Aripiprazole Lauroxil Pharmacokinetics: Application of Modeling and Simulation for Dosing Considerations of a Long-Acting Injectable Antipsychotic in Persons With Schizophrenia

Marjie L. Hard, Ph.D.[1], Brian Sadler, Ph.D.[2], Richard Mills, Ph.D.[3], Karen Rowland Yeo, Ph.D.[4], Ryan Turncliff, Ph.D.[1], Leslie Citrome, M.D., M.P.H.[5]
[1]Alkermes, Inc., Waltham, MA, USA; [2]ICON, Gaithersburg, MD, USA; [3]ICON, Marlow, UK; [4]Simcyp Ltd., Sheffield, UK , [5]New York Medical College, Department of Psychiatry and Behavioral Sciences, Valhalla, NY, USA

Poster #55

ABSTRACT

Introduction: Aripiprazole lauroxil (AL) is a prodrug of aripiprazole, formulated as an extended-release suspension for intramuscular injection and recently approved for the treatment of schizophrenia. Following intramuscular injection, aripiprazole lauroxil is converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. Aripiprazole is subsequently metabolized by CYP3A4 and CYP2D6.

Methods: A population pharmacokinetic (PopPK) model of AL developed using data collected from 616 subjects with schizophrenia was used to evaluate the impact of missed doses, and re-initiation of treatment with monthly AL administration of 441, 662 or 882 mg. The PopPK model was also used to assess an additional dose regimen, 882 mg administered every 6 weeks. Separately, a physiologically-based pharmacokinetic (PBPK) model was constructed to evaluate the effect of drug-drug interaction and the effect of metabolic enzyme polymorphisms on aripiprazole exposure.

Results: The extended PK profile of AL results in sustained therapeutic coverage following a missed AL dose. Therefore, no oral aripiprazole supplementation is required when the time from the last injection is ≤6 weeks for 441 mg, or ≤8 weeks for 662 mg and 882 mg. The basis of these recommendations are consistent with a repeated dose PK study, where aripiprazole concentrations were observed to persist in plasma, and decline minimally within 8 weeks, following discontinuation of the fourth monthly AL dose. Based on simulations using the PopPK model, a dosing interval of every 6 weeks for the 882 mg dose resulted in aripiprazole concentrations within the therapeutic window established for 441 and 882 mg every 4 weeks. Evaluation of the impact of strong CYP2D6 or CYP3A4 inhibitors, or CYP3A4 inducers on the PK of aripiprazole using the PBPK model showed moderate changes in the systemic exposure of aripiprazole, irrespective of CYP2D6 genotype, and that AL dose adjustments are warranted when the CYP450 modulator is co-administered for >2 weeks.

Conclusion: AL demonstrates PK characteristics that may minimize the potential impact of poor adherence to treatment when a dose is missed. The availability of 3 dose strengths and 2 dosing intervals yields aripiprazole concentrations that span the oral aripiprazole dose range, and allows for individual patient dose adjustment for drug-drug interactions or metabolic status, thus providing flexibility in treating patients with schizophrenia.

BACKGROUND

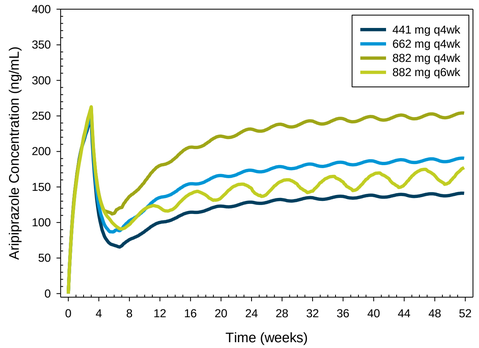
- Aripiprazole lauroxil (AL) is a novel long-acting injectable atypical antipsychotic approved for the treatment of schizophrenia with doses of 441 mg, 662 mg or 882 mg administered monthly (q4wk) or 882 mg dose every 6 weeks (q6wk).
- In a randomized, placebo-controlled study, AL demonstrated robust efficacy and was well tolerated in patients with schizophrenia administered 441 mg q4wk or 882 mg q4wk.[1]
- The proprietary technology (LinkeRx®) utilized to develop AL allows for controlled release after injection and extends exposure to the active molecule.[2]
- Following dissolution, AL undergoes enzyme-mediated hydrolysis to form aripiprazole, which is subsequently metabolized to dehydro-aripiprazole by CYP3A4 and CYP2D6.
- The technology, combined with AL's unique formulation, results in extended exposure to aripiprazole, and allows for multiple dose strengths and dosing intervals, which provides flexibility for individualized patient care.
- Here we describe the use of model-based methods to describe the PK of AL to support dosing and administration guidelines approved by the U.S. Food and Drug Administration.

METHODS

- A population PK (PopPK) model was developed following single and multiple dose administration of AL from 4 Phase 1 and a Phase 3 study using 21,620 aripiprazole and dehydro-aripiprazole plasma concentrations from 616 subjects with schizophrenia.
- The PopPK model was developed for both aripiprazole and dehydro-aripiprazole PK following administration of AL, as well as oral aripiprazole.
- Using the final PopPK model, Monte-Carlo simulations were performed using Pharsight Trial Simulator version 2.2.2 to evaluate a variety of different dosing scenarios, including the impact of delayed dosing, with and without oral supplementation of varying intervals.
- For each simulation, 500 individual aripiprazole concentration-time profiles were generated.
- Separately, a minimal physiologically-based pharmacokinetic (PBPK) model was developed for the purposes of evaluating the drug-drug interaction potential for AL and the effect of CYP2D6 metabolizer status on AL PK.
- The Simcyp Population-Based Simulator (version 13.0) was used to predict plasma concentration-time profiles of aripiprazole following administration of AL (n=150/scenario) and to evaluate the likely impact of co-administration of ketoconazole (a potent CYP3A4 inhibitor), quinidine (a potent CYP2D6 inhibitor) and carbamazepine (a CYP3A4 inducer) on the kinetics of aripiprazole.
- The PBPK model was developed to ensure that the relative contributions of CYP2D6 and CYP3A4 to the clearance of aripiprazole were established.

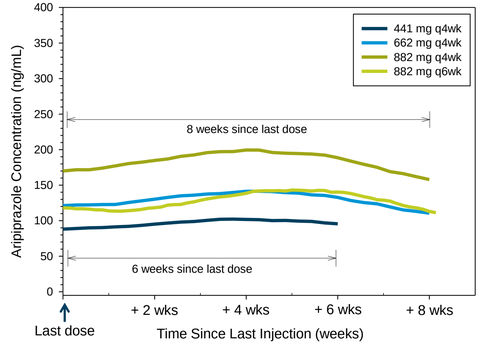
RESULTS

Figure 1. Median Simulated Aripiprazole Concentrations



- Aripiprazole concentrations were simulated following repeated dosing of AL, with concomitant oral aripiprazole, for 21 days after the first injection for the regimens with demonstrated robust efficacy, 441 mg q4wk and 882 mg q4wk.[2]
- Additional dose regimens, 662 mg q4wk and 882 mg q6wk, are also available and result in aripiprazole concentrations that fall entirely within the therapeutic range established for AL.

Figure 2. Median Simulated Aripiprazole Concentrations Following a Missed Dose



- Aripiprazole concentrations are persistent and sustained following a missed AL dose.
- Aripiprazole concentrations decline minimally when the time since last injection is 6-8 weeks.

Table 1. Recommendation for Concomitant Oral Aripiprazole Supplementation Following Missed Doses[3]

Dose of Patient's Last AL Injection	Length of Time Since Last Injection		
	No Oral Supplementation Required	Supplement With 7 Days Oral Aripiprazole	Supplement With 21 Days Oral Aripiprazole
441 mg q4wk	≤ 6 weeks	> 6 and ≤ 7 weeks	> 7 weeks
662 mg q4wk	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg q4wk	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg q6wk	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks

- No oral aripiprazole supplementation is required when the time from the last injection is ≤6 weeks for 441 mg q4wk, or ≤8 weeks for 662 mg q4wk, 882 mg q4wk and 882 mg q6wk.
- Longer delays require 7-21 days of oral aripiprazole supplementation.

Table 2. Aripiprazole Exposure ($AUC_{0\text{-}28}$ [day*ng/mL]) With and Without Strong CYP3A4 or CYP2D6 Inhibitors

AL Dose	Inhibitor*	AUC Without Inhibitor	AUC With Inhibitor for > 2 weeks	AUC After Dose Adjustment (see Table 4)
441 mg	Ketoconazole	2733	3771	3771
662 mg	Ketoconazole	4099	5657	3771
882 mg	Ketoconazole	5466	7542	5657
441 mg	Quinidine	2733	4134	4134
662 mg	Quinidine	4099	6201	4134
882 mg	Quinidine	5466	8268	6201

* Ketoconazole is a potent CYP3A4 inhibitor; quinidine is a potent CYP2D6 inhibitor.

- Systemic exposure is not significantly altered when concomitant CYP450 modulator is administered for < 2 weeks (data not shown).
- Reduction of 882 mg and 662 mg AL to next lower dose in presence of inhibitor results in exposure comparable to when no inhibitor is present.
- Continuation of 441 mg AL in presence of inhibitor keeps exposure within target range.

Table 3. Aripiprazole Exposure ($AUC_{0\text{-}28}$ [day*ng/mL]) With and Without a Strong CYP3A4 Inducer

AL Dose	Inducer	AUC Without Inhibitor	AUC With Inducer for > 2 weeks	AUC After Dose Adjustment (see Table 4)
441 mg	Carbamazepine	2745	2119	3178
662 mg	Carbamazepine	4117	3178	3178
882 mg	Carbamazepine	5490	4238	4238

- Continuation of 882 mg and 662 mg in the presence of inducer, or increasing 441 mg to 662 mg AL keeps exposure within target range.

Table 4. Dose Adjustments With Concomitant CYP450 Modulator Use for > 2 Weeks[3]

Concomitant Medicine	Dose Change for AL*
Strong CYP3A4 Inhibitor	Reduce the dose of AL to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated. *For patients known to be poor metabolizers of CYP2D6*: Reduce dose to 441 mg from 662 mg or 882 mg. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated.
Strong CYP2D6 Inhibitor	Reduce the dose of AL to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated. *For patients known to be poor metabolizers of CYP2D6*: No dose adjustment required.
Both Strong CYP3A4 Inhibitor and Strong CYP2D6 Inhibitor	Avoid use for patients at 662 mg or 882 mg dose. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated.
CYP3A4 Inducers	No dose adjustment for 662 mg and 882 mg dose, increase the 441 mg dose to 662 mg.

* For 882 mg q6wk, the next lower strength is 441 mg q4wk.

- Since CYP2D6 poor metabolizers have an inherent reduction in the ability to eliminate CYP2D6 substrates, specific recommendations for this population are made.

LIMITATIONS

- Recommendations for missed doses and dose adjustments for CYP450 modulator use are based on PK-based modeling and simulation. No clinical studies have been conducted to evaluate these recommendations.

CONCLUSIONS

- The prolonged exposure profile of aripiprazole following AL administration provides sustained therapeutic coverage and eliminates the need for oral aripiprazole supplementation in the event of late or missed doses for up to 4 weeks.
- The availability of 3 dose strengths provides options for dosage adjustments to be made for CYP450 considerations.
- Modeling and simulation approaches were used to develop dosing guidelines for AL that were approved by the U.S. FDA for the treatment of persons with schizophrenia, including new doses and dose regimens, as well as recommendations for drug-drug interaction dose adjustments based on CYP2D6 phenotype.
- The PK and product characteristics of AL provide flexibility in treating patients with schizophrenia.

DISCLOSURES

- Drs. Hard and Turncliff are employees of Alkermes, Inc.
- Drs. Sadler and Mills are employees of ICON.
- Dr. Rowland Yeo is an employee of Simcyp Ltd.
- In the past 36 months, Dr. Citrome has engaged in collaborative research with, or received consulting or speaking fees from: Acadia, Alexza, Alkermes, Allergan, AstraZeneca, Avanir, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Forum, Genentech, Janssen, Jazz, Lundbeck, Merck, Medivation, Mylan, Neurocrine, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, Teva, Valeant and Vanda.

REFERENCES

1. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry* 2015; 76:1085-1090.
2. Remenar JF. Making the leap from daily oral dosing to long-acting injectables: lessons from the antipsychotics. *Mol Pharm* 2014;11:1739-1749.
3. ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing information. Waltham, MA: Alkermes, Inc. October 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207533s000lbl.pdf.

Alkermes®
Patient inspired®

USMedInfo@Alkermes.com

American Society of Clinical Psychopharmacology
2016 Annual Meeting May 30 – June 3, 2016, Scottsdale, AZ