCom, London, UK, and was funded by Alkermes, Inc.

References

1. ARISTADA®, USPI. 2017. Available at: https://www.aristadahcp.com/downloadables/ARISTADA-PI.pdf (Accessed May 2017).
2. Hard ML, et al. Poster SA20. 16th International Congress on Schizophrenia Research. San Diego, CA, USA; March 24–28, 2017.
3. Meltzer HY, et al. *J Clin Psychiatry*. 2015;76:1085–1090.
4. Nasrallah HA, et al. *J Clin Psychiatry*. 2016;77:1519–1525.