Aripiprazole Lauroxil
Pharmacokinetic Profile of This Long-Acting Injectable Antipsychotic in Persons With Schizophrenia

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Abstract:
Background: Aripiprazole lauroxil is an extended-release prodrug of aripiprazole for intramuscular injection, approved for schizophrenia treatment. We developed a population pharmacokinetic (PopPK) model to characterize aripiprazole lauroxil PK and evaluate dosing scenarios likely to be encountered in clinical practice.

Methods: Data from 616 patients with schizophrenia, collected from 5 clinical studies, were used to construct the PopPK model. The model was subsequently used to evaluate various dose levels and frequency and the impact of dosing delay on aripiprazole concentrations.

Findings: The results of the model indicate that aripiprazole is released into the systemic circulation after 5 to 6 days, and release continues for an additional 36 days. The slow increase in aripiprazole concentration after injection necessitates the coadministration of oral aripiprazole for 21 days with the first injection. Based on the PopPK model simulations, a dosing interval of 882 mg every 6 weeks results in aripiprazole concentrations that fall within the concentration range associated with the efficacious dose range. Aripiprazole lauroxil administration results in prolonged exposure, such that dose delays of 2 to 4 weeks, depending on the dose regimen, do not require oral aripiprazole supplementation upon resumption of dosing.

Conclusions: This PopPK model and model-based simulations were effective means for evaluating aripiprazole lauroxil dosing regimens and management of missed doses. Such analyses play an important role in determining the use of this long-acting antipsychotic in clinical practice.

Key Words: aripiprazole, aripiprazole lauroxil, atypical antipsychotic, long-acting injectable, pharmacokinetics

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Although effective medications are available for the treatment of schizophrenia, a large majority of the patients relapse within 5 years, most commonly because of poor adherence to oral agents.1,2 Nonadherence has been associated with adverse functional and psychopathological outcomes.3 Current guidelines recommend the consideration of long-acting injectable (LAI) antipsychotics for individuals with schizophrenia who would prefer such a treatment, or for whom avoiding covert nonadherence (either intentional or unintentional) to antipsychotic medication is a clinical priority.4,5

Oral aripiprazole is a well-established medication for the treatment of schizophrenia.6,7 Aripiprazole lauroxil is a covalent nonester modification of aripiprazole to form N-lauroylxymethyl aripiprazole that is approved for the treatment of schizophrenia by intramuscular injection into the gluteal or deltoid muscle. Aripiprazole lauroxil was developed to provide sustained release in a predictable and consistent manner and to maximize the potential clinical benefits of a long-acting platform.8,9

The proprietary technology (LinkerRx®; Alkermes, Inc, Waltham, Mass) used to develop aripiprazole lauroxil is a versatile chemistry platform designed to create new molecular entities with modified properties that result in extended systemic release after administration. This technology was used to produce a nonester prodrug of aripiprazole (Fig. 1). With this system, a linker is used to attach aripiprazole to a fatty acid tail to form aripiprazole lauroxil. This approach was used to lower the solubility of aripiprazole to develop a dosage form that allows for controlled release after injection and extend exposure to the active molecule.10 Once the aqueous suspension is injected into the gluteal or deltoid muscle, the conversion of aripiprazole lauroxil to aripiprazole is governed by the slow dissolution of aripiprazole lauroxil and subsequent enzyme-mediated cleavage by esterases, generating N-hydroxymethyl aripiprazole and lauric acid. Lauric acid, also called dodecanoic acid, is a fatty acid found in coconut oil, human breast milk, and cow’s milk.11 Subsequent rapid, nonenzymatic spontaneous cleavage (water-mediated hydrolysis) of N-hydroxymethyl aripiprazole yields aripiprazole and formaldehyde (Fig. 1). Formaldehyde is ubiquitous in living organisms and formed in the metabolism of endogenous amino acids; the amount produced by aripiprazole lauroxil metabolism (approximately 1 mg/d for 882 mg monthly) is well below the amounts that occur as a result of basic metabolism and diet.12 Once aripiprazole is formed, elimination of plasma aripiprazole is primarily hepatic where the cytochrome P450 (CYP) 3A4 and cytochrome P450 2D6 (CYP2D6) enzymes transform aripiprazole to dehydro-aripiprazole.13 Cytochrome P450 2D6 is subject to genetic polymorphism, which results in pharmacokinetic differences among CYP2D6 metabolizer phenotypes after the administration of oral aripiprazole.14,15

Aripiprazole lauroxil demonstrated efficacy for the treatment of patients experiencing an acute exacerbation of schizophrenia, including statistically significant and clinically meaningful improvements in psychotic symptoms over the course of 12 weeks at dosage levels of 441 mg and 882 mg given every 4 weeks (q4wk).16 Here, we describe the use of a population pharmacokinetic (PopPK) model developed to evaluate dosing of aripiprazole...
lauroxil and management of missed doses for the treatment of schizophrenia.

MATERIALS AND METHODS

We developed a PopPK model using data obtained after single- and multiple-dose administration of aripiprazole lauroxil and after administration of oral aripiprazole across 5 clinical trials, including 4 phase 1 trials (NCT01493726) in patients with chronic stable schizophrenia and 1 phase 3 trial (NCT01469039) in patients with acute exacerbation of schizophrenia (Table 1). Collection of PK samples from the 4 phase 1 studies (studies ALK9072-001 [single ascending dose], ALK9072-002 [multiple ascending dose], ALK9072-101 [gluteal vs deltoid administration], and ALK9072-102 [deltoid multiple dose]) and 1 phase 3 efficacy study (ALK9072-003) were analyzed for aripiprazole lauroxil, N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole. Only aripiprazole and dehydro-aripiprazole were included in the PopPK analysis.

Plasma samples were prepared by a protein-precipitation extraction procedure and analyzed using high-performance liquid chromatography coupled to a tandem mass spectrometry detector (LC/MS/MS). The concentrations of all analytes were calculated using a 1/x^2 linear regression with a lower limit of quantification of 1.00 ng/mL. Chromatographic separations were performed on a reversed phase column (UPLC SB-C8 1.8 μm, 2.1 × 100 m; from Agilent Technologies, Santa Clara, Calif). The mobile phases were pH unadjusted 0.1% formic acid in 10 mM ammonium acetate (A) and acetonitrile (B). A gradient elution was used, starting at 30% B and ramping to 37% in 0.2 minutes, then increasing to 95% B in 2.9 minutes with a flow rate of 0.4 mL/min, holding at 95% B for 3.1 minutes with a flow rate of 0.8 mL/min, and then lowering back to 30% B in 0.2 minutes with a flow rate of 0.4 mL/min. The total run time was 7.0 minutes. The protonated analytes were quantified by selected reaction monitoring in the positive ionization mode by triple quadrupole mass spectrometer. The method was developed to detect aripiprazole lauroxil, N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole, as well as their respective deuterated standards, for analyte transitions of 664.4 to 464.2, 482.2 to 452.3, 446.2 to 285.2, and 452.2 to 289.1, respectively. The within-day variability ranged from −3.5% to 9.3% across the analytes tested, and the between-day variability ranged from −1.5% to 6.0%. The intrabatch and interbatch precision (percentage coefficient of variation) across all analytes was 0.0% to 8.4%.

Cytochrome P450 2D6 polymorphisms were evaluated by using Sanger sequencing, TaqMan chemistry, or gel-based genotyping methods. Subjects were classified as extensive, intermediate, or poor (PM) metabolizers based on haplotype of the genotyped variants. Subjects were classified as PMs if they possessed 2 non-functioning alleles, intermediate metabolizers if they had 1 non-functioning allele and 1 normal-functioning allele, or extensive metabolizers for any other combination. If the genotype for a single nucleotide polymorphism could not be determined or was missing, then the metabolizer status was unknown unless it could be extrapolated from the known genotypes.

FIGURE 1. Conversion of aripiprazole lauroxil to aripiprazole. Aripiprazole lauroxil is a prodrug of aripiprazole. After intramuscular injection of aripiprazole lauroxil, there is a slow dissolution of the drug particles (A), which is followed by enzyme-mediated cleavage, generating N-hydroxymethyl aripiprazole and lauric acid (B). Water-mediated hydrolysis converts N-hydroxymethyl aripiprazole to aripiprazole and formaldehyde (C).
Injection site was not a significant covariate in the model, confirming observations from a single-dose study that gluteal and deltoid sites of administration are interchangeable. Additional dosing regimens, including those in the placebo group received oral placebo on days 1, 29, and 57; patients in the aripiprazole lauroxil group received daily oral aripiprazole (15 mg), aripiprazole lauroxil 441 mg IM on days 1, 29, 57, and 85 (deltoid injection site), injections alternating between left and right side) A total of 838 aripiprazole and dehydro-aripiprazole were included in the model for each simulation, 500 individual aripiprazole concentration-time profiles were generated. Simulations were conducted to describe aripiprazole concentration-time profiles after repeated administration of aripiprazole lauroxil at dosages of 441 mg and 882 mg q4wk, the dose regimens that demonstrated antipsychotic efficacy in a phase 3 clinical trial. Additional details describing the model development methodology can be found in the Supplementary Data Content, Supplemental Digital Content 1, http://links.lww.com/JCP/A432. The final PopPK model was developed using a total of 21,620 aripiprazole and dehydro-aripiprazole concentration-time profiles for aripiprazole and dehydro-aripiprazole that contained depot compartments for each aripiprazole lauroxil administration as illustrated in Figure 2. The final model included covariates that described an increase in central volume of distribution for aripiprazole with body weight and a 20% decrease in apparent aripiprazole clearance for CYP2D6 PMs compared with non-PMs (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/JCP/A432).

**TABLE 1. Clinical Trials Included in the PopPK Analysis**

| Study | Population* | Study Design and Dosing |
|-------|-------------|------------------------|
| ALK9072-001 | Chronic stable schizophrenia (N = 40; 70% male; median age, 45 y) | Multicenter, randomized, double-blind, placebo-controlled, single-ascending dose study; oral aripiprazole 10 mg QD on days 1–5; randomized to receive aripiprazole lauroxil (221 mg, 441 mg, or 588 mg) or placebo IM on day 27 (gluteal injection site) A total of 2,733 aripiprazole and dehydro-aripiprazole were included in the model |
| ALK9072-002 | Chronic stable schizophrenia (N = 84; 77% male; median age, 46 y) | Multicenter, randomized, double-blind, placebo-controlled, multiple-dose study; oral aripiprazole 10 mg QD on days 1–5; randomized to receive aripiprazole lauroxil (441 mg, 662 mg, or 882 mg) or placebo IM on days 34, 62, 90, and 118 (gluteal injection site) A total of 7,888 aripiprazole and dehydro-aripiprazole were included in the model |
| ALK9072-101 | Chronic stable schizophrenia (N = 46; 70% male; median age, 45.5 y) | Multicenter, randomized, open-label, single-dose study; aripiprazole lauroxil 441 mg IM on day 1 (gluteal or deltoid injection site) A total of 2,546 aripiprazole and dehydro-aripiprazole were included in the model |
| ALK9072-102 | Chronic stable schizophrenia (N = 39; 64% male; median age, 47 y) | Multicenter, randomized, double-blind, placebo-controlled, multiple-dose study; aripiprazole lauroxil 441 mg IM on days 1, 29, 57, and 85 (deltoid injection site, injections alternating between left and right side) A total of 838 aripiprazole and dehydro-aripiprazole were included in the model |
| ALK9072-003 | Acute exacerbation of schizophrenia (N = 407; 69% male; median age, 40 y) | Multicenter, randomized, double-blind, placebo-controlled study; randomized to aripiprazole lauroxil (441 mg or 882 mg) or placebo IM on days 1, 29, and 57; patients in the aripiprazole lauroxil group received daily oral aripiprazole (15 mg), and those in the placebo group received oral placebo on days 1–21 under double-blind conditions (gluteal injection site) A total of 7,615 aripiprazole and dehydro-aripiprazole were included in the model |
| ALK9072-003EXT | Stable schizophrenia (N = 478; 58% male; median age, 39 y) | Multicenter, 52-week extension study of ALK9072-003; patients who received 441 mg or 882 mg aripiprazole lauroxil in ALK9072-003 continued the same dose, and those in the placebo group received either 441 mg or 882 mg aripiprazole lauroxil, depending on whether they were originally randomized to low-volume or high-volume placebo; new patients who did not participate in ALK9072-003 received 882 mg aripiprazole lauroxil |

*Patients included in the PopPK analysis, with the exception of ALK9072-003EXT. †Two sentinel patients received aripiprazole lauroxil 221 mg in the deltoid muscle.
IM indicates intramuscular; QD, daily.

The PopPK model was developed using a total of 21,620 aripiprazole and dehydro-aripiprazole plasma concentration measurements obtained from 616 patients with schizophrenia. Several covariates were tested for their influence on aripiprazole PK, which most notably included CYP2D6 phenotype, injection site (gluteal vs deltoid), and body weight (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A432). Injection site was not a significant covariate in the model, confirming observations from a single-dose study that gluteal and deltoid sites of administration are interchangeable. Additional details describing the model development methodology can be found in the Supplementary Data Content, Supplemental Digital Content 1, http://links.lww.com/JCP/A432.

Using the final PopPK model, Monte Carlo simulations were performed using Pharsight Trial Simulator version 2.2.2 (Certara USA, Inc, Princeton, NJ) and the structural model parameters and relevant covariates to evaluate a variety of different dosing scenarios. For each simulation, 500 individual aripiprazole concentration-time profiles were generated. Simulations were conducted to describe aripiprazole concentration-time profiles after repeated administration of aripiprazole lauroxil at dosages of 441 mg and 882 mg q4wk, the dose regimens that demonstrated antipsychotic efficacy in a phase 3 clinical trial. Additional dosing regimens, including 662 mg q4wk and 882 mg every 6 weeks (q6wk), were also explored. The impact of delayed dosing was also evaluated. Aripiprazole-equivalent doses of 300 mg, 450 mg, and 600 mg were used for modeling and simulation, which correspond to 441 mg, 662 mg, and 882 mg of aripiprazole lauroxil, respectively.

Pharmacokinetic data were also collected from a long-term extension study of the phase 3 trial. These data were not included in the PopPK model, but are described.

**RESULTS**

**Population Pharmacokinetics of Aripiprazole Lauroxil**

A PopPK model was developed that accurately described concentration-time profiles for aripiprazole and dehydro-aripiprazole after intramuscular administration of aripiprazole lauroxil and administration of oral aripiprazole in patients with schizophrenia by a 2-compartment disposition model for aripiprazole and dehydro-aripiprazole that contained depot compartments for each aripiprazole lauroxil administration as illustrated in Figure 2. The final model included covariates that described an increase in central volume of distribution for aripiprazole with body weight and a 20% decrease in apparent aripiprazole clearance for CYP2D6 PMs compared with non-PMs (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/JCP/A432). Aripiprazole lauroxil concentrations are not routinely measurable in human plasma, and as previously noted, N-hydroxymethyl aripiprazole is considered a minor metabolite, accounting for less than 10% of total drug-related material. Inclusion of N-hydroxymethyl aripiprazole data in the model did not further optimize the PopPK model; thus, the model was based on aripiprazole and dehydro-aripiprazole concentrations only.
Conversion of aripiprazole lauroxil to aripiprazole was described by a zero-order process, with the duration of appearance (36 days) estimated and a lag time (5.4 days) from the intramuscular administration site to the appearance of aripiprazole in the central compartment, suggesting that maximal aripiprazole concentrations are attained approximately 41 days after a single aripiprazole lauroxil administration (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/JCP/A432).

Simulations

Simulations were performed to describe aripiprazole concentration-time profiles after administration of aripiprazole lauroxil under various scenarios likely to be encountered in clinical practice.

Multiple-Dose Pharmacokinetics

Multiple-dose simulations for the dosing regimens evaluated in the phase 3, 12-week, randomized, double-blind, placebo-controlled efficacy trial were conducted for monthly doses of 441 mg and 882 mg aripiprazole lauroxil, with concomitant oral aripiprazole (15 mg) for 21 days after the first injection. Median aripiprazole concentrations after multiple monthly doses are shown in Figure 3. With these dosing regimens, aripiprazole reaches therapeutic concentrations within 4 days of treatment initiation and reaches steady state in more than 90% of simulated patients after the fourth monthly dose. Simulated concentrations after the fourth monthly dose, as well as data collected from an open-label, 52-week, long-term safety study in patients with stable schizophrenia, indicate no additional accumulation with long-term use (Fig. 4). Steady-state exposure estimates for aripiprazole after aripiprazole lauroxil administration are presented in Table 2; dehydro-aripiprazole exposure was approximately 38% of the aripiprazole exposure at steady state. The steady-state values for maximum aripiprazole concentrations ($C_{max,ss}$) and minimum aripiprazole concentrations ($C_{min,ss}$) indicate minimal fluctuation across the dosing interval for 441 mg and 882 mg q4wk, where the $C_{max,ss}$ and $C_{min,ss}$ values differ by only 10 to 15 ng/mL for these 2 regimens. These
results are consistent with the appearance of the aripiprazole concentration-time curve.

The 441 mg and 882 mg q4wk dosing regimens have previously been shown to result in efficacy with clinically meaningful improvements in schizophrenia that were demonstrated early in treatment and persisted throughout the study.16 Thus, aripiprazole concentrations resulting from administration of 441 mg q4wk and 882 mg q4wk, in conjunction with a 21-day oral supplementation period, are efficacious and are representative of a therapeutic concentration range for aripiprazole after administration of aripiprazole lauroxil.

**Alternative Dosing Regimens**

Aripiprazole concentrations after aripiprazole lauroxil administration are characterized by a prolonged release and sustained appearance of aripiprazole in the systemic circulation, resulting in concentrations that persist in the plasma for an extended time. In addition, formulation attributes allow for the feasibility of an intermediate dose of 662 mg. Simulations of a 662 mg q4wk dose regimen lead to aripiprazole concentrations within the therapeutic concentration range established for aripiprazole lauroxil (Fig. 3, Table 2), affording clinicians an additional dose option.

Multiple-dose simulations evaluating dosing intervals of longer than q4wk were also evaluated. Aripiprazole concentrations (Fig. 3) and resultant exposure estimates (Table 2) after repeated administration of 882 mg q6wk were compared with the monthly dosing regimens at steady state. As shown in Table 2, the 25th and 75th percentiles for PK parameters for the 662 mg q4wk and 882 mg q6wk regimens fall entirely within the lower and upper bounds of the reference range, the 25th percentile for 441 mg q4wk and 75th percentile for 882 mg q4wk. These simulations show that an 882 mg q6wk regimen leads to aripiprazole exposures that fall within the concentration range of the established therapeutic dose regimens of 441 mg q4wk and 882 mg q4wk. These results suggest that aripiprazole lauroxil q6wk is an effective dosing regimen and provides the opportunity for an extended dose interval for 882 mg.

**Missed Doses**

The impact of short-term delays (1–4 weeks), as well as prolonged nonadherence (>4 weeks), in dosing of aripiprazole lauroxil was evaluated. The time that could elapse before oral aripiprazole supplementation with the next intramuscular dose would be required was also assessed. Aripiprazole concentrations decreased by less than 10% and less than 25% when the time from last injection was 6 weeks and 8 weeks, respectively, irrespective of dose administered. It was not until 12 weeks after last injection that concentrations decreased by more than 50%.

Given the prolonged-release characteristics of aripiprazole lauroxil, when administration of a dose was delayed by up to 4 weeks after steady state was achieved, only marginal decreases in median aripiprazole plasma concentrations were observed for each of the evaluated dosing regimens (Fig. 5). Resumption of dosing without oral aripiprazole supplementation returns aripiprazole to concentrations associated with the therapeutic dose.
range when the time since last injection is 8 weeks or less for the 662 mg or 882 mg doses and 6 weeks or less for the 441 mg dose.

**DISCUSSION**

Given the complex PK of LAIs, the use of a population modeling approach to characterize the PK of aripiprazole lauroxil using data pooled from multiple studies is a useful method to fully understand the PK properties of this LAI. The final PopPK model was composed of central and peripheral compartments for aripiprazole and dehydro-aripiprazole and included model-supported covariates of body weight on central volume of distribution for aripiprazole and CYP2D6 metabolizer status on apparent aripiprazole clearance. No effect of age, sex, race, injection site location, injection volume, or dose level (see Supplementary Data Content, Supplemental Digital Content 1, http://links.lww.com/JCP/A432) was observed. Once the PopPK model was available, it was used to provide a PK rationale for dosing regimens of aripiprazole lauroxil including the dosage strengths, flexibility in dosing interval, and handling of missed doses.

Aripiprazole lauroxil exhibits absorption rate-limited elimination or “flip-flop” kinetics. After the slow dissolution of aripiprazole lauroxil that governs the release of the drug, the bio-transformation of aripiprazole lauroxil involves enzyme-mediated cleavage to form N-hydroxymethyl aripiprazole, which subsequently undergoes water-mediated hydrolysis, releasing aripiprazole. N-hydroxymethyl aripiprazole concentrations follow a similar time course to that of aripiprazole, but it is present at low levels, accounting for less than 10% of total drug-related material. Because N-hydroxymethyl aripiprazole hydrolysis is ongoing, it does not continue to accumulate with long-term administration once steady state is achieved. The dehydro-aripiprazole concentration-time course followed that of aripiprazole. Dehydro-aripiprazole accounted for approximately 38% of the aripiprazole exposure after aripiprazole lauroxil administration, which is comparable with what has been reported for oral aripiprazole.

The physiochemical properties of aripiprazole lauroxil result in slow dissolution and an extended PK profile that allows for flexibility, with respect to dose and dosing interval. Consistent with the slow dissolution of aripiprazole lauroxil that governs the release of drug, the PopPK model characterized the uptake of aripiprazole after aripiprazole lauroxil administration as having a 5.4-day lag time and a 36-day duration of absorption for a total duration of input into the systemic circulation of 41 days. These results suggest that aripiprazole concentrations increase throughout the dosing interval, and aripiprazole continues to enter the circulation from the previous injections when the subsequent monthly injections are administered.

Persistence of aripiprazole in the circulation has been observed with a single aripiprazole lauroxil injection, with aripiprazole present 3 months after administration. This persistence is also evident from the minimal fluctuation in concentrations across a dose interval as indicated by the occurrence of $C_{\text{min}}$ values that are not too distant from the $C_{\text{max}}$ values at steady state for any given dose.

The clinical implications of the PK characteristics of aripiprazole lauroxil are 2-fold. First, as a result of the slow-release characteristic of aripiprazole lauroxil, supplementation with oral aripiprazole after the first injection is required to rapidly achieve therapeutic concentrations. However, once the patient has finished oral supplementation and receives subsequent injections, the sustained and persistent release of aripiprazole into the plasma is consistent with the desired goal of having a long-acting formulation. For patients who do not return on time for their scheduled injection visit, the model-based simulations suggest that the persistent exposure to aripiprazole offers an additional window of time during which the health care provider has opportunity to locate a patient and administer the next injection without having to resume oral medication.

Aripiprazole concentrations increase steadily with each consecutive injection until steady state is reached, which occurs after the fourth monthly injection. Once steady state is achieved, no further accumulation occurs with long-term use because the totality of drug released from each injection at steady state reaches 100% because of the contributions from all previous injections. This is similar to what has been described for other LAI antipsychotics such as olanzapine long-acting injection. Because aripiprazole concentrations continue to increase for several weeks after the injection and do not begin to decline until after the next injection is administered, the dosing frequency of aripiprazole lauroxil cannot be determined based solely on half-life. In other words, although a half-life of 17 to 20 days has been reported, the start of the elimination phase of aripiprazole after aripiprazole lauroxil injection only begins after achievement of maximal concentrations ($C_{\text{max}}$ being approximately 41 days), explaining the persistence of aripiprazole concentrations for a duration that exceeds what the estimated half-life would suggest. Thus, consideration of factors beyond the elimination phase is important to understand the complex nature of LAI drug-release profiles and to optimize clinical effectiveness.

Our results suggest the potential use of PopPK modeling to identify an additional dose (662 mg q4wk) and dose interval (882 mg q6wk) not studied in a 12-week phase 3 clinical trial that demonstrated the safety and efficacy of 441 q4wk and 882 mg

![FIGURE 5](image-url) Median-simulated aripiprazole plasma concentrations after a missed aripiprazole lauroxil dose at steady state for (A) 441 mg q4wk, (B) 662 mg q4wk, and (C) 882 mg q4wk and q6wk doses, respectively. The asterisks represent the resumption of aripiprazole lauroxil after a missed dose.
q6wk in patients with schizophrenia. These findings play an instrumental role in the determination of dose and dose interval options used in clinical practice.

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AUTHOR DISCLOSURE INFORMATION

Dr Hard is an employee and stockholder of Alkermes, Inc. Dr Turncliff was an employee and stockholder at Alkermes, Inc, during the conduct of this study: Drs Sadler and Mills are ICON employees and contracted by Alkermes to perform the work described in this manuscript. 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.

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