

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207533Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

(Addendum to PBPK, Pharmacometric, Clin Pharm Reviews and Clin Pharm Addendum)

---

---

<b>NDA #:</b>	207533
<b>Proposed Brand Name:</b>	ARISTADA
<b>Generic Name:</b>	Aripiprazole Lauroxil
<b>Dosage Form:</b>	IM Injection (Extended-Release Suspension for IM Injection)
<b>Dosage Strength:</b>	441-mg, 662 mg, 882 mg- single use pre-filled syringe
<b>Indication:</b>	Treatment of Schizophrenia in adults
<b>Sponsor:</b>	Alkermes
<b>Submission Type:</b>	505(b)(2), NCE
<b>Submission Date:</b>	August 22 <sup>nd</sup> , 2014
<b>OCP Review Team:</b>	Praveen Balimane, Xiaofeng Wang, Kevin Krudys, Jeff Kraft, Christian Grimstein, Ping Zhao, Hao Zhu

---

---

The Office of Clinical Pharmacology (OCP) prepared the following clinical pharmacology reviews in connection with the Alkermes NDA for Aristada (aripiprazole lauroxil) extended-release injectable suspension (NDA 207533):

- Physiological-based Pharmacokinetic Modeling Review (PBPK Review) finalized April 29, 2015
- Pharmacometric Review (Pharmacometric Review) finalized April 22, 2015
- Clinical Pharmacology Review (Clin Pharm Review) finalized April 20, 2015
  - Clinical Pharmacology Review (Amendment to OCP Review) (Clin Pharm Addendum) finalized June 10, 2015
- Pharmacogenomics Review finalized July 1, 2015

The Clin Pharm Review and Clin Pharm Addendum include findings regarding the adequacy of the pharmacokinetic (PK) bridge, dosing recommendations, drug-drug interaction dose adjustment recommendations, and the impact of dose dumping. The Pharmacometric Review and PBPK Review include more specific data and simulations to support these findings. Since these reviews were drafted by a combination of different scientists, this document is intended to provide an additional overview of the OCP's conclusions and clarify the sources of data that have been relied on for approval of the Aristada NDA.

### Pharmacokinetic Bridging

#### Relative Bioavailability

Aristada is a 505(b)(2) NDA which was submitted by Alkermes. Alkermes conducted its own studies and relies on FDA's finding of safety and effectiveness for the listed drug Abilify (aripiprazole) Tablets (NDA 21436) to support approval. The applicant has submitted adequate pharmacokinetic (PK) data to establish a scientifically sound PK link (or "PK bridge") between its aripiprazole lauroxil product and the listed drug to justify reliance on the listed drug. To

establish the PK bridge, the applicant conducted four Phase 1 studies (ALK9072-001, ALK9072-101, ALK9072-002, ALK9072-102) and one Phase 3 study (ALK9072-003). The applicant conducted population PK modeling by simultaneously fitting Abilify Tablet data from two Phase 1 studies (ALK9072-001, ALK9072-002) and one Phase 3 study (ALK9072-003) and IM aripiprazole lauroxil data (from all five studies) to obtain the relative bioavailability of aripiprazole following IM aripiprazole lauroxil compared to the listed drug, Abilify Tablets (e.g., Pharmacometrics Review, pp. 14-25). The data demonstrated that the relative bioavailability of aripiprazole following administration of IM aripiprazole lauroxil was 58% compared to Abilify tablets. (Clin Pharm Review, pp. 25). All of the data for the PK bridging was generated by Alkermes and submitted in the Aristada NDA. The population PK modelling approach is a scientifically robust approach and was found to be acceptable for establishing the PK bridge.

## Exposure Window

The steady-state exposure levels of aripiprazole for the approved dose range of Abilify Tablets (low of 10 mg/day and high of 30 mg/day) were derived using the data submitted in the NDA by Alkermes. These levels were compared to Alkermes' data on the exposure levels of aripiprazole observed after administration of IM aripiprazole lauroxil. This comparison provided evidence of efficacy of the proposed doses and regimens of aripiprazole lauroxil.

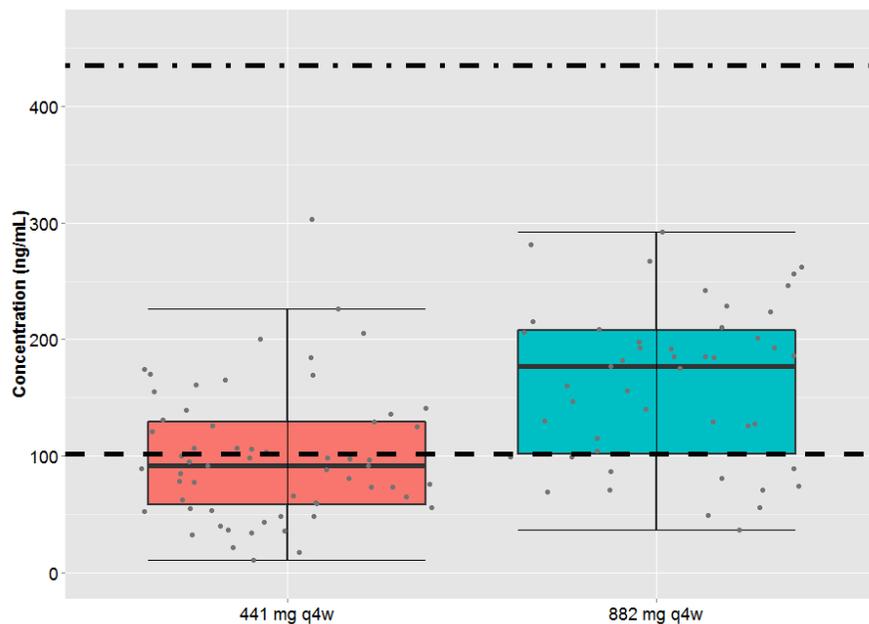
In studies ALK9072-001 and ALK9072-002, Alkermes generated data on the exposure levels of aripiprazole from Abilify Tablets.<sup>1</sup> Subjects in studies ALK9072-001 and ALK9072-002 received Abilify Tablets (Abilify, 10 mg) once daily for 5 days to assess individual tolerability and pharmacokinetics of Abilify Tablets after oral administration of Abilify Tablets. On day one, plasma concentrations of aripiprazole were collected before administration of Abilify Tablets and at 1, 4, 8, 12 and 24 hours after administration. Samples were also collected before administration of the Abilify Tablets on subsequent days, through Day 5. PK data was available in 126 subjects from these two studies. Because aripiprazole's accumulation is predictable from single-dose pharmacokinetics, the reviewer was able to use nonparametric superposition of the Day 1 data from studies ALK9072-001 and ALK9072-002 to predict steady state concentrations. Analyses were performed using Phoenix<sup>®</sup> Version 1.3. The mean steady state C<sub>min</sub> of aripiprazole following the administration of 10 mg of Abilify Tablets daily was calculated to be 102 ng/mL. Aripiprazole pharmacokinetics is dose proportional at steady state, so the reviewer was also able to calculate the mean steady state C<sub>max</sub> following 30 mg daily. The result was 435 ng/mL. The data Alkermes generated and submitted in NDA 207533 was sufficient to establish the exposure level to aripiprazole for the approved dose range for Abilify Tablets.<sup>2</sup> The Figure

---

<sup>1</sup> Subjects in study ALK9072-003 received Abilify tablets concurrently with IM aripiprazole lauroxil. Therefore the contribution of Abilify tablets to the measured aripiprazole concentration cannot be identified. Thus, the data from this study was not used to generate steady state aripiprazole levels from Abilify Tablets.

<sup>2</sup> We note that in the Clinical Pharmacology review (page 9 and Figure 2), the observed exposure levels for the approved dose range (10 mg to 30 mg QD) of oral aripiprazole were derived using the historical oral aripiprazole exposures for Abilify Tablets (NDA 21436). The lower bound, 93.3 ng/mL was defined as the mean steady state C<sub>min</sub> following 10 mg daily oral doses and the upper bound, 427 ng/mL, was defined as the mean steady state C<sub>max</sub> following 30 mg oral doses. These bounds are displayed as red dashed lines on many plots in the Pharmacometrics Review (e.g., page 1 and Figure 1 on page 2) and the Clinical Pharmacology review (e.g., Figure 2 on page 9). In the course of conducting a thorough review, the reviewers merely referred to that information for completeness although it was not necessary to do so. We further note that Alkermes' data contains exposure levels

below illustrates the exposure window of aripiprazole along with the observed aripiprazole concentrations on day 85 following IM aripiprazole lauroxil administration:<sup>3</sup> As the Figure shows, the observed aripiprazole concentrations following aripiprazole lauroxil are sufficiently similar to the exposure window established for Abilify Tablets.



### **Simulations to Inform Dosing Recommendations**

The Pharmacometric Review includes simulations using Alkermes' population PK model to assess the concentration-time profiles of the two unstudied dosing regimens (662 mg monthly and 882 mg every 6 weeks),<sup>4</sup> the dosing recommendations for treatment initiation, the dosing recommendation for missed/delayed doses, and the impact of dose dumping. The data that Alkermes submitted, along with the Agency's finding of safety and effectiveness for Abilify tablets as reflected in the labeling, was sufficient to establish the safety and effectiveness of all dose levels and regimens of Aristada (e.g., Clinical Pharmacology Review (pp. 7-14)).<sup>5</sup>

---

for Abilify tablets that provide the basis for our conclusions. As would be expected, only small differences in the exposure level for Abilify tablets between the historical data and the data Alkermes generated exist, due to factors such as sample size and patient demographics. Most importantly, the conclusions of the review remain the same regardless of the source of data used to derive the exposure levels for the approved dose range of Abilify.

<sup>3</sup> The black dashed lines represent the exposure window for the approved dose range of Abilify (low of 10 mg/day and high of 30 mg/day) established using the data submitted in the Alkermes NDA. The boxplots represent the aripiprazole concentrations on day 85 following IM aripiprazole lauroxil administration in the Phase 3 study (ALK9072-003). The exposure window established using the data submitted in the NDA by Alkermes also applies to all other plots containing the exposure window in the Pharmacometrics Review (Figures 1, 4, 5-9) and the Clin Pharm Review (Figures 2 and 10-14).

<sup>4</sup> We can conclude that these doses (662 mg monthly and 882 every six weeks) are effective because the simulated median steady state average concentrations fall well within the range of observed exposures of oral Abilify Tablets based on the studies conducted by Alkermes.

<sup>5</sup> The reviewers (at Pharmacometric Review pp. 38-39 and Clin Pharm Review in Figure 6, pp-13) used an independent model with data from the Abilify Tablet NDA (21436) to simulate steady state exposure levels for all

## **Drug-Drug Interaction Recommendations**

The PBPK Review assessed the adequacy of drug-drug interaction recommendations for Aristada. The “Background” section of the PBPK Review (pg. 6) refers to the Abilify Maintena NDA labeling and clinical pharmacology review noting that Alkermes used the same approach to develop drug-drug interaction recommendations in its draft product insert (Table 1). Such description was not necessary to support approval of Aristada. As noted below, the drug-drug interaction recommendations for the Aristada NDA can be derived solely from studies conducted by Alkermes or reliance on the Agency’s previous findings of safety and effectiveness for the listed drug (Abilify Tablets).

In addition, the PBPK Review for Aristada refers to or mentions the Abilify Tablet NDA package (21436) and a publication by Boulton *et. al.* in the following places:

- Appendix Table 1: Input parameter for aripiprazole PBPK model (p. 17) refers to certain review sections in the Abilify Tablet NDA (21436) and the publicly available literature article by Boulton *et. al.*
- Appendix Figures 1, 2, 3 and 4: Refers to Boulton *et. al.* and Clinical Study 98-206 and 98-207 in Abilify Tablet NDA (21436) review.

These table and figures were generated by the applicant based on information that is publicly available on the internet (i.e. published Boulton study and Abilify Tablet NDA review) and were included in Alkermes’s PBPK study report (Reference 1 of the PBPK review). The applicant presented these results to demonstrate that the aripiprazole model (which is a component of the applicant’s final Aristada model) was able to describe historical PK data under different clinical situations for drug-drug interactions.

The reviewer included these data for completeness in the review of overall adequacy of the applicant’s final PBPK model for Aristada, but the data itself were not needed to develop drug-drug interaction recommendations for Aristada. (References to applicant’s PBPK report have been made in the caption or footnote of these table and figures in PBPK review.) Rather, Alkermes can rely on the Agency’s previous findings of drug-drug interactions for the listed drug Abilify tablets as described in the labeling (Abilify label: Sections 7 and 12.3) as well as published data in the literature on the listed drug. The drug-drug interaction recommendations for Aristada were further adjusted based on modeling simulations using data Alkermes collected in its own Phase 1 and Phase 3 studies (e.g., PBPK Review, pp. 7-15, Appendix Tables 3-8 and figures 6-8). The drug-drug interaction recommendations for Aristada can be derived solely from data and information submitted by Alkermes on aripiprazole lauroxil and the Agency’s previous findings of safety and effectiveness for the listed drug Abilify Tablets as described in the labeling. It was not necessary to refer to additional information.

In sum, OCP concludes that Alkermes provided adequate data to support approval of the Aristada NDA and that the NDA is acceptable from a clinical pharmacology standpoint. The NDA includes a scientifically appropriate PK bridge to justify reliance on the findings of safety

Abilify Tablet dose levels to confirm the analyses already conducted by Alkermes, although it was not necessary to do so to support approval of Aristada.

and effectiveness for the listed drug (Abilify Tablets) and Alkermes' data along with findings for the listed drug, Abilify tablets, were used to inform dosing recommendations and to determine the drug-drug interaction recommendations for Aristada.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

PRAVEEN BALIMANE  
10/01/2015

XIAOFENG WANG  
10/01/2015

KEVIN M KRUDYS  
10/01/2015

PING ZHAO  
10/01/2015

HAO ZHU  
10/01/2015

**OFFICE OF CLINICAL PHARMACOLOGY  
GENOMICS GROUP REVIEW**

---

<b>NDA/BLA Number</b>	207533
<b>Submission Date</b>	08/22/2014
<b>Applicant Name</b>	Alkermes Inc.
<b>Generic Name</b>	Aripiprazole Lauroxil
<b>Proposed Indication</b>	Schizophrenia
<b>Primary Reviewer</b>	Jeff Kraft, Ph.D.
<b>Secondary Reviewer</b>	Christian Grimstein, Ph.D.

---

**EXECUTIVE SUMMARY**

The sponsor's classification of subjects as Extensive (EM), Intermediate (IM), or Poor (PM) metabolizers based on the haplotype of the genotype alleles is acceptable. Concordance of metabolizer status between the sponsor's assignments and the reviewer's assignments was 100%. In the reviewer's assessment, the metabolizer status of subjects can be reliably utilized in the PopPK analyses, which demonstrates that CYP2D6 metabolizer status has a significant impact on aripiprazole exposures.

**1 Background**

Aripiprazole lauroxil is an extended-release injectable suspension, for intramuscular use in the gluteal or deltoid muscle. Aripiprazole is a small molecule modulator of multiple monoaminergic receptors whose activity is thought to be primarily mediated through a combination of partial agonist activity to the dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at the serotonin 5-HT2A receptors. The proposed indication for aripiprazole lauroxil is for the treatment of schizophrenia. This NDA is a 505(b)(2) submission that will rely in part on the FDA's previous findings of safety and efficacy for oral aripiprazole (Abilify®).

Based on the information contained in the Abilify® package insert (aripiprazole), aripiprazole is primarily metabolized by three biotransformation pathways (dehydrogenation, N-dealkylation, and hydroxylation) in humans. The enzymes responsible for the three biotransformation pathways in humans were determined by in vitro metabolism studies with recombinant human cytochrome P450 isoforms and human liver microsomes. Both CYP3A4 and CYP2D6 were responsible for dehydrogenation and hydroxylation; whereas N-dealkylation was catalyzed by CYP3A4.

The sponsor has proposed dosing recommendations for CYP2D6 PMs, (b) (4)  
PopPK data showing PMs have a 23% decrease in CL/F (*PopPK Study Report, Figure 4-8*) and PBPK analyses predicting IMs and PMs have 26% and 79% higher C<sub>ss</sub> as compared to EMs, respectively (*Study Report ALK9072-052, page 49, table 8*). (b) (4)

The purpose of this review is to evaluate the CYP2D6 genotype information submitted by the sponsor and confirm the metabolizer status of subjects utilized in the PopPK analysis for aripiprazole lauroxil.

## 2 Submission Contents Related to Genomics

The sponsor submitted the following reports and datasets related to the pharmacogenetic (PGx) analysis of aripiprazole lauroxil:

Table 1: Reports and Datasets Pertaining to PGx Analyses of Aripiprazole Lauroxil

<i>ID</i>	<i>Report Description</i>	<i>Datasets</i>
---	Subject Level Genotypes for Study 001	adxg.xpt
---	Subject Level Genotypes for Study 002	adpg.xpt
---	Subject Level Genotypes for Study 003	adpg.xpt
---	Subject Level Genotypes for Study 101	adpg.xpt
---	Subject Level Genotypes for Study 102	adpg.xpt
ALK9072-050 / ALK9072-051	Population Pharmacokinetic Analysis of Aripiprazole and Dehydro-Aripiprazole Following IM Administration of Aripiprazole Lauroxil in Schizophrenic Patients	---
ALK9072-052	Quantitative Prediction of the Systemic Exposure of Aripiprazole after Administration of Aripiprazole Lauroxil using Prior In Vitro And In Vivo Data: Potential For Drug-Drug Interactions as a Victim	---
AVP02-00-00	Validation Plan for CYP2D6 Multiplex PCR	---
AVP029-00	Validation Plan for CYP2D6*16	---
AVP039-27-02	Detection of CYP2D6 *2 (rs16947), *2L (rs1985842), *3 (rs35742686), *4 (rs3892097), *6 (rs5030655), *7 (rs5030867), *8 (rs5030865), *9 (rs5030656), *10 (rs1065852), *14 (rs5030865), *17 (rs28371706), *19 (rs72549353), *21 (rs72549352), *25 (rs-N/A), *29 (rs59421388), *38 (rs72549351), *41 (rs28371725), *45 (rs28371710), and *46 (rs28371696) using Sanger Sequencing Technology	---
AVP068-00-02	Cross Validation of CYP2D6 *5(Gene Deletion) and GD (Gene Duplication) Gel Based Genotyping Procedure	---
AVP120-00	Detection of CYP2C19*17 (rs12248560), and CYP2D6 *2 (rs16947) and *41 (rs28371725) using TaqMan Chemistry	---

A summary of the studies included in the PopPK analysis which investigated the effects of CYP2D6 metabolizer status on aripiprazole lauroxil PK is provided in table 2 below. Data from a total of five clinical trials were included in the analysis, which consisted of four phase 1 trials and one phase 3 trial in subjects with schizophrenia.

The PopPK dataset included 616 subjects; subjects with evaluable dosing, actual sampling time, and N-hydroxymethyl aripiprazole, aripiprazole and dehydro-aripiprazole concentration data were included in the analysis. DNA samples were collected from subjects who consented to optional participation in PGx research during each study. Of the 616 subjects who were utilized for the PopPK analyses, all subjects were also listed in the genotype dataset. DNA samples were analyzed for genetic variants in the genes encoding CYP2D6. Table 3 lists the variants investigated, methods utilized, and functional consequences of these variants.

Table 2: Clinical Trials Utilized for PopPK Analyses

<i>Study</i>	<i>Description</i>	<i>Number of Subjects in PopPK Dataset</i>	<i>Number of Subjects in Genotype Dataset</i>
ALK9072-101	A Phase 1, Randomized, Open Label, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072 Following Administration to the Deltoid or Gluteal Muscle in Subjects with Chronic Stable Schizophrenia	46	46
ALK9072-102	A Phase 1, Randomized, Double-blind, Placebo-controlled, Multiple-dose Study to Evaluate the Safety and Tolerability of ALKS 9072 Following Deltoid Administration in Subjects with Chronic Stable Schizophrenia	39	54
ALK9072-001	A Phase 1, Randomized, Double-blind, Placebo-controlled, Single-ascending-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072 in Subjects with Chronic Stable Schizophrenia	40	40
ALK9072-002	A Phase 1, Randomized, Double-blind, Placebo-controlled, Multiple-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072 in Subjects with Chronic Stable Schizophrenia	84	77
ALK9072-003	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of ALKS 9072 in Subjects with Acute Exacerbation of Schizophrenia	407	554
<b>TOTAL</b>		<b>616</b>	<b>771</b>

Source: PopPK study report (ALK9072-050/ALK9072-051), Table 3-1, Table 10.

Table 3: Polymorphisms Tested and Genotyping Methods Utilized for CYP2D6

<i>Polymorphism</i>	<i>Identifier</i>	<i>Genotyping Method</i>	<i>CYP2D6 Enzymatic Activity</i>
CYP2D6*2	rs16947	Taqman	Normal
CYP2D6*3	rs35742686	Sanger	None
CYP2D6*4	rs3892097	Sanger	None
CYP2D6*5	Deletion	Gel-Based	None
CYP2D6*6	rs5030655	Sanger	None
CYP2D6*7	rs5030867	Sanger	None
CYP2D6*16	N/A	Gel-Based	None

Source: Reports AVP039-27-02, AVP068-00-02, AVP129-00, and AVP120-00.

### 3 Key Questions and Summary of Findings

#### 3.1 Is the sponsor's predicted metabolizer status classification accurate based on reported genotype data?

*Yes. While the sponsor genotyped only alleles associated with lack of functional CYP2D6, the assigned metabolizer status categories were completely concordant with the reviewer's assignments.*

##### **Sponsor's Analyses:**

Subjects were classified as Extensive (EM), Intermediate (IM), or Poor (PM) metabolizers based on haplotype of the genotyped variants. Subjects were classified as PMs if they possessed 2 non-functioning alleles, IMs if they had one non-functioning allele and one normal functioning allele, or EMs for any other combination. If genotype for a SNP could not be determined or was missing, then the metabolizer status was unknown unless it could be extrapolated from the known genotypes. A summary of the sponsor's assigned metabolizer status for all subjects in the PopPk dataset are provided in Table 4.

Table 4: Sponsor's Assignment of CYP2D6 Metabolizer Status

<i>Metabolizer Status</i>	<i>Number of Subjects</i>	<i>Percentage of PopPK Subjects (N=616)</i>
<i>Extensive</i>	360	59%
<i>Intermediate</i>	163	26%
<i>Poor</i>	23	4%
<i>Inconclusive/Missing</i>	70	11%

Source: PopPK study report (ALK9072-050/ALK9072-051), Table 10.

##### **Reviewer's Analyses:**

Subjects were re-classified using identical methodologies as listed above using the sponsor's provided subject level genotype dataset. The reviewer notes that all sponsor calls were concordant with the reviewer's calls. It should be noted that the sponsor only genotyped a limited number of alleles in order to classify subjects as EMs, IMs, or PMs and that these alleles all abolish function of CYP2D6 gene activity. There are several known variants (e.g. \*10, \*9, \*41) that lead to decreased activity for CYP2D6 that the sponsor did not genotype which could lead to some subjects currently classified as EMs to be reclassified as IMs if these other variants were genotyped. The reviewer does not anticipate that the failure to genotype known IM variants will

impact proposed dosing recommendations based on CYP2D6 metabolizer status given that these recommendations are similar for CYP2D6 EMs and IMs.

#### **4 Summary and Conclusions**

Overall, the sponsor's classification of subjects as EM, IM, or PM based on the haplotype of the genotyped alleles is acceptable. Concordance between the sponsor's assignments and the reviewer's was 100%. All the subjects metabolizer status assignments were confirmed by the reviewer, therefore, the CYP2D6 metabolizer status data, utilized by the sponsor in the PopPK analyses demonstrating that CYP2D6 metabolizer status has a significant impact on aripiprazole exposures, is robust and reliable.

#### **5 Recommendations**

None.

##### **5.1 Post-marketing studies**

None.

##### **5.2 Label Recommendations**

None.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JEFFREY B KRAFT  
07/01/2015

CHRISTIAN GRIMSTEIN  
07/01/2015

**ADENDUM TO ORIGINAL BIOPHARMACEUTICS REVIEW**

**Division of Biopharmaceutics - Office of Pharmaceutical Quality**

<b>Application No.:</b>	NDA 207533	<b>Biopharmaceutics Reviewer:</b> Elsbeth Chikhale, Ph.D.	
<b>Submission Date:</b>	August 22, 2014		
<b>Division:</b>	Division of Psychiatry Products	<b>Biopharmaceutics Branch Chief (acting):</b> Angelica Dorantes, Ph.D.	
<b>Applicant:</b>	Alkermes	<b>Acting Division Director:</b> Paul Seo, Ph.D.	
<b>Trade Name:</b>	ARISTADA™	<b>Date Assigned:</b>	October 8, 2014
<b>Generic Name:</b>	Aripiprazole lauroxil extended release injectable suspension	<b>Date of Review:</b>	June 18, 2015
<b>Indication:</b>	Treatment of schizophrenia	<b>Type of Submission:</b> 505(b)(2) Original New Drug Application	
<b>Dosage form/ Strengths:</b>	Extended release injectable suspension / 441 mg/ <sup>(b)(4)</sup> mL, 662 mg/ <sup>(b)(4)</sup> mL, and 882 mg/ <sup>(b)(4)</sup> mL		
<b>Route of Administration:</b>	Intramuscular (IM) injection		

**BACKGROUND**

***Submission:***

This 505(b)(2) Application for the proposed ARISTADA™ (aripiprazole lauroxil) extended-release injectable suspension, relies on FDA’s previous findings of safety and efficacy for the listed drug (LD), Abilify® (aripiprazole) Tablets marketed by Otsuka America Pharmaceutical, Inc. approved under NDA 21436.

Reference is made to the original Biopharmaceutics Review for this NDA, dated April 22, 2015. An agreement on the final acceptance criteria for the dissolution test was not reached at the time of the original Biopharmaceutics Review (April 22, 2015).

***Biopharmaceutics Information Request:***

The following information request was sent to the Applicant on April 29, 2015 as part of the product quality discipline review letter:

*As per FDA and ICH recommendations the dissolution acceptance ranges should be mean ± <sup>(b)(4)</sup> % for the initial and middle time point, and NLT <sup>(b)(4)</sup> % at the final time point.*

*Specifically, based on the provided dissolution data, we recommend that the dissolution acceptance criteria range for the 24 hours sampling time point be revised to <sup>(b)(4)</sup> %.*

*Implement the following acceptance criteria for the dissolution test of your product for release and on stability.*

<i>FDA's Recommended Dissolution Acceptance Criteria for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension</i>	
<i>Sampling Time</i>	<i>% Drug Dissolved</i>
6 hours	(b) (4) %
24 hours	(b) (4) %
96 hours	NLT (b) (4) %

Revise the specifications table accordingly and provide a copy of the updated specifications table of the proposed drug product.

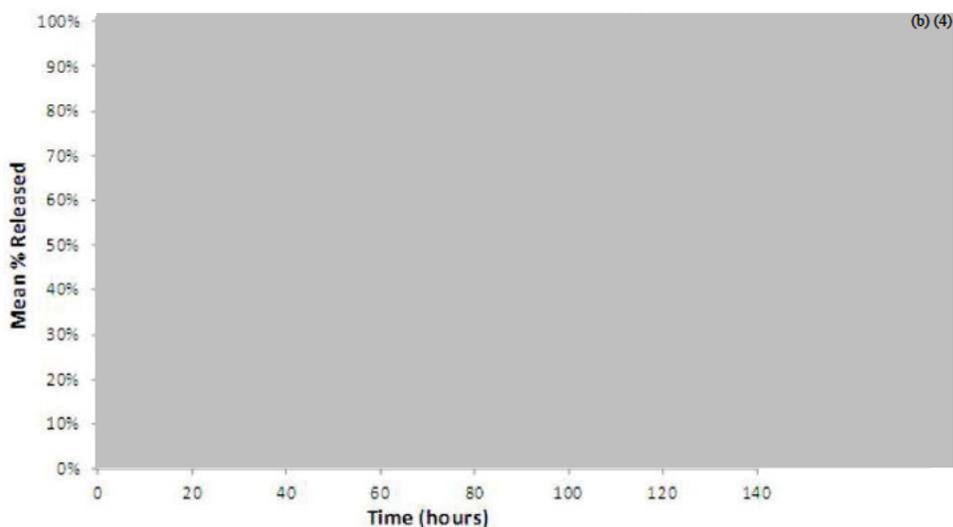
**Applicant's Response to the Biopharmaceutics Information Request:**

The Applicant provided the following response to the Biopharmaceutics Information Request in an NDA amendment dated 5/15/15:



(b) (4)

Figure 1: Comparison of the In Vitro Profiles for Different Dosage Strengths in Common 1000 mL Volume



(b) (4)

Table 1: Release Profiles for Dose Range in Common 1000 mL Volume

Dose	Media Volume (mL)	Mean % Released							Absolute Difference Range vs. 882 mg in 1000 mL
		6 h	24 h	30 h	48 h	72 h	96 h	120 h	
441 mg	1000	(b) (4)							(b) (4)
662 mg	1000								
882 mg	1000								

Table 2: Comparison between Scaled and Common Volumes for the 441 mg Dose

Lot	Mean % Released at 24 Hour Time Point	
	Scaled Volume (b) (4)	Common Volume (b) (4)
453-0008BA	(b) (4)	(b) (4)
453-0020AB	(b) (4)	(b) (4)
453-0021AA	(b) (4)	(b) (4)
453-0023AA	(b) (4)	(b) (4)
453-0024AA	(b) (4)	(b) (4)
453-0025AA	(b) (4)	(b) (4)

The Applicant proposes to implement a  $\pm$  (b) (4)% range for the dissolution acceptance criteria by establishing separate specifications for each dose, as presented in the following Table.

Table 3: Proposed Dissolution Acceptance criteria for Common 1000 ml Volume

Dissolution Acceptance Criteria for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension			
Sampling Time	% Drug Dissolved		
	441 mg	662 mg	882 mg
6 hours	(b) (4)		
24 hours	(b) (4)		
96 hours	(b) (4)		

**Reviewer's Assessment of the Applicant's Response to the Biopharmaceutics Information Request:**

(b) (4)

Aripiprazole Lauroxil Concentration (mg/mL)<sup>a</sup>

(b) (4)

The original

Biopharmaceutics review has described the selection of the dissolution method, which was found to be acceptable. The Applicant's proposal to set different dissolution acceptance criteria for each strength is considered acceptable. Therefore, the following proposed dissolution acceptance criteria for the 3 strengths are acceptable:

Dissolution Acceptance Criteria for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension			
	% Drug Dissolved		
Sampling Time	441 mg	662 mg	882 mg
6 hours	(b) (4)		
24 hours	(b) (4)		
96 hours	(b) (4)		

The Applicant was asked to revise the drug product specification table accordingly. The revised drug product specification table was submitted in an amendment dated 6/12/15. The revised drug product specification table reflects the above acceptable dissolution acceptance criteria.

**RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 207533 for ARISTADA™ (aripiprazole lauroxil) extended release suspension for IM injection 441 mg/ (b) (4) mL, 662 mg/ (b) (4) mL, and 882 mg/ (b) (4) mL is recommended for **APPROVAL**.


 Digitally signed by Elsbeth G. Chikhale -S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136142, cn=Elsbeth G. Chikhale -S  
 Date: 2015.06.18 12:09:17 -04'00'

**Elsbeth Chikhale, Ph.D.**  
Biopharmaceutics Reviewer  
Division of Biopharmaceutics/OPQ


 Digitally signed by Angelica Dorantes -S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300070843, cn=Angelica Dorantes -S  
 Date: 2015.06.18 12:13:13 -04'00'

**Angelica Dorantes, Ph.D.**  
Acting Biopharmaceutics Branch Chief  
Division of Biopharmaceutics/OPQ

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Division of Biopharmaceutics - Office of Pharmaceutical Quality</b>			
<b>Application No.:</b>	NDA 207533	<b>Biopharmaceutics Reviewer:</b> Elsbeth Chikhale, Ph.D.	
<b>Submission Date:</b>	August 22, 2014		
<b>Division:</b>	Division of Psychiatry Products	<b>Biopharmaceutics Branch Chief (acting):</b> Angelica Dorantes, Ph.D.	
<b>Applicant:</b>	Alkermes	<b>Acting Division Director:</b> Paul Seo, Ph.D.	
<b>Trade Name:</b>	ARISTADA™	<b>Date Assigned:</b>	October 8, 2014
<b>Generic Name:</b>	Aripiprazole lauroxil extended release injectable suspension	<b>Date of Review:</b>	April 22, 2015
<b>Indication:</b>	Treatment of schizophrenia	<b>Type of Submission:</b> 505(b)(1) Original (rolling) New Drug Application - Priority	
<b>Dosage form/strengths</b>	Extended release injectable suspension /441 mg/ <sup>(b)(4)</sup> mL, 662 mg/ <sup>(b)(4)</sup> mL, and 882 mg/ <sup>(b)(4)</sup> mL		
<b>Route of Administration</b>	Intramuscular (IM) injection		

**OVERALL SUMMARY**

***Submission:***

This 505(b)(2) application for the proposed ARISTADA™ (aripiprazole lauroxil) extended-release injectable suspension, relies on FDA’s previous findings of safety and efficacy for the listed drug (LD), Abilify® (aripiprazole) Tablets marketed by Otsuka America Pharmaceutical, Inc. approved under NDA 21436.

The proposed drug product is considered a drug-device combination product because it is supplied as a kit containing a pre-filled syringe and safety needles. The product is indicated for the treatment of schizophrenia, and will be administered as an intramuscular injection by either the deltoid (441 mg) or gluteal route (442 mg, 662 mg, and 882 mg) monthly or once every 6 weeks. Aripiprazole lauroxil is a covalent non-ester modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole and is considered a new molecular entity (NME).

The proposed drug product is designed to provide patients with a long acting injectable (LAI) medication, which is claimed to be achieved by the initial dissolution of the aripiprazole lauroxil, followed by enzymatic hydrolysis to *N*-hydroxy-methyl aripiprazole, which then converts to aripiprazole and formaldehyde. The Applicant did not conduct a relative bioavailability or bioequivalence study between the listed drug (tablets) and the proposed drug (IM injectable suspension). Instead the Applicant conducted several (phase 1 and phase 3) PK, safety, and efficacy studies using two different formulations of the proposed drug product.

**Review:**

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the proposed dissolution methodology for the proposed product
- 2) the proposed dissolution acceptance criteria for the proposed product
- 3) the bridging of the formulations throughout development

**CONCLUSIONS:**

The Division of Biopharmaceutics has evaluated the information provided in NDA 207533 and concludes the following:

**1) Dissolution method:**

The following dissolution method is acceptable:

USP Apparatus	II
Media	50 mM Phosphate buffer, 6% SDS, 90 mM Sodium Sulfate, pH 8.00
Media Temperature	37.0 ± 0.5
Paddle Speed (rpm)	75

**2) Dissolution acceptance criteria:**

The proposed (b)(4) dissolution acceptance criteria range of (b)(4)% for the 24 hours sampling time point is not acceptable. The following dissolution acceptance criteria are recommended for batch release and on stability

- At 6 hour: (b)(4)%
- At 24 hour: (b)(4)%
- At 96 hour: NLT (b)(4)%

The above recommended criteria will send to the Applicant in a product quality discipline review letter.

**3) Bridging of the formulations:**

All relevant studies and the pivotal clinical studies used drug product batches with the proposed commercial formulation. Therefore, additional bridging is not needed.

**Information request to be included in the product quality discipline review letter:**

*As per FDA and ICH recommendations the dissolution acceptance ranges should be mean ± (b)(4)% for the initial and middle time point, and NLT (b)(4)% at the final time point.*

*Specifically, based on the provided dissolution data, we recommend that the dissolution acceptance criteria range for the 24 hours sampling time point be revised to (b)(4)%.*

*Implement the following acceptance criteria for the dissolution test of your product for release and on stability.*

<i>FDA's Recommended Dissolution Acceptance Criteria for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension</i>	
<b>Sampling Time</b>	<b>% Drug Dissolved</b>
<i>6 hours</i>	(b)(4)%
<i>24 hours</i>	(b)(4)%
<i>96 hours</i>	NLT (b)(4)%

*Revise the specifications table accordingly and provide a copy of the updated specifications table of the proposed drug product.*

**RECOMMENDATION:**

At this time of the review process (GRMP date) an agreement on the final acceptance criteria for the dissolution test has not been reached with the Applicant. Therefore, the Biopharmaceutics recommendation on the approvability of NDA 207533 for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension is **PENDING**.

It is noted that after the dissolution acceptance criteria are finalized with the Applicant, an Addendum to this original review with the final Biopharmaceutics recommendation on the acceptability of this NDA will be uploaded in Panorama.

**Elsbeth G. Chikhale - S**  
Digitally signed by Elsbeth G. Chikhale -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136142, cn=Elsbeth G. Chikhale -S  
Date: 2015.04.22 21:41:52 -04'00'

**Elsbeth Chikhale, Ph.D.**  
Biopharmaceutics Reviewer  
Division of Biopharmaceutics/OPQ

**Angelica Dorantes -S**  
Digitally signed by Angelica Dorantes -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300070843, cn=Angelica Dorantes -S  
Date: 2015.04.22 21:45:19 -04'00'

**Angelica Dorantes, Ph.D.**  
Biopharmaceutics Team Leader  
Division of Biopharmaceutics/OPQ

## BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

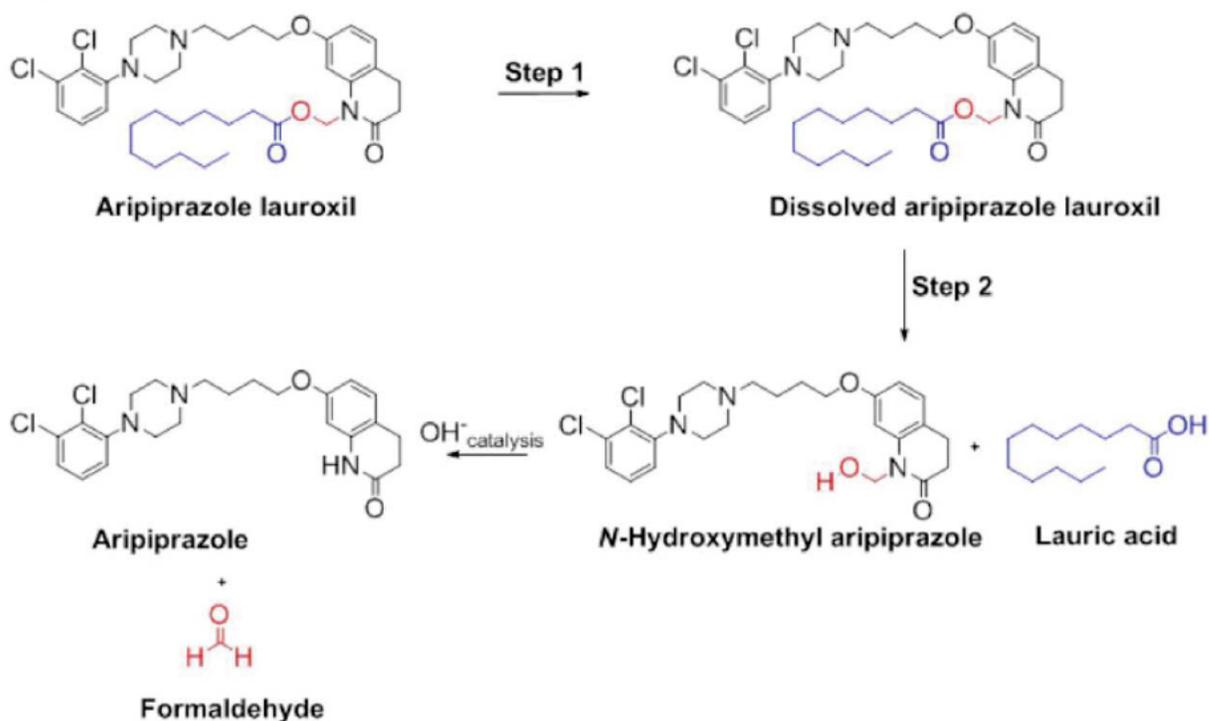
### BIOPHARMACEUTICS INFORMATION:

The Applicant is seeking approval of a 505(b)(2) New Drug Application (NDA) for aripiprazole lauroxil extended-release injectable suspension, which relies on FDA's previous findings of safety and efficacy for the listed drug (LD), Abilify® (aripiprazole) Tablets marketed by Otsuka America Pharmaceutical, Inc. approved under NDA 21436.

(b) (4)

The proposed product is designed to dissolve, followed by enzymatic hydrolysis to N-hydroxymethyl aripiprazole which degrades to aripiprazole. Serum levels of the ester were reported to be below the method's limit of detection. N-Hydroxymethyl aripiprazole levels are generally 5-10% that of aripiprazole in human serum.

**Figure 1: Illustration of Release Mechanism of the Dosage Form**



(b) (4)

Dissolution is considered a critical quality attribute for the proposed drug products and will be tested as part of the drug product release and stability testing.

**PROPOSED FORMULATION:**

The qualitative and quantitative composition of the proposed drug product is shown in the table below:

Component	Amount per Unit Dose Strength Expressed as					
	mg			% w/w		
	441 mg	662 mg	882 mg	441 mg	662 mg	882 mg
(b) (4) Aripiprazole Lauroxil	441	662	882	(b) (4)		
Sorbitan Monolaurate	(b) (4)					
Polysorbate 20						
Sodium Chloride						
Sodium Phosphate Dibasic Anhydrous						
Sodium Phosphate Monobasic						
Water for injection						
Total per unit dose strength						
Total volume per unit dose strength (mL)	1.6	2.4	3.2	NA	NA	NA
Overfill factor	(b) (4)			NA	NA	NA
Total weight in PFS (mg) <sup>a</sup>	(b) (4)			NA	NA	NA
Total volume in PFS (mL) <sup>a</sup>	(b) (4)			NA	NA	NA

NA = not applicable

The drug product is supplied as a kit containing the pre-filled syringe and safety needles. The proposed dosing is to take a dose of 441 mg, 662 mg or 882 mg monthly or 882 mg dose every 6 weeks.

**PROPOSED DISSOLUTION METHODS AND ACCEPTANCE CRITERIA:****The proposed dissolution method is:**

Apparatus 2 (paddle), 50 mM Phosphate buffer, 90 mM Sodium Sulfate, 6% SDS, 1000 mL total medium volume, pH 8.00 at 37°C, and 75 rpm

**Dissolution Method Development Report:**

The dissolution method development report (report702-03463 in 3.2.P.5.6) includes the following information:

➤ **Background:**

Conversion to aripiprazole *in vivo* is governed by (b) (4), followed by hydrolysis that results in extended systemic exposure of aripiprazole (Figure 1). (b) (4)

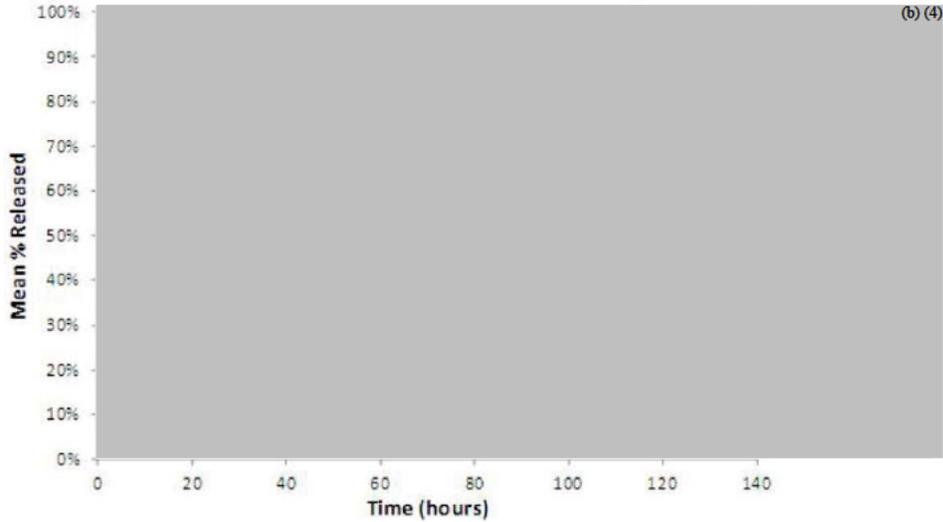


The dissolution method has been validated for repeatability, intermediate precision and sample stability. The HPLC method used for sample analysis has been validated for specificity, linearity, range, standard stability and robustness. Accuracy was inferred from specificity, linearity and precision of the method.

The proposed dissolution method parameters are summarized in the Table below.

USP Apparatus	II
Media	50 mM Phosphate buffer, 6% SDS, 90 mM Sodium Sulfate, pH 8.00
Media Temperature	37.0 ± 0.5
Sample Preparation <sup>1</sup>	441 mg: (b) (4)
	662 mg:
	882 mg:
Paddle Speed (rpm)	75
Sampling Method	Manual
Sampling Time points (hours)	6, 24, 30, 48, 72, 96, 120
Sampling windows	± 15 minutes for 6 and 24 hour time points ± 30 minutes for 30 hour – 120 hour time points
Sampling Procedure	(b) (4)

Representative dissolution profiles obtained using the proposed dissolution method, are shown in the Figure below.



**Reviewer’s assessment of the proposed dissolution method: ACCEPTABLE**

The proposed dissolution test parameters have been justified with respect the selected dissolution media, paddle speed, pH, and high surfactant concentration in the medium. (b) (4)

(b) (4)

The proposed dissolution method can still be used as a quality control test for drug product release and stability testing.

**Proposed dissolution acceptance criteria:**

The Applicant’s proposed criteria for the dissolution test are as follow:

- 6 hour: (b) (4) %
- 24 hour: (b) (4) %
- 96 hour: NLT (b) (4) %

**Applicant’s justification for the proposed dissolution acceptance criteria:**

Drug dissolution data for the 20 batches used in the clinical efficacy and safety studies, and 7 registration stability batches (27 batches total) were used to establish the dissolution specification criteria. Six, 24 and 96 hour sampling time points were selected to adequately characterize the ascending and plateau phases of the drug release curve (initial, middle and terminal phases of the drug release profile) based on the following dissolution data:

Dose	Media Volume (mL)	Mean % Released						
		6 h	24 h	30 h	48 h	72 h	96 h	120 h
441 mg	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
662 mg		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
882 mg		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The dissolution data at the 6, 24 and 96 hour time points do not change significantly during the stability study of the packaged product at the recommended storage conditions of 25 °C/60% RH. The overall dissolution data support a (b) (4) range for the 24 hours sampling time point. Therefore the Applicant will be requested to revise the criteria range to (b) (4) % at the 24 hours sampling time point.

**Reviewer’s initial assessment of the proposed dissolution acceptance criteria: PENDING**

***The following information request will be sent to the Applicant:***

*As per FDA and ICH recommendations the dissolution acceptance ranges should be mean ± (b) (4) % for the initial and middle time point, and NLT (b) (4) % at the final time point.*

*Specifically, based on the provided dissolution data, we recommend that the dissolution acceptance criteria range for the 24 hours sampling time point be revised to (b) (4) %.*

*Implement the following acceptance criteria for the dissolution test of your product for release and on stability.*

<i>FDA’s Recommended Dissolution Acceptance Criteria for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension</i>	
<b><i>Sampling Time</i></b>	<b><i>% Drug Dissolved</i></b>
<i>6 hours</i>	(b) (4) %
<i>24 hours</i>	(b) (4) %
<i>96 hours</i>	<i>NLT</i> (b) (4) %

*Revise the specifications table accordingly and provide a copy of the updated specifications table of the proposed drug product.*

**BRIDGING OF THE FORMULATIONS:**

(b) (4)  
 . While this formulation was adequate to support the early phase clinical study, (b) (4) was not optimal. Therefore, a formulation change was made (b) (4) which enabled development of a pre-filled syringe.

The compositions of the two formulations used during drug product development are provided in the Table below.

Phase 1a Formulation			Proposed Commercial Formulation		
Component	Amount (wt %)	Function	Component	Amount (wt %)	Function
(b) (4) drug substance	(b) (4)	Active	(b) (4) drug substance	(b) (4)	(b) (4)
		(b) (4)	Sorbitan Monolaurate (SML)		
Polysorbate 20 (PS20)		(b) (4)	Polysorbate 20 (PS20)		
Sodium Chloride			Sodium Chloride		
Sodium Phosphate Dibasic Anhydrous			Sodium Phosphate Dibasic Anhydrous		
Sodium Phosphate Monobasic			Sodium Phosphate Monobasic		
WFI			WFI		

The first formulation was only used in study # ALK9072-001 (phase 1a). Study ALK9072-001 evaluated the safety, tolerability, and pharmacokinetics of the early formulation in subjects with chronic stable schizophrenia. All other studies (including safety, tolerability, pharmacokinetic studies) and the pivotal clinical studies used drug products with the proposed commercial formulation. Therefore, additional bridging is not needed.

**Reviewer’s assessment of the bridging studies: *SATISFACTORY***

All relevant studies and the pivotal clinical studies used drug products with the proposed commercial formulation. Therefore, additional bridging is not needed.

**RISK EVALUATION: ACCEPTABLE**

The risk assessment evaluation for the dissolution CQA component is presented in the Table below.

**Drug Product Risk Assessment Table**

Initial Quality Assessment			Final Quality Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments
Dissolution	(b) (4)	M	The dissolution method is adequate and appropriate sampling time points have been established. (b) (4)	Acceptable (M)	(b) (4)

**REVIEWER'S OVERALL CONCLUSIONS:**

The Division of Biopharmaceutics has evaluated the information provided in NDA 207533 and concludes the following:

- 1) **Dissolution method:** The following dissolution method is acceptable:

USP Apparatus	II
Media	50 mM Phosphate buffer, 6% SDS, 90 mM Sodium Sulfate, pH 8.00
Media Temperature	37.0 ± 0.5
Paddle Speed (rpm)	75

- 2) **Dissolution acceptance criteria:**

The proposed (b) (4) dissolution acceptance criteria range of (b) (4) % for the 24 hours sampling time point is not acceptable. The following dissolution acceptance criteria are recommended for batch release and on stability. The Applicant will be requested to implement in a product quality discipline review letter.

At 6 hour: (b) (4) %  
 At 24 hour: (b) (4) %  
 At 96 hour: NLT (b) (4) %

- 3) **Bridging of the formulations:**

All relevant studies and the pivotal clinical studies used drug products with the proposed commercial formulation. Therefore, additional bridging is not needed.

**RECOMMENDATION:**

At this time of the review (GRMP date), the dissolution acceptance criteria have not been finalized and an information request to revise the dissolution acceptance criteria will be send to the Applicant. Therefore, the Biopharmaceutics recommendation on the approvability of NDA 207533 is **PENDING**.

## Clinical Pharmacology Review (Amendment to OCP Review)

---

<b>NDA #:</b>	207533
<b>Proposed Brand Name:</b>	ARISTADA
<b>Generic Name:</b>	Aripiprazole Lauroxil
<b>Dosage Form:</b>	IM Injection (Extended-Release Suspension for IM Injection)
<b>Dosage Strength:</b>	441-mg, 662 mg, 882 mg- single use pre-filled syringe
<b>Indication:</b>	Treatment of Schizophrenia in adults
<b>Sponsor:</b>	Alkermes
<b>Submission Type:</b>	505(b)(2), NCE
<b>Submission Date:</b>	August 22 <sup>nd</sup> , 2014
<b>OCP Review Team:</b>	Praveen Balimane, Xiaofeng Wang, Kevin Krudys, Jeff Kraft, Christian Grimstein, Ping Zhao, Hao Zhu

---

This review is an amendment to the OCP review for NDA 207533 (IM injection of aripiprazole lauroxil for schizophrenia) which was submitted into DARRTS on April 20<sup>th</sup>, 2015. The table below (Table 1) is a corrected dosage adjustment table which replaces the following in the original OCP review:

- Page 4: Dose adjustment table
- Pages 18 and 19: Recommendation's for dose adjustments for drug interactions

In addition, reviews for individual study reports are also included in the Appendix.

**Table 1: Corrected Table for Dosage Adjustments:**

- No dosage changes recommended for ARISTADA, if CYP modulators are added for less than 2 weeks
- Make the following dosage changes to ARISTADA if CYP modulators are added for greater than 2 weeks

Concomitant medicine	Dosage adjustments for ARISTADA
Strong CYP3A4 inhibitor	<p>Reduce the dose of ARISTADA to the next lower strength. No dosage adjustment is required for patients receiving 441 mg ARISTADA, if tolerated.</p> <p><i>For patients known to be poor metabolizers of CYP2D6:</i> Reduce dose to 441 mg from both higher doses. No dosage adjustment is required for patients receiving 441 mg ARISTADA, if tolerated.</p>

Strong CYP2D6 inhibitor	Reduce the dose of ARISTADA to the next lower strength. No dosage adjustment is required for patients receiving 441 mg ARISTADA, if tolerated.  <i>For patients known to be poor metabolizers of CYP2D6:</i> No dosage adjustment is required
Both Strong CYP3A4 inhibitor and Strong CYP2D6 inhibitor	Avoid use for patients on the 662 mg or 882 mg dosage. No dosage adjustment is required for patients receiving 441 mg ARISTADA, if tolerated.
CYP3A4 inducers	No dosage adjustment is required for 662 mg and 882 mg dosage. Increase the dosage for patients on 441 mg dose to 662 mg.

- For patients receiving concomitant oral aripiprazole medications during the first 21-day treatment of ARISTADA, doses of supplemental oral aripiprazole should be adjusted based on oral aripiprazole label.
- For the 882 mg/6 week dose level, the next lower strength should be 441 mg/4 week.

*Appendix: Reviews for Individual Clinical Study Reports*

**#1: ALKS 9072-001: Single Dose Study (Gluteal)**  
NDA 207533 (Aripiprazole Lauroxil XR suspension IM injection)

<b>Report #</b> ALKS9072-001	<b>Study Period:</b> 21 Sep 2010 to 23 May 2011	<b>EDR Link</b> <a href="#">\\cdsesub1\evsprod\NDA207533\0000\m5\52- tab-list</a>
<b>Title</b>	A Phase 1, Randomized, Double-blind, Placebo-controlled, Single-ascending-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072 in Subjects with Chronic Stable Schizophrenia	

## Study Design & Objective

### Objective:

*Primary:* To determine the safety and tolerability of ALKS 9072 over a range of single doses in adult subjects with chronic stable schizophrenia.

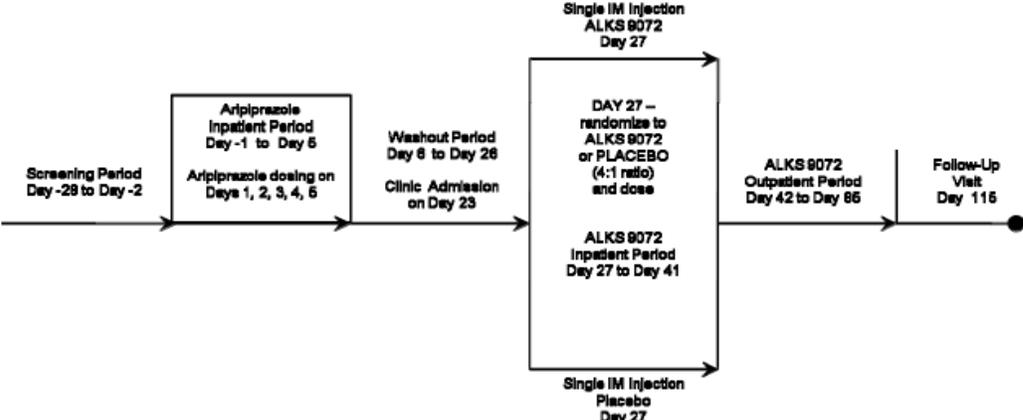
*Secondary:* To determine the pharmacokinetics (PK) of ALKS 9072 and its metabolites over a range of single doses in adult subjects with chronic stable schizophrenia.

### Study Design:

This was a multicenter, randomized, double-blind, placebo-controlled, escalating single dose study designed to evaluate the safety and PK of ALKS 9072 in subjects with chronic stable schizophrenia. Following a screening visit, subjects were enrolled into 3 sequential cohorts at dose levels of 150-mg (Cohort A), 300-mg (Cohort B), and 400-mg (Cohort C) aripiprazole equivalents. Within each cohort, subjects received oral aripiprazole (Abilify® 10 mg) once daily for 5 days to assess individual tolerability to, and PK of aripiprazole. Following a minimum 21-day washout, subjects were randomized in a 4:1 ratio to receive a single intramuscular (IM) injection of ALKS 9072 or placebo. For Cohort A only, 12 subjects were dosed in 2 subgroups. The first subgroup (n=2) began the study at least 2 weeks before the second subgroup (n=10), and both subjects in the first subgroup received ALKS 9072 in a single-blinded manner. The 2-week separation allowed for a preliminary assessment of safety and tolerability to ALKS 9072 before the remaining 10 subjects in Cohort A were randomized to ALKS 9072 or placebo (4:1). Cohorts B and C each enrolled and randomized 10 subjects (4:1 ALKS 9072:placebo). Dose escalation in subsequent cohorts (Cohort B [300 mg] and Cohort C [400 mg]) was staggered and based on a review of interim safety and PK data from the previous cohort. Serial blood samples were collected beginning on Day 1 (first day of oral aripiprazole administration) and on Day 27 (first day of ALKS 9072/placebo administration) and continuing through Day 115 to assess plasma concentrations and PK of ALKS 9072, aripiprazole, and dehydro-aripiprazole, as appropriate for each study drug. All subjects were evaluated at frequent intervals for safety, tolerability, and PK for at least 8 weeks after administration of ALKS 9072 or placebo, and again at a safety follow-up visit conducted approximately 3 months after IM dosing. Safety evaluations included adverse event (AE) monitoring, clinical laboratory testing, physical examinations, vital sign assessments (including orthostatic heart rate and blood pressure during the inpatient periods), 12-lead electrocardiograms (ECGs), injection site evaluations, and extrapyramidal symptom (EPS) and suicide risk assessments.

Cohort A = 221 mg aripiprazole lauroxil  
Cohort B = 441 mg aripiprazole lauroxil  
Cohort C = 588 mg aripiprazole lauroxil  
Placebo group

Single-Dose Randomized Double-Blind Parallel Multi-Center 2-Period Patients

<p><b>Screening:</b> Following a screening visit, subjects were enrolled into 3 sequential cohorts</p>	<p><b>Washout:</b> 20 days after oral aripiprazole</p>
<p>Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:</p>	
<p><b>Treatments:</b></p> <p>40 subjects were enrolled and treated  Cohort A* = 221 mg aripiprazole lauroxil (N=10)  Cohort B* = 441 mg aripiprazole lauroxil (N=8)  Cohort C* = 588 mg aripiprazole lauroxil (N=8)  Placebo (N=6)  Oral aripiprazole only (N=8)(10 mg given daily for 5 days followed by washout for 20 days)</p> <p>*intramuscular injection to gluteal muscle</p> 	
<p><b>Sampling Times (PK, plasma)</b></p> <p><b>Pharmacokinetics:</b> The following PK parameters were determined for ALKS 9072, aripiprazole, and dehydro-aripiprazole as appropriate for each study drug:</p> <ul style="list-style-type: none"> <li>• maximum plasma concentration (<math>C_{max}</math>)</li> <li>• time to maximum plasma concentration (<math>T_{max}</math>)</li> <li>• trough plasma concentration (<math>C_{trough}</math>) (Days 2 through 6; Oral Aripiprazole Only)</li> <li>• area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration (<math>AUC_{0-last}</math>)</li> <li>• area under the plasma concentration-time curve from time zero to the relevant time point (<math>AUC_{0-t}</math>)</li> <li>• area under the plasma concentration-time curve from time zero to infinity (<math>AUC_{0-\infty}</math>)</li> <li>• terminal elimination half-life (<math>t_{1/2}</math>)</li> </ul>	

Intensive PK sampling was performed on Day 1 and Day 27 at the following time points: predose, and 1, 4, 8, and 12 hours post-dose. Single PK sampling was performed on all other study days.

**Analytical Method:** The performance of the analytical method is acceptable. Yes  No

**LC/MS/MS:**

A validated liquid chromatography / tandem mass spectrometry (LC/MS/MS) method for analysis of ALKS 9072 (RDC-3317), aripiprazole (RDC-9864), and dehydro-aripiprazole (RDC-3954) in human plasma was used with a quantitation range of 1.00 ng/mL to 500 ng/mL.

Aliquot volume for each sample was 50.0  $\mu$  L. The bioanalytical analysis was performed by (b) (4)

**Validation summary:**

Parameter	Aripiprazole	Dehydro-aripiprazole	Aripiprazole Lauroxil
LLOQ-ULOQ (ng/mL)	1-500	1-500	1-500
Accuracy (%bias)	0%	1%	5%
Precision (%CV)	9.1%	3%	6.5%
Selectivity	No significant interference	No significant interference	No significant interference

**Statistical Method:**

All subjects who received at least one dose of study drug (oral aripiprazole, ALKS 9072, or placebo) were included in the Safety Population. The PK Population included all subjects who received at least one dose of active study drug in either the oral aripiprazole inpatient or ALKS 9072 inpatient/outpatient period and had a measureable concentration of one or more analyte of interest.

Safety data were summarized separately for the Oral Aripiprazole Phase and the ALKS 9072 Phase. Data were also summarized by cohort and treatment group (A, B, and C) and overall (all ALKS 9072 vs. all placebo). PK parameters were calculated using non-compartmental techniques, using actual elapsed time from dosing to estimate individual plasma PK parameters. Dose linearity and proportionality of aripiprazole exposure following ALKS 9072 administration were also assessed.

**Study Population :**

Randomized/Completed/ Discontinued	40/36/4 (1 due to incarceration and 3 "other" reason and lost to follow-up)
Age [Median (range)]	45.3 (21-55) yr
Male/Female	28/12
Race (Caucasian/Black/Asian/other)	0/38/1/1

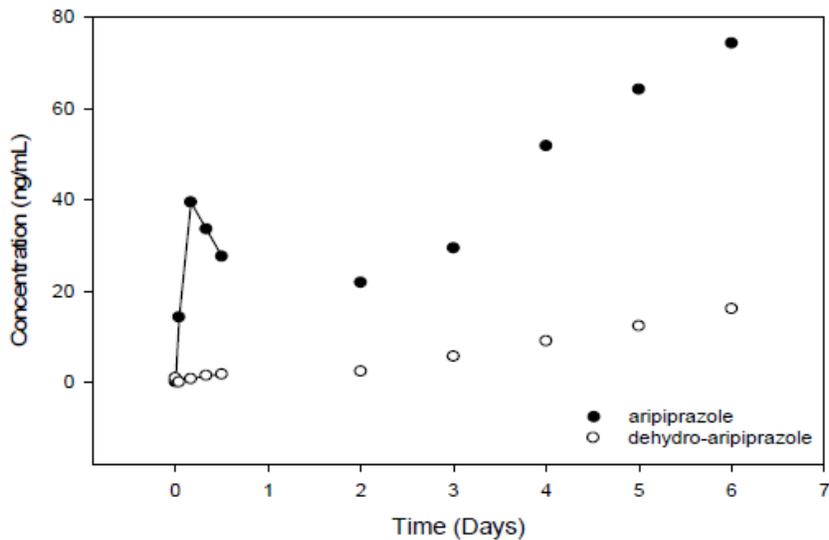
**Results**

The PK Population included 8 subjects in the Oral Aripiprazole Only group, 10 subjects in the ALKS 9072 150 mg group, 8 subjects in the ALKS 9072 300 mg group, and 8 subjects in the ALKS 9072 400 mg group.

**Aripiprazole Pharmacokinetics: 10 mg Oral Administration**

Mean maximum concentrations of aripiprazole following a 10 mg dose on Day 1 was 41.4 ng/mL and was achieved by 4.0 hours (median  $T_{max}$ ). Exposure as assessed by mean  $AUC_{0-last}$  was 647 ng\*hr/mL. The formation of the dehydro-aripiprazole metabolite was slow and maximum concentrations (mean  $C_{max}$  = 2.7 ng/mL) were achieved by 23.8 hours (median  $T_{max}$ ). The mean  $AUC_{0-last}$  for dehydroaripiprazole was 40.9 ng\*hr/mL. The PK of aripiprazole and dehydro-aripiprazole following oral administration were consistent with published literature.

**Figure 1:** Mean Concentrations of Aripiprazole and Dehydro-aripiprazole Following 5 days of Oral Administration (10 mg)



**Table 1:** Summary of Pharmacokinetic Parameters Following Oral Administration of Aripiprazole 10 mg

		Parameter	Overall <sup>a</sup> (N=40)
Aripiprazole	C <sub>max</sub> (ng/mL)	n	40
		Mean (SD)	41.4 (14.2)
		Geometric Mean	37.4
		Median	40.9
		Min, Max	3.41, 81.40
T <sub>max</sub> (hr)	n	40	
	Mean (SD)	4.7 (2.5)	
	Median	4.0	
	Min, Max	1.0, 12.0	
AUC <sub>(0-last)</sub> (hr*ng/mL)	n	40	
	Mean (SD)	647.2 (195.1)	
	Geometric Mean	591.2	
	Median	638.5	
	Min, Max	55.3, 1045.0	
Dehydro-aripiprazole	C <sub>max</sub> (ng/mL)	n	37
		Mean (SD)	2.7 (1.2)
		Geometric Mean	2.4
		Median	2.4
		Min, Max	1.2, 7.6
T <sub>max</sub> (hr)	n	37	
	Mean (SD)	23.4 (1.9)	
	Median	23.8	
	Min, Max	12.0, 24.0	
AUC <sub>(0-last)</sub> (hr*ng/mL)	n	37	
	Mean (SD)	40.9 (25.6)	
	Geometric Mean	35.1	
	Median	38.4	
	Min, Max	8.1, 158.4	

a= oral aripiprazole for N=8

### ***Aripiprazole Lauroxil Pharmacokinetics: IM injection***

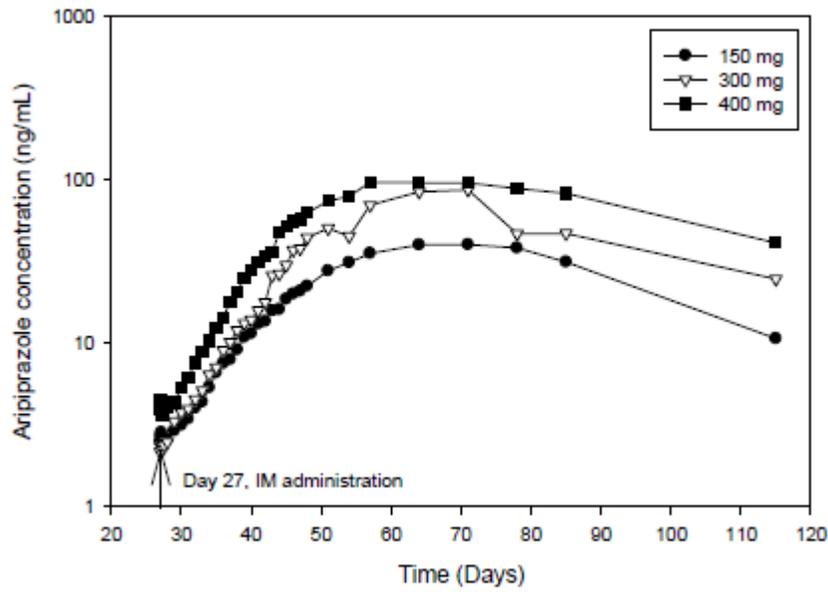
#### *Aripiprazole Pharmacokinetics:*

Mean aripiprazole C<sub>max</sub> values ranged from 43 to 114 ng/mL across the dose range of 150 mg to 400 mg, and were achieved by approximately 37-48 days (median T<sub>max</sub>) after dosing. The mean t<sub>1/2</sub> of aripiprazole following ALKS 9072 administration was independent of dose and ranged from 17 to 22 days. The significant prolongation in aripiprazole t<sub>1/2</sub> compared to oral aripiprazole (approximately 60 hours) is attributed to the dissolution and formation rate-limited elimination of aripiprazole following ALKS 9072 administration.

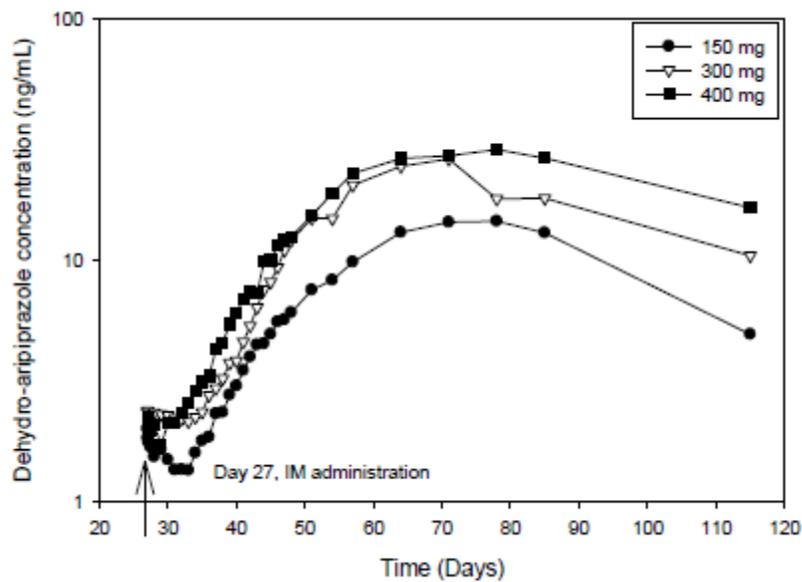
#### *Dehydro-aripiprazole Pharmacokinetics:*

Mean maximum dehydro-aripiprazole concentrations ranged from 14.9 to 32.1 ng/mL and were achieved by approximately 48-51 days after dosing (median T<sub>max</sub>). Total dehydro-aripiprazole exposure (AUC<sub>0-last</sub>) was approximately 29-35% of that for aripiprazole exposure across all dose levels. The mean t<sub>1/2</sub> of dehydro-aripiprazole was consistent with that observed for aripiprazole following ALKS 9072 administration. This is consistent with formation rate-limited elimination for dehydro-aripiprazole and dissolution rate-limited exposure for aripiprazole derived from ALKS 9072 administration.

**Figure 2:** Mean Concentrations of Aripiprazole Following IM Administration of a single IM dose of Aripiprazole Lauroxil



**Figure 3:** Mean Concentrations of Dehydro-aripiprazole Following IM Administration of a single IM dose of Aripiprazole Lauroxil



**Table 2:** Summary of Pharmacokinetic Parameters for Aripiprazole Following a single-dose Administration of Aripiprazole Lauroxil

Parameter	ALKS 9072 150 mg	ALKS9072 300 mg		ALKS 9072 400 mg
		All Subjects	Excluding Subject 12001	
	(N=10)	(N=8)	(N=7)	(N=8)
<b>C<sub>max</sub> (ng/mL)</b>				
n	10	8	7	8
Mean (SD)	43.0 (22.0)	91.6 (77.6)	66.3 (32.2)	113.6 (32.0)
Geometric Mean	38.4	72.7	60.3	109.2
Median	34.0	65.4	65.3	109.9
Min, Max	20.1, 86.9	31.4, 269	31.4, 127	59.3, 162
<b>T<sub>max</sub> (hr)</b>				
n	10	8	7	8
Mean (SD)	929 (229)	1140 (237)	1176 (232)	1055 (280)
Median	889	1140	1223	1056
Min, Max	696, 1225	888, 1393	888, 1393	721, 1394
<b>AUC<sub>0-last</sub> (hr*ng/mL)</b>				
N	10	8	7	8
Mean (SD)	47665 (28584)	76139 (30284)	67993 (21231)	132349 (26659)
Geometric Mean	39375	71377	65294	129808
Median	40169	67480	64963	131593
Min, Max	11192, 99287	44692, 133158	44692, 105609	84064, 172298
<b>AUC<sub>0-∞</sub> (hr*ng/mL)</b>				
N	6	2	2	5
Mean (SD)	65159 (30603)	91062 (57179)	91062 (57179)	149500 (11980)
Geometric Mean	59615	81593	81593	149117
Median	54415	91062	91062	149276
Min, Max	36399, 109277	50630, 131493	50630, 131493	136747, 164006
<b>t<sub>1/2</sub> (hr)</b>				
n	6	2	2	5
Mean (SD)	408 (80)	531 (103)	531 (103)	433 (116)
Geometric Mean	401	526	526	419
Median	409	531	531	437
Min, Max	302, 532	458, 604	458, 604	261, 583

**Table 3:** Summary of Pharmacokinetic Parameters for Dehydro-aripiprazole Following a single-dose Administration of Aripiprazole Lauroxil

Parameter	ALKS 9072 150 mg (N=10)	ALKS 9072 300 mg		ALKS 9072 400 mg (N=8)
		All Subjects (N=8)	Excluding Subject 12001 (N=7)	
<b>C<sub>max</sub> (ng/mL)</b>				
n	10	8	7	8
Mean (SD)	14.9 (6.8)	28.6 (21.9)	21.4 (8.8)	32.1 (9.9)
Geometric Mean	13.6	23.8	20.1	30.3
Median	12.2	19.9	17.4	33.7
Min, Max	6.9, 26	13.9, 78.8	13.9, 38.5	12.7, 42.9
<b>T<sub>max</sub> (hr)</b>				
n	10	8	7	8
Mean (SD)	1095 (267)	1161 (219)	1176 (232)	1243 (367)
Median	1212	1140	1223	1224
Min, Max	649, 1393	888, 1393	888, 1393	889, 2041
<b>AUC<sub>0-last</sub> (hr*ng/mL)</b>				
n	10	8	7	8
Mean (SD)	16715 (9172)	25442 (10508)	23315 (9308)	38468 (9909)
Geometric Mean	14043	23786	22059	36941
Median	14244	21109	20174	41701
Min, Max	3080, 29888	14779, 42793	14779, 42793	17231, 47536
<b>AUC<sub>0-∞</sub> (hr*ng/mL)</b>				
n	6	0	0	3
Mean (SD)	24487 (10429)	NC	NC	43667 (5310)
Geometric Mean	22551	NC	NC	43457
Median	24113	NC	NC	42328
Min, Max	13165, 36025	NC	NC	39155, 49518
<b>t<sub>1/2</sub> (hr)</b>				
n	6	0	0	3
Mean (SD)	482 (124)	NC	NC	424 (125)
Geometric Mean	467	NC	NC	410
Median	525	NC	NC	475
Min, Max	311, 603	NC	NC	282, 515

### **Dose Proportionality Assessment**

Dose proportionality assessments were performed on aripiprazole and dehydro-aripiprazole C<sub>max</sub>, AUC<sub>0-30 days</sub>, and AUC<sub>0-∞</sub> using a power model. Dose proportionality was said to exist if the slope coefficient  $\beta = 1$  for these dose-dependent parameters. Although the 95% confidence intervals (CI) were wide, statistical analysis of C<sub>max</sub>, AUC<sub>0-30 days</sub>, and AUC<sub>0-∞</sub> values for aripiprazole indicated dose proportionality for ALKS 9072 across the dose range tested. Similarly, dose proportionality can be assumed for dehydro-aripiprazole based on C<sub>max</sub> and AUC<sub>0-30 days</sub>. The limited data for

dehydroaripiprazole AUC<sub>0-∞</sub> precluded a clear assessment of dose proportionality.

**Table 4: Dose Proportionality Assessment of Aripiprazole and Dehydro-aripiprazole**  
 Across the Dose Range of 221 mg to 588 mg of Aripiprazole Lauroxil

	Slope Estimate (β) +/- SE	95% Confidence Interval	Goodness of Fit (r <sup>2</sup> )
<b>Aripiprazole</b>			
log (C <sub>max</sub> )	1.04 +/- 0.236	(0.55, 1.52)	0.445
log (AUC <sub>0-30 Days</sub> )	0.95 +/- 0.272	(0.39, 1.51)	0.346
log (AUC <sub>0-∞</sub> )	0.88 +/- 0.239	(0.36, 1.41)	0.555
<b>Dehydro-aripiprazole</b>			
log (C <sub>max</sub> )	0.81 +/- 0.218	(0.36, 1.26)	0.368
log (AUC <sub>0-30 Days</sub> )	0.74 +/- 0.260	(0.21, 1.28)	0.262
log (AUC <sub>0-∞</sub> )	0.67 +/- 0.279	(0.01, 1.33)	0.450

Power model was used to assess dose proportionality. The model used was  $\log(\text{parameter}) = a + \beta * \log(\text{dose})$ .

**Site Inspected**

Requested: Yes  No

Performed: Yes  No  N/A

**Safety**

Was there any death or serious adverse events?  Yes  No  NA

The incidence of treatment-emergent adverse events (TEAEs) was similar among treatment groups: 6/8 (75%) subjects in the Oral Aripiprazole Only group, 21/26 (81%) subjects in the combined ALKS 9072 dose groups, and 5/6 (83%) subjects in the placebo group. In the ALKS 9072 cohorts, 7/10 (70%) subjects in the 150 mg dose group, all 8 (100%) subjects in the 300 mg dose group, and 6/8 (75%) subjects in the 400 mg dose group reported at least one TEAE. The most commonly reported TEAEs in the combined ALKS 9072 groups reported at any time during the entire study period were headache (46%), upper respiratory tract infection (23%), and abdominal discomfort and nasopharyngitis (19% each). Headache was also the most commonly reported AE in the Oral Aripiprazole Only group (13%) and in the placebo group (33%). During the ALKS 9072/Placebo Period, the only notable difference in individual TEAEs reported by subjects in the combined ALKS 9072 groups vs. the placebo group were headache (9 [35%] subjects in the ALKS 9072 combined groups compared with 1 [17%] subject in the placebo group); abdominal discomfort (4 [15%]

subjects in the ALKS 9072 combined groups and no subject in the placebo group); and vomiting (3 [12%] subjects in the ALKS 9072 combined groups and no subject in the placebo group).

Most TEAEs were assessed by the investigator as not related to study drug. Study drug-related (possibly, probably, or definitely related) TEAEs were reported in 3/8 (38%) subjects in the Oral Aripiprazole Only group; 6/40 (15%) subjects during the Oral Aripiprazole Period; and 3/26 (12%) subjects in the combined ALKS 9072 dose groups and 1 (17%) subject in the placebo group during the ALKS 9072/Placebo Period.

Only 1 subject experienced a TEAE that was severe in intensity: drug (cocaine) dependence relapse, which occurred 78 days after the single dose of ALKS 9072 400 mg. All other TEAEs were mild or moderate in severity.

None of the subjects experienced a fatal event. One subject in the ALKS 9072 400 mg cohort experienced a treatment-emergent serious adverse event (SAE) (drug dependence that required hospitalization); the SAE was not related to treatment with study drug. In addition, one subject (Oral Aripiprazole Only group) experienced a TEAE (priapism during the washout period following oral aripiprazole) that led to study withdrawal; the event of priapism was assessed as related to oral aripiprazole.

There were no apparent drug effects on vital signs, ECG recordings, ESRS scores, or C-SSRS during either treatment period or between ALKS 9072 and placebo treatments.

Pain at the injection site was reported as an ISR in 2 (8%) of the 26 subjects who received ALKS 9072; in both cases, the mild injection site pain was attributed by the investigator to the injection procedure rather than study drug and resolved within days.

The only notable mean change from baseline for clinical chemistry and hematology analytes were increases in glucose and creatine phosphokinase (CK), which occurred during both treatment periods and in all treatment groups without any apparent ALKS 9072 dose effect, and increases in prolactin levels during the Oral Aripiprazole Only period and decreases in prolactin levels during the ALKS 9072/Placebo Period. One subject experienced laboratory test abnormalities (elevated CK and liver enzymes) that were considered by the investigator to be clinically significant and reported as AEs.

## Conclusion

- Single IM doses of Aripiprazole Lauroxil over the dose range of 221 mg to 588 mg were well tolerated in subjects with chronic schizophrenia, with a safety profile similar to that observed with oral aripiprazole 10 mg daily for 5 days.
- The PK of aripiprazole and dehydro-aripiprazole following administration of Aripiprazole Lauroxil demonstrated extended  $T_{max}$  and prolonged  $t_{1/2}$  compared with published results for oral aripiprazole, which supports the extended-release properties of Aripiprazole Lauroxil.

## Comments

The Office of Clinical Pharmacology has reviewed the study report and agrees with the sponsors analysis.

Aripiprazole Lauroxil given as an IM injection at gluteal muscle leads to a sustained PK profile for aripiprazole and dehydro-aripiprazole with extremely long T-halves. The pharmacokinetic parameters (Tmax, T-half etc.) derived from this single dose study have been incorporated into the label.

Most TEAE's observed in this study were after oral aripiprazole dosing, so IM aripiprazole laurxoil is not involved in causing the AE. Though 1 subject had a severe TEAE on day 78, based on the PK profile, none of the subjects had any dose dumping (Tmax was >25 days, with no appreciable exposures up to 1 week) or abnormally high Cmax.

Thus, IM injection of Aripiprazole Lauroxil over the dose range of 221 mg to 588 mg were well tolerated and provide a sustained PK profile for aripiprazole and dehydro-aripiprazole with extremely long T-halves which will likely lead to accumulation at steady state.

## #2: ALKS 9072-101: Single Dose Study (Deltoid vs. Gluteal)

NDA 207533 (Aripiprazole Lauroxil XR suspension IM injection)

Report # ALKS9072-101	Study Period: 20 Aug 2012 to 14 Jan 2013	EDR Link  \\cdsesub1\evsp rod\NDA207533 \0000\m5\52- tab-list
Title	A Phase 1, Randomized, Open Label, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072 Following Administration to the Deltoid or Gluteal Muscle in Subjects with Chronic Stable Schizophrenia	
<b>Study Design &amp; Objective</b>  <b>Objective:</b> <ul style="list-style-type: none"><li>• To determine the safety and tolerability of ALKS 9072 300 mg, administered as a single intramuscular (IM) injection in the deltoid or gluteal muscle to adult subjects with chronic stable schizophrenia or schizoaffective disorder</li><li>• To determine the pharmacokinetics (PK) of ALKS 9072 and its metabolites after a single IM injection of ALKS 9072 300 mg in the deltoid or gluteal muscle to adult subjects with chronic stable schizophrenia or schizoaffective disorder</li><li>• To characterize the relative bioavailability of ALKS 9072 following administration to the deltoid muscle in reference to ALKS 9072 exposure following administration to the gluteal muscle</li></ul> <b>Study Design:</b> <p>This was a multicenter, randomized, open label, single-dose study designed to evaluate the safety, tolerability, and PK of ALKS 9072 following administration to the deltoid or gluteal muscle in subjects with chronic stable schizophrenia or schizoaffective disorder, and to characterize the relative bioavailability of ALKS 9072 following deltoid or gluteal administration.</p> <p>Unless otherwise stated, throughout this report, the doses of ALKS 9072 refer to the amounts of aripiprazole free base equivalent.</p> <p>After screening, eligible subjects were admitted to the clinic for an 8-day inpatient stay. The first 2 subjects were sentinel subjects and were assigned to Cohort A. These 2 subjects received an open label ALKS 9072 150 mg IM injection in the deltoid muscle. After the safety data from Cohort A were reviewed, a total of 44 subjects in Cohort B were randomized in a 1:1 ratio to receive an open</p>		

label ALKS 9072 300 mg IM injection in either the deltoid or gluteal muscle. Subjects were allowed to enroll in this study only once. After discharge from the inpatient stay, there were 18 outpatient study visits(Days 9–89) for safety, tolerability, and PK assessments.

Safety assessments included evaluations of treatment emergent adverse events (TEAEs), injection site reactions (ISRs), vital signs (including orthostatic heart rate and blood pressure during the inpatient periods), concomitant medications; results of physical examinations, electrocardiograms (ECGs), and clinical laboratory tests, and the scores of the Columbia Suicide Severity Rating Scale (C-SSRS) and the Extrapyramidal Symptom Rating Scale (ESRS).

Disease severity was assessed using the Clinical Global Impression of Severity Scale (CGI-S) and the Positive and Negative Syndrome Scale (PANSS).

Blood samples were collected at prespecified time points to determine concentrations of ALKS 9072, aripiprazole, *N*-hydroxymethyl-aripiprazole, and dehydro-aripiprazole after IM dosing. Before dosing, a blood sample was collected from each subject for analysis of cytochrome P450 (CYP) genotypes.

Bioequivalence

Bioavailability

Randomized Open-Label Parallel Multi-Center 1-Period Patients

**Screening:** Following a screening visit, eligible subjects were admitted to the clinic for an 8-day inpatient stay

**Washout:** NA

Inpatient stay  Y  N:

**Treatments:**

**N= 46 patients**

Cohort A\* = 221 mg aripiprazole lauroxil (N=2 sentinel subjects, deltoid only)

Cohort B\*\* = 441 mg aripiprazole lauroxil (N=44, Randomized 1:1 to deltoid or gluteal muscle)

\*intramuscular injection to gluteal muscle

\*\* intramuscular injection to gluteal or deltoid muscle

**Sampling Times (PK, plasma)**

**Pharmacokinetics:** The following PK parameters were determined for ALKS 9072, aripiprazole, dehydro-aripiprazole and *N*-hydroxymethyl-aripiprazole, as appropriate for each study drug:

- maximum plasma concentration (C<sub>max</sub>)

- time to maximum plasma concentration (Tmax)
- trough plasma concentration (Ctrough) (Days 2 through 6; Oral Aripiprazole Only)
- area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration (AUC0-last)
- area under the plasma concentration-time curve from time zero to the relevant time point (AUC0-t)
- area under the plasma concentration-time curve from time zero to infinity (AUC0-∞)
- terminal elimination half-life (t1/2)

Relative bioavailability of ALKS 9072, aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl-aripiprazole, as appropriate for each analyte, was also determined for deltoid versus gluteal IM administration of ALKS 9072.

**Analytical Method:** The performance of the analytical method is acceptable. Yes  No

**LC/MS/MS:**

A validated liquid chromatography / tandem mass spectrometry (LC/MS/MS) method for analysis of ALKS 9072 (RDC-3317), aripiprazole (RDC-9864), and dehydro-aripiprazole (RDC-3954) in human plasma was used with a quantitation range of 1.00 ng/mL to 500 ng/mL. Aliquot volume for each sample was 50.0 µL. The bioanalytical analysis was performed by (b) (4)

Validation summary:

Parameter	Aripiprazole	Dehydr-aripiprazole	Aripiprazole Lauroxil	N-hydroxy-aripiprazole
LLOQ-ULOQ (ng/mL)	1-500	1-500	1-500	1-500
Accuracy (%bias)	0%	1%	5%	2%
Precision (%CV)	9.1%	3%	6.5%	5.9%
Selectivity	No significant interference	No significant interference	No significant interference	No significant interference

**Statistical Method:**

All subjects who received at least 1 dose of study drug were included in the Safety Population used for safety and tolerability analyses. The PK Population included all subjects who received at least 1 dose of study drug and had sufficient plasma concentration data to facilitate calculation at least 1 of the PK parameters (C<sub>max</sub> or an AUC) for at least 1 analyte.

Safety and disease severity data were summarized by treatment group and overall. Safety and disease severity data were presented using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, minimum, and maximum values) for continuous variables and frequencies and percentages for categorical variables.

Individual plasma concentrations and concentration-time data for ALKS 9072, *N*-hydroxymethyl-aripiprazole, aripiprazole, and dehydro-aripiprazole were presented and summarized both graphically and in tabular form. PK parameters were summarized by dosing group using 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.

**Study Population :** Male and female subjects who were 18 to 55 years old (inclusive), diagnosed with chronic stable schizophrenia or schizoaffective disorder, were otherwise healthy, and were documented to well tolerate aripiprazole exposure were eligible for study participation.

Randomized/Completed/ Discontinued	46/43/3  (2 = lost to follow-up, 1= other)
Age [Median (range)]	42.5 (22-55) yr
Male/Female	32/14
Race (Caucasian/Black/Asian/other)	10/35/1/0

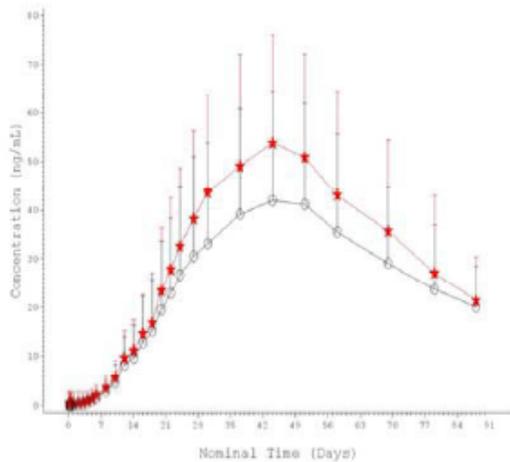
**Results****Pharmacokinetics**

- Plasma profiles of aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethyl-aripiprazole after a single 150 or 300 mg IM injection of ALKS 9072 demonstrated the slow dissolution properties of the prodrug with no evidence of early aripiprazole release, regardless of the administration site.

- Deltoid administration of an IM ALKS 9072 300-mg dose produced higher mean exposure (based on AUC<sub>0-last</sub>) of aripiprazole (23%), dehydro-aripiprazole (24%), and *N*-hydroxymethyl-aripiprazole (40%) than gluteal administration.
- Although mean exposure was higher after deltoid administration, the range of exposures for deltoid and gluteal administration overlapped, suggesting that deltoid and gluteal IM administrations of ALKS 9072 result in similar safety, tolerability, and efficacy.

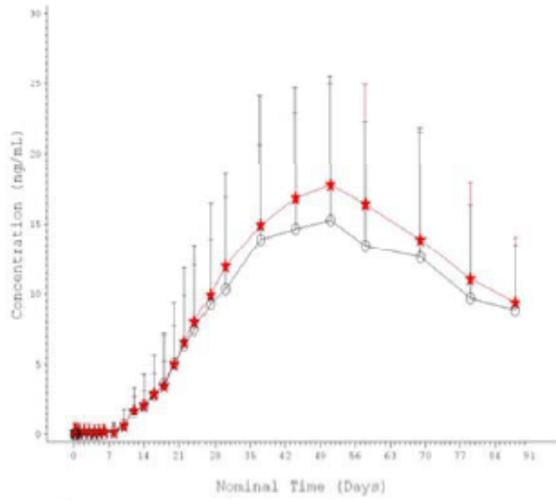
**Figure 1:** Mean Concentrations of Aripiprazole Following Deltoid or Gluteal

Administration of ALKS 9072 300 mg (Deltoid site = filled star, Gluteal site = empty circle)

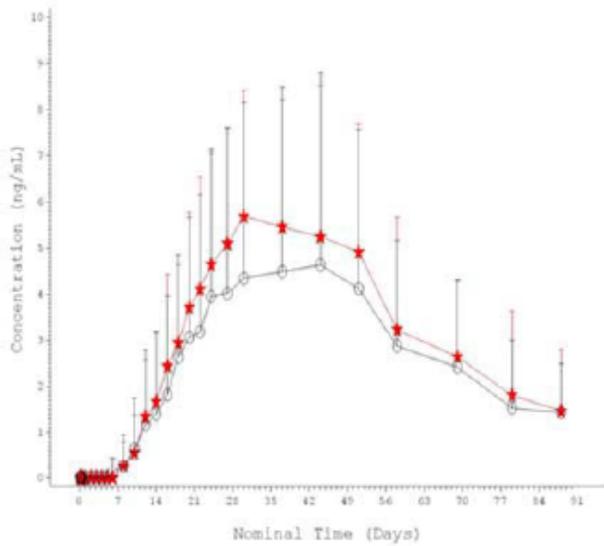


**Figure 2:** Mean Concentrations of Dehydro-Aripiprazole Following Deltoid or Gluteal

Administration of ALKS 9072 300 mg (Deltoid site = filled star, Gluteal site = empty circle)



**Figure 3:** Mean Concentrations of N-hydroxymethyl-Aripiprazole Following Deltoid or Gluteal Administration of ALKS 9072 300 mg (Deltoid site = filled star, Gluteal site = empty circle)



**Table 1:** Summary of Aripiprazole, Dehdro-aripiprazole and N-hydroxymethyl-Aripiprazole

Pharmacokinetic Parameters Following Deltoid or Gluteal Administration of ALKS 9072 300 mg

Parameters	Aripiprazole		Dehydro-aripiprazole		N-hydroxymethyl-Aripiprazole	
	Deltoid site	Gluteal site	Deltoid site	Gluteal site	Deltoid site	Gluteal site
Cmax (ng/mL)	57.4 (21.6)	46.8 (23.6)	19.8 (7.03)	16.8 (10.8)	6.68 (2.63)	5.84 (3.72)
Tmax (days)	44.1	50	50.7	52.1	37	43
AUC0-last (days·ng /mL)	2744 (1150)	2275 (1077)	904 (365)	815 (539)	263 (145)	243 (190)
AUC0-∞ (days·ng /mL)	3351 (1558)	3598 (746)	1104 (432)	1600 (812)	388 (112)	484 (135)
t1/2 (days)	15.4 (4.64)	19.4 (3.82)	15.9 (2.08)	19.2 (4.56)	73.4 (19.4)	74.7 (21.4)

Data= mean (sd)

**Table 2:** Relative Bioavailability Assessment of Aripiprazole, Dehydro-aripiprazole, and N-hydroxymethyl-aripiprazole Following Deltoid and Gluteal Administration of ALKS 9072

Parameter	Deltoid	Gluteal	Deltoid/Gluteal	
	GM	GM	GMR	90% (CI)
Aripiprazole				
AUC0-last (days·ng /mL)	2495	2022	1.23	(0.96, 1.58)
Cmax (ng/mL)	53.4	40.9	1.31	(1.02, 1.67)

Dehydro-Aripiprazole				
AUC <sub>0</sub> -last (days·ng /mL)	821	663	1.24	(0.92, 1.67)
C <sub>max</sub> (ng/mL)	18.3	13.7	1.34	(1.00, 1.79)
N-hydroxymethyl-Aripiprazole				
AUC <sub>0</sub> -last (days·ng /mL)	205	146	1.40	(0.81, 2.41)
C <sub>max</sub> (ng/mL)	6.05	4.68	1.29	(0.95, 1.77)

Abbreviations: CI=confidence interval; GM=geometric mean; GMR=geometric mean ratio.

#### Site Inspected

Requested: Yes  No

Performed: Yes  No  N/A

#### Safety

- Was there any death or serious adverse events?  Yes  No  NA

Single IM doses of ALKS 9072 150 or 300 mg injection in the deltoid or gluteal muscle were well tolerated in male and female subjects with chronic stable schizophrenia.

- There were no deaths during the study. After randomization, there was 1 SAE of depression requiring hospitalization, which the investigator considered moderate in intensity and not related to study drug. In addition, 1 subject who was not randomized experienced an SAE of life threatening hypertension. This pretreatment SAE occurred during the screening and the subject was a screen failure.
- There were no discontinuations due to TEAEs.
- All TEAEs were mild or moderate in intensity.
- The most commonly reported TEAEs overall were injection site pain in 20 subjects (43.5%), headache in 6 subjects (13.0%); insomnia and toothache in 5 subjects (10.9%) each; abdominal discomfort, diarrhoea, and constipation in 4 subjects (8.7%) each; and akathisia, back pain, dyskinesia, dystonia, and nasopharyngitis in 3 subjects (6.5%) each.
- There were more injection site pain, dystonia, and sedation TEAEs that were considered by the investigator to be related to study drug than other TEAEs.
- Most of the common TEAEs occurred at a similar frequency across the 2 ALKS 9072 300 mg groups, with the exceptions of injection site pain (63.6% in the deltoid group vs 27.3% in the gluteal group) and headache (22.7% in the deltoid group vs 4.5% in the gluteal group).
- Injection site reactions included injection site pain (20 subjects) and injection site induration (2

subjects). All these events were mild.

- There were no apparent drug effects on vital signs, ECG recordings, ESRS scores, or the C-SSRS.
- Disease severity did not appear to change appreciably during the study. Based on CGI-S scores, most subjects were mildly ill at baseline and at the end of the study.
- Mean changes from baseline for the PANSS total score and each of the 3 subscales were similar between the ALKS 9072 300 mg deltoid group and the ALKS 9072 300 mg gluteal group.

### Conclusion

- Injection into the deltoid muscle resulted in higher mean exposure to aripiprazole (23%), dehydro-aripiprazole (24%) and *N*-hydroxymethyl-aripiprazole (40%), although the range of exposures observed between the 2 administration sites overlapped.
- Deltoid and gluteal administrations of ALKS 9072 result in similar safety and tolerability. The PK data suggest that deltoid and gluteal administrations of ALKS 9072 result in similar efficacy.

### Comments

The Office of Clinical Pharmacology has reviewed the study report and agrees with the sponsors analysis.

The PK study (441 mg of Aripiprazole Lurozil IM injection) demonstrates that both gluteal and deltoid sites results in similar exposure of all relevant drug-related moieties. Both the sites also demonstrated similar safety and tolerability. None of the subjects (dosed on gluteal or on deltoid site) demonstrated any dose dumping since all subjects had  $T_{max} > 30$  days and none of them had abnormally higher  $C_{max}$  compared to mean value.

However, no comparative study (for effect of injection site) has been performed for the higher doses (662 and 882 mg)—So, we cannot be sure how the 2 sites will behave for the higher doses. With significantly lower muscle mass in deltoid, the higher doses (662 and 882 mg) might lead to a “greater potential” of “dose dumping “ on deltoid injections (vs. gluteal) and can potentially lead to higher than anticipated exposures on administered 662 and 882 mg IM injections to deltoid muscle.

**#3: ALKS 9072-002: Multi-Dose Study (Gluteal)**  
 NDA 207533 (Aripiprazole Lauroxil XR suspension IM injection)

Report # ALKS9072-002	Study Period: 19 Dec 2011 to 25 June 2013	EDR Link  \\cdsesub1\evsprod\NDA 207533\0000\m5\52-tab-list
-----------------------	---	---

**Title:** A Phase 1, Randomized, Double-blind, Placebo-controlled, Multiple-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072 in Subjects with Chronic Stable Schizophrenia

**Study Design & Objective**

**Objective:**

**Primary:**

- To determine the pharmacokinetics (PK) of aripiprazole lauroxil (ALKS 9072) and its metabolites after 4 monthly doses in adult subjects with chronic stable schizophrenia

**Secondary:**

- To determine the safety and tolerability of aripiprazole lauroxil after 4 monthly doses in adult subjects with chronic stable schizophrenia
- To determine the dose regimen of aripiprazole lauroxil in adult subjects with chronic stable schizophrenia

**Exploratory:**

To assess the efficacy of aripiprazole lauroxil for the treatment of chronic stable schizophrenia

**Study Design:**

This was a multicenter, randomized, double-blind, placebo-controlled, multiple-dose study designed to evaluate aripiprazole lauroxil, an extended-release, injectable, suspended prodrug of aripiprazole, in subjects with chronic stable schizophrenia.

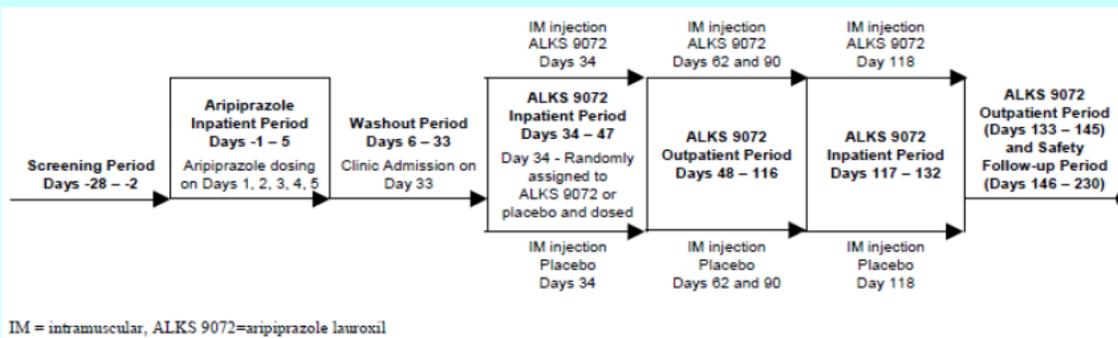
After the Screening Period, eligible subjects received oral aripiprazole (Abilify®, 10 mg) once daily for 5 days (Days 1 to 5) to assess individual tolerability and PK of aripiprazole after oral administration. On Day 34, subjects were assigned sequentially to 1 of 3 cohorts. Within each cohort, subjects were randomly assigned to receive 4 monthly intramuscular (IM) injections of either active or placebo. All injections in this study were administered into the gluteal muscle. The ratio of treatment assignment was 3:1 (active:placebo) in Cohorts 1 and 2, and 6:1 (active:placebo) in Cohort 3. The cohorts and their respective treatments are:

Cohort No.	Treatment
1	aripiprazole lauroxil 300 mg or placebo
2	aripiprazole lauroxil 450 mg or placebo
3	aripiprazole lauroxil 600 mg or placebo

Unless otherwise stated, throughout this report, the doses of aripiprazole lauroxil refer to the amounts of aripiprazole free base equivalent.

All subjects were evaluated frequently for safety, tolerability, and PK throughout the study, until approximately 3 months after the last IM injection.

Figure: Study schematic



<input type="checkbox"/> Bioequivalence	<input type="checkbox"/> Bioavailability
Randomized Double-Blind Placebo control Parallel Multi-Center Multi-Dose Patients	
<b>Screening:</b> After the Screening Period (28 days), eligible subjects received oral aripiprazole (Abilify®, 10 mg) once daily for 5 days (Days 1 to 5)	<b>Washout:</b> 28 days wash-out after oral aripiprazole dosing before giving the IM dose of Aripiprazole Lauroxil
Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:	
<b>Treatments:</b> Male and female adults who were diagnosed with chronic stable schizophrenia given intramuscular injection to gluteal muscle	

Cohort No.	Treatment
1	aripiprazole lauroxil 300 mg or placebo
2	aripiprazole lauroxil 450 mg or placebo
3	aripiprazole lauroxil 600 mg or placebo

### Sampling Times (PK, plasma)

**Pharmacokinetics:** PK analyses were performed on the PK population, defined as all subjects who had at least 1 reportable concentration of aripiprazole lauroxil or its metabolites.

Individual plasma concentrations and concentration-time data for aripiprazole lauroxil, aripiprazole, and dehydro-aripiprazole are presented graphically and in tabular form by using descriptive statistics as data allow. PK variables are summarized by treatment group by using descriptive statistics. Concentration data are summarized according to nominal (protocol-specified) sampling times. PK variables were calculated by using noncompartmental analysis, by using actual elapsed time from dosing to estimate individual plasma PK variables. Dose linearity and proportionality and time to steady state after multiple aripiprazole lauroxil administrations were assessed as data allow for each analyte.

-Maximum plasma concentration ( $C_{max}$ )

- Time to maximum plasma concentration ( $T_{max}$ )
- Trough plasma concentration ( $C_{trough}$ )
- Average plasma concentration at steady state ( $C_{ave}$ )
- Area under the plasma concentration-time curve from time 0 to the last quantifiable plasma concentration ( $AUC_{0-last}$ )
- Area under the plasma concentration-time curve from time 0 to infinity ( $AUC_{0-\infty}$ )
- Area under the plasma concentration-time curve over the dosing interval ( $AUC_{0-tau}$ )
- Terminal elimination half-life ( $T_{1/2}$ )

**Analytical Method:** The performance of the analytical method is acceptable. Yes  No

**LC/MS/MS:**

A validated liquid chromatography / tandem mass spectrometry (LC/MS/MS) method for analysis of ALKS 9072 (RDC-3317), aripiprazole (RDC-9864), and dehydro-aripiprazole (RDC-3954) in human plasma was used with a quantitation range of 1.00 ng/mL to 500 ng/mL. Aliquot volume for each sample was 50.0 µL. The bioanalytical analysis was performed by (b) (4)

**Validation summary:**

Parameter	Aripiprazole	Dehydr-aripiprazole	Aripiprazole Lauroxil	N-hydroxy-aripiprazole
LLOQ-ULOQ (ng/mL)	1-500	1-500	1-500	1-500
Accuracy (%bias)	0%	1%	5%	2%
Precision (%CV)	9.1%	3%	6.5%	5.9%
Selectivity	No significant interference	No significant interference	No significant interference	No significant interference

**Statistical Method:**

In general, summary statistics (n, mean, standard deviation, median, and minimum and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) were provided by treatment group for all variables. Source data for the summary tables and statistical analyses are presented as subject data listings.

Data are presented for 3 periods (where applicable) that are distinct from the study phases shown in the schedule of events: the Oral Aripiprazole Period (includes data from before dosing through baseline of the Aripiprazole Lauroxil Period), the Aripiprazole Lauroxil Period (includes data from Baseline in the Aripiprazole Lauroxil Period through Day 146), and the Follow-up Period (includes data from Day 146 through Day 230). Baseline for the Oral Aripiprazole Period was the last assessment before dosing on Day 1 for each variable. Baseline for the Aripiprazole Lauroxil Period was the last assessment before dosing on Day 34 and is defined separately for each variable.

**Study Population :**

A total of 87 subjects entered the Oral Aripiprazole Period; 78 (89.7%) of them completed the Oral Aripiprazole Period. A total of 76 subjects entered the Aripiprazole Lauroxil Period and were

randomized: 30 to the aripiprazole lauroxil 300 mg group (23 [76.7%] completed); 12 to the aripiprazole lauroxil 450 mg group (11 [91.7%] completed); 14 to the aripiprazole lauroxil 600 mg group (9 [64.3%] completed), and 20 to the placebo group (14 [70%] completed). Overall, the majority of the subjects were black or African American (92.1% overall, 85% in placebo group, 90.0% in the aripiprazole lauroxil 300 mg group, and 100% in the aripiprazole lauroxil 450 and 600 mg groups). The mean body weight in the aripiprazole lauroxil 600 mg appeared higher (93.1 kg) than the other 3 groups (83.4 to 88.5 kg).

Randomized/Completed/ Discontinued	(to IM dosing) 76/57/19  (4 each for: subject choice, lost to follow up, protocol violation/ 3 for AE, 2 each for: other and physician's decision)
Age [Mean (SD)]	43.8 (8.25) yr
Male/Female	61/15
Race (Caucasian/Black/Asian/other)	6/70/0/0

**Results**

**Pharmacokinetics**

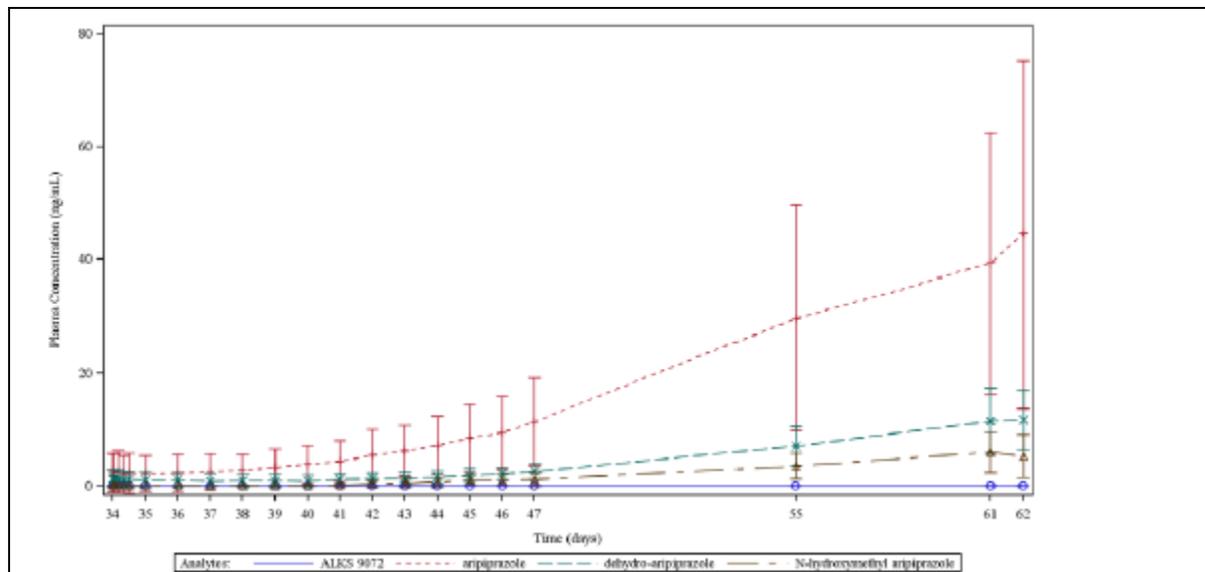
**Aripiprazole Lauroxil Period**

**Table 1: Pharmacokinetic Parameter Summary for IM Aripiprazole Lauroxil after 1<sup>st</sup> dose and 4<sup>th</sup> dose**

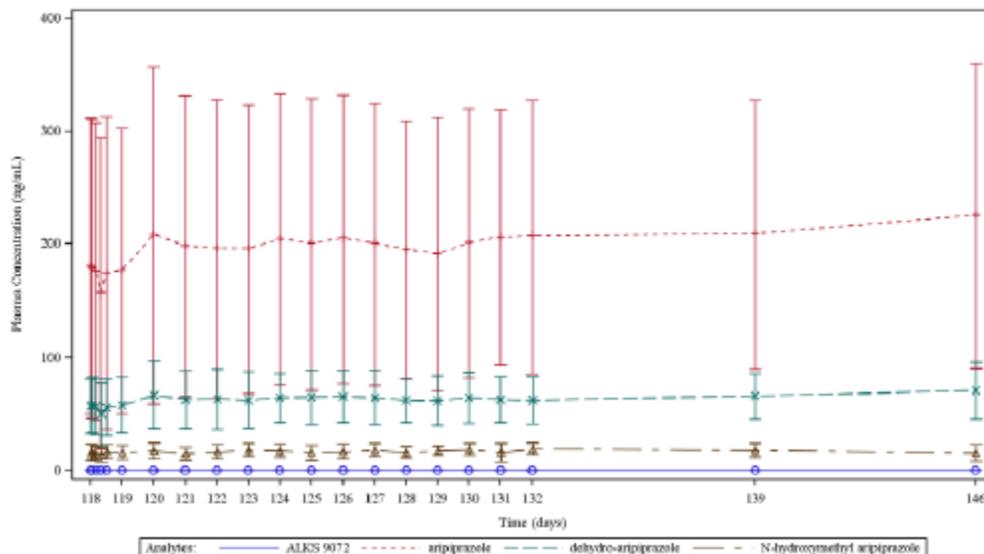
Dose level	Analyte	PK after 1 <sup>st</sup> dose				PK after 4 <sup>th</sup> dose			
		C <sub>max</sub> (day)	T <sub>max</sub> (day)	AUC <sub>tau</sub> (day*ng/ mL)	T <sub>1/2</sub> (day)	C <sub>max</sub> (day)	T <sub>max</sub> (day)	AUC <sub>tau</sub> (day*ng/ mL)	T <sub>1/2</sub> (day)
441 mg AL	Aripiprazole	-	-	439 (397)	-	133 (46)	21.1	2937 (954)	29 (6)

	Dehydroaripiprazole	-	-	122 (107)	-	51 (19)	28.1	1087 (406)	30 (6)
	N-hydroxymethyl aripiprazole	-	-	67(80)	-	18 (13)	13	323 (146)	30 (8)
<b>662mg AL</b>	Aripiprazole	-	-	356 (170)	-	207 (79)	28	4458 (1887)	29 (10)
	Dehydroaripiprazole	-	-	108 (67)	-	75 (38)	42	1605 (889)	27 (2)
	N-hydroxymethyl aripiprazole	-	-	43 (31)	-	22 (9)	13	454 (197)	30 (4)
<b>882 mg AL</b>	Aripiprazole	-	-	487 (340)	-	215 (136)	6	5559 (3452)	35 (6)
	Dehydroaripiprazole	-	-	119 (60)	-	73 (27)	12	1700 (624)	34 (6)
	N-hydroxymethyl aripiprazole	-	-	57 (35)	-	21 (6)	3	471 (158)	31 (4)

**Representative Figure 1:** Mean ( $\pm$  SD) Plasma Concentration-Time Profiles for All Analytes following the First Dose (top panel) and Fourth Dose (bottom panel) of 882 mg IM Aripiprazole Lauroxil (Days 36-42)



Source: Figure 14.2.4.1



Following the first IM administration of aripiprazole lauroxil, average concentrations for all analytes increased steadily prior to the next drug administration across all dose levels. The highest concentrations were observed for aripiprazole, followed by dehydro-aripiprazole, and then *N*-hydroxymethylaripiprazole. Concentrations for all analytes are significantly elevated following repeat dosing of aripiprazole lauroxil.

A generally flat concentration-time profile (ie, small peak:trough) was evident for all analytes and demonstrated the continuous and sustained drug concentrations following repeated IM administrations.

Plasma concentrations for all analytes over the study period (Days 34 to 230) demonstrated the

steady increases in drug concentrations following repeated IM administrations. Following the fourth (last) administration on Day 118, concentrations persisted for an extended period, and began to decline prior to the last sampling time point on Day 230.

#### ***Pharmacokinetics of Aripiprazole Lauroxil***

There were no measurable concentrations of aripiprazole lauroxil in any sample following IM administration of aripiprazole lauroxil 300, 450, or 600 mg, with the exception of a subject who had an early release concentration-time profile.

#### ***Pharmacokinetics of Aripiprazole***

Aripiprazole exposure, based on  $C_{max}$  and  $AUC_{0-\tau}$ , increased with increasing dose. Mean  $C_{ave}$  following the fourth dose was 105, 159 and 198 ng/mL for the aripiprazole lauroxil 300, 450 and 600 mg groups, respectively. Maximum drug concentrations were achieved by approximately 21 to 28 days for the aripiprazole lauroxil 300 and 450 mg groups (median  $T_{max}$ ). For the aripiprazole lauroxil 600 mg dose group, however, the median time to maximum concentrations was approximately 6 days following the fourth dose. The mean elimination half-life of aripiprazole following the fourth aripiprazole lauroxil IM administration was independent of dose and ranged from 29 to 35 days. The significant prolongation in aripiprazole half-life compared to oral aripiprazole (approximately 75 hours) is consistent with previous study results and is attributed to the dissolution and formation rate-limited elimination of aripiprazole following aripiprazole lauroxil IM administration.

When the aripiprazole exposure data was examined by 2D6 metabolizer status after the first dose, the highest exposure was evident for poor metabolizers albeit the number of poor metabolizer subjects was low ( $n = 2$  for the aripiprazole lauroxil 300 mg group and  $n=1$  for the 600 mg group). Based on mean  $AUC_{0-\tau}$  estimates, exposure to aripiprazole was approximately 3 to 4 times higher in poor metabolizers when compared to extensive metabolizers. Intermediate and extensive metabolizers had comparable exposures for aripiprazole. Differences, based on metabolizing status, were not as evident at the fourth dose. Where the 1 poor metabolizer subject in the aripiprazole lauroxil 600 mg group had almost a 4-fold higher exposure as compared to the mean  $AUC_{0-\tau}$  for extensive metabolizers, the mean exposures in the aripiprazole lauroxil 300 mg group were comparable between poor and extensive metabolizers.

#### ***Pharmacokinetics of Dehydro-aripiprazole***

Dehydro-aripiprazole concentrations and exposure increased with increasing dose and paralleled that of aripiprazole. Maximum drug concentrations were achieved by approximately 28 to 42 days

(median  $T_{max}$ ) after dosing for the aripiprazole lauroxil 300 and 450 mg groups after the fourth dose. For the aripiprazole lauroxil 600 mg group, however, the median time to maximum concentrations was achieved at approximately 12 days following the fourth dose. The mean elimination half-life of dehydroaripiprazole following aripiprazole lauroxil IM administration was independent of dose and ranged from 27 to 34 days.

### ***Pharmacokinetics of N-hydroxymethylaripiprazole***

*N*-hydroxymethylaripiprazole concentrations and exposure increased with increasing dose and paralleled that of aripiprazole after the first dose. After the fourth dose, maximum concentrations in all groups were achieved by approximately 3 to 13 days.

### ***Metabolite to Parent Ratios***

The metabolite to parent (dehydro-aripiprazole/aripiprazole) ratios after the first dose were 17% to 43% for the aripiprazole lauroxil 300 mg group, 16% to 45% for the aripiprazole lauroxil 450 mg group, and 13% to 41% for the aripiprazole lauroxil 600 mg group. After the fourth dose, slightly higher metabolite to parent ratios were evident and were 25% to 49% for the aripiprazole lauroxil 300 mg group, 23% to 50% for the aripiprazole lauroxil 450 mg group, and 21% to 51% for the aripiprazole lauroxil 600 mg group.

### ***Accumulation Ratios***

On average, accumulation ratios for aripiprazole were 8.9, 13.3, and 10.7, for the aripiprazole lauroxil 300, 450, and 600 mg groups, respectively. For dehydro-aripiprazole, accumulation ratios were slightly higher when compared to aripiprazole and were 11.8, 17.2, and 15.3, for the aripiprazole lauroxil 300, 450, and 600 mg groups. For *N*-hydroxymethylaripiprazole, accumulation ratios were 9.0, 16.4, and 9.2, for the aripiprazole lauroxil 300, 450, and 600 mg groups. These data demonstrate significant accumulation with repeated dosing of aripiprazole lauroxil.

### ***Dose proportionality***

Dose proportionality assessments were performed on aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole  $AUC_{0-tau}$  after the first dose and  $C_{max}$  and  $AUC_{0-tau}$  after the fourth dose.

Based on the 90% confidence interval  $C_{max}$  estimates after the fourth dose appeared to be less than dose proportional for aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole.  $AUC_{0-tau}$

tau

estimates for aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole were less than dose proportional after the first dose but were dose proportional after the fourth dose having a 90% confidence interval that contained 1.

**Table 2:** Dose Proportionality Assessment of Aripiprazole, Dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole Exposure Following 4 IM dosing of Aripiprazole Lauroxil across a Dose Range of 441 mg to 882 mg

Analyte	Parameter	Slope	90% CI
aripiprazole	C <sub>max</sub>	0.630	(0.268, 0.991)
	AUC <sub>0-24</sub>	0.801	(0.429, 1.174)
dehydro-aripiprazole	C <sub>max</sub>	0.582	(0.221, 0.944)
	AUC <sub>0-24</sub>	0.658	(0.278, 1.038)
<i>N</i> -hydroxymethyl aripiprazole	C <sub>max</sub>	0.388	(-0.002, 0.779)
	AUC <sub>0-24</sub>	0.640	(0.236, 1.044)

#### Site Inspected

Requested: Yes  No

Performed: Yes  No  N/A

#### Safety

▪ Was there any death or serious adverse events?  Yes  No  NA

No deaths occurred during the study. The majority of TEAEs throughout the study and across treatment groups were mild or moderate in severity.

During the Aripiprazole Lauroxil Period, 90.8% of subjects experienced at least 1 TEAE. Of these, 72.4% were related to the IM Study drug. Four subjects (5.3%) experienced SAEs; none was considered related to the IM study drug. Three subject (3.9%) discontinued the study due to TEAE (2 [10%] in the placebo group and 1 [8.3%] in the aripiprazole lauroxil 450 mg group).

Overall, the most frequent TEAEs were Nervous system disorders (30 subjects [39.5%]), Gastrointestinal disorders (28 [36.8%]), General disorders and administration site conditions (28 [36.8%]), and Investigations (22 [28.9%]).

During the Aripiprazole Lauroxil Period, the most frequent overall TEAEs were injection site pain (23 subjects [30.3%]), weight increased (17 [22.4%]), headache (13 [17.1%]), anxiety (11 [14.5%]), and sedation (10 [13.2%]).

The most frequent TEAEs in the placebo group was weight gain (7 [35%]), followed by toothache (5 [25%]), and injection site pain, headache, and dyspepsia (3 subject each [15%]).

Injection site pain was the most frequent TEAE in all 3 aripiprazole lauroxil groups (8 [26.7%] in the aripiprazole lauroxil 300 mg group, 8 [66.7%] in the 450 mg group, and 4 [28.6%] in the 600 mg group).

The other most frequent TEAEs besides injection site pain were headache (6 [20%]) and weight increased (5 [16.7%]) in the aripiprazole lauroxil 300 mg group, anxiety (5 [41.7%]) and headache (3 [25%]) in the aripiprazole lauroxil 450 mg group, and weight increased (3 [21.4%]), sedation, constipation, alanine aminotransferase increased (2 [14.3%] each) in the aripiprazole lauroxil 600 mg group.

Overall, 23 subjects (30.3%) experienced injection site reactions. Injection site pain was the most commonly reported injection site reaction, and occurred with a higher frequency in the aripiprazole

lauroxil 450 mg group (66.7%), followed by the other 2 aripiprazole lauroxil groups (28.6% in the aripiprazole lauroxil 600 mg group and 26.7% in the aripiprazole lauroxil 300 mg group), and the placebo group (15.0%).

There were no clinically meaningful findings in vital signs, clinical laboratory evaluations, ECG findings, or ESRS results.

Based on responses to the C-SSRS questionnaire, no subjects in either treatment group exhibited suicidal behavior during the study period. Suicidal ideation was displayed by 6 subjects (7.9% overall) during the study period. There was 1 case of active suicidal ideation with some intent to act without specific plan; this occurred in a subject in the aripiprazole lauroxil 600 mg group (Subject 001-029). This event was reported as an AE (moderate, definitely not related). The event resolved 11 days later.

## Conclusion

### Pharmacokinetic Conclusions

- Exposure to aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole increased with increasing dose of IM aripiprazole lauroxil over the 300 to 600 mg dose range tested.
- Significant accumulation of aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole was evident following 4 repeated monthly doses. Increases in

exposure ranged from 8.9- to 16-fold across all analytes.

- The  $T_{1/2}$  estimates for aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethylaripiprazole were long (27 to 35 days) following the fourth dose and were independent of the dose administered.
- The metabolite to parent ratios (dehydro-aripiprazole/aripiprazole) after the first dose were 16% to 45% over the 300 to 600 mg dose range. After the fourth dose, slightly higher metabolite to parent ratios were evident and were approximately 21% to 51%.
- Exposure increases based on  $AUC_{0-\tau}$  were dose proportional after the fourth dose, but appeared to be less than dose proportional after the first dose.
- For all doses and analytes, concentrations appeared to approach steady-state with 4 doses.
- When the aripiprazole exposure data was examined by 2D6 metabolizer status after the first dose, the highest exposure was evident for poor metabolizers. Intermediate and extensive metabolizers had comparable exposures for aripiprazole.

#### Safety Conclusions:

- Multiple IM injections of aripiprazole lauroxil (300, 450, and 600 mg) to the gluteal muscle were well tolerated in adults with chronic stable schizophrenia. There were no deaths. SAEs were infrequent, with 8 events in 6 subjects during the study, 2 of which were related to exacerbations of the disease under study.
- Most TEAEs were mild or moderate in intensity, transient, and resolved before the end of the study.
- Injection site pain was the most frequent TEAE in all 3 aripiprazole lauroxil groups (8 [26.7] in the aripiprazole lauroxil 300 mg group, 8 [66.7%] in the 450 mg group, and 4 [28.6%] in the 600 mg group).

#### Comments

The Office of Clinical Pharmacology has reviewed the study report and agrees with sponsor's analysis.

Independent data analysis was performed by us using the prior single dose PK data (from study ALK9072-001) to simulate the profile after multiple dosing of IM aripiprazole lauroxil. Our analysis independently confirmed the sponsor's assertion that after 4 monthly IM doses a near steady state was achieved and that no significant accumulation is expected on additional dosing. Moreover, the exposure levels (i.e. concentration in ng/ml) from simulated multi-dose profile were similar to observed levels seen in the current 4 month dosing study.

**#4: ALKS 9072-102: Multi-Dose Study (Deltoid)**  
 NDA 207533 (Aripiprazole Lauroxil XR suspension IM injection)

Report # ALKS9072-102	Study Period: 12 Sep 2012 to 28 June 2013	EDR Link  \\cdsesub1\evsprod\NDA207533\0000\m5\52-tab-list
-----------------------	---	--

<b>Title</b>	A Phase 1, Randomized, Double-blind, Placebo-controlled, Multiple-dose Study to Evaluate the Safety and Tolerability of ALKS 9072 Following Deltoid Administration in Subjects with Chronic Stable Schizophrenia
--------------	--

**Study Design & Objective**

**Objective:**  
 The objective of the study was to determine the safety and tolerability of aripiprazole lauroxil (ALKS 9072) as an IM injection in the deltoid muscle after 4 monthly doses in adults with chronic stable schizophrenia.

**Study Design:**  
 This was a multicenter, randomized, double-blind, placebo-controlled, multiple-dose study designed to evaluate the safety and tolerability of aripiprazole lauroxil following deltoid administration in subjects with stable chronic schizophrenia. After screening, 53 eligible subjects were randomly assigned to receive an IM injection in the deltoid muscle of aripiprazole lauroxil (300 mg dose, aripiprazole free base equivalent) or placebo in a ratio of 3:1 (aripiprazole lauroxil:placebo). Subjects received the first injection on Day 1 and then received 3 additional injections, each 28 days after the prior dose (monthly). Injections were administered to alternating arms. After the fourth injection (Day 85), subjects were followed for an additional 4 months (to Day 197).

Screening Period  
 Days -28 to -2

Day 1  
 1st IM Injection  
 Randomly assigned to  
 ALKS 9072 or Placebo (3:1 ratio)

Day 29  
 2nd IM Injection

Day 57  
 3rd IM

Day 85  
 4th IM Injection

Day 113  
 End of Treatment

Follow up

Day 197  
 End of Study

IM=intramuscular, ALKS 9072=aripiprazole lauroxil

<input type="checkbox"/> Bioequivalence		<input type="checkbox"/> Bioavailability		
Randomized Double-Blind Placebo control Parallel Multi-Center Multi-Dose Patients				
Screening: After the Screening Period (28 days), eligible subjects received either treatment or placebo (3:1)		Washout: NA		
Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:				
<p><b>Treatments:</b></p> <p>Male and female adults who were diagnosed with chronic stable schizophrenia Aripiprazole lauroxil (300 mg free base aripiprazole equivalents) was administered by IM injection into the deltoid muscle. The study duration for each completing subject was approximately 8 months, including about 1 month for screening, a 4-month treatment period of aripiprazole lauroxil or placebo, and an approximately 3-month follow-up period.</p>				
<p><b>Sampling Times (PK, plasma)</b></p> <p>On Day 1 (1<sup>st</sup> dosing day), PK samples were collected 4-8 hours post-dose. On other dosing days (Days 29, 57, and 85), PK samples were collected pre-dose. On non-dosing days (Days- 7, 14, 43, 71, 92, 106, 113, 141, and 169) PK samples were collected at any time</p>				
<p><b>Pharmacokinetics:</b></p> <p>Pharmacokinetic (PK) samples were collected for inclusion in a population PK analysis to be conducted separately from this study. Plasma concentrations for aripiprazole lauroxil and its metabolites were measured and listed; PK analyses were not part of this study.</p>				
<p><b>Analytical Method:</b> The performance of the analytical method is acceptable. Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>				
<p><b>LC/MS/MS:</b></p> <p>A validated liquid chromatography / tandem mass spectrometry (LC/MS/MS) method for analysis of ALKS 9072 (RDC-3317), aripiprazole (RDC-9864), and dehydro-aripiprazole (RDC-3954) in human plasma was used with a quantitation range of 1.00 ng/mL to 500 ng/mL. Aliquot volume for each sample was 50.0 µL. The bioanalytical analysis was performed by <span style="background-color: #cccccc; padding: 0 20px;"> </span> <sup>(b) (4)</sup></p> <p><span style="background-color: #cccccc; display: inline-block; width: 200px; height: 15px;"></span></p>				
Validation summary:				
Parameter	Aripiprazole	Dehydr-	Aripiprazole	N-hydroxy-

		aripiprazole	Lauroxil	aripiprazole (non-validated)
LLOQ-ULOQ (ng/mL)	1-500	1-500	1-500	1-500
Accuracy (%bias)	0%	1%	5%	2%
Precision (%CV)	9.1%	3%	6.5%	5.9%
Selectivity	No significant interference	No significant interference	No significant interference	No significant interference

**Statistical Method:**

**Pharmacokinetics and/or Pharmacodynamics:** Plasma concentrations for aripiprazole lauroxil and its metabolites were listed.

**Sample size considerations:** The sample size was based on clinical experience and judgment relative to study design and objectives. A sample size of at least 39 subjects on active drug was considered adequate clinical information to meet the objectives of the study.

**Study Population :**

A total of 53 subjects were randomized to treatment and received at least 1 dose of study medication; 40 subjects were randomized to aripiprazole lauroxil and 13 subjects to placebo. Twenty-nine subjects (20 in the aripiprazole lauroxil group; 9 subjects in the placebo group) completed the study as defined in the protocol.

Randomized/Completed/ Discontinued	53/29/24  (14= lost follow-up, 5=withdrew themselves, 2= withdrawn due to AE, 1 each for non-compliance, physician's decision and other )
Age [Mean (SD)]	45.2 (7.3) yr
Male/Female	35/18
Race (Caucasian/Black/Asian/other)	12/41/0/0

**Results**

<b>Pharmacokinetics</b>	
No separate PK analysis performed with the data set. The PK data was utilized for population PK analysis.	
<b>Site Inspected</b>	
<b>Requested:</b> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	<b>Performed:</b> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>
<b>Safety</b>	
<ul style="list-style-type: none"> <li>▪ Was there any death or serious adverse events? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA</li> <li>· Eighty percent of subjects in the aripiprazole lauroxil group and 76.9% of subjects in the placebo group experienced at least 1 TEAE. Overall, 56.6% of subjects experienced treatment-related TEAEs, with similar proportions of subjects in each treatment group experiencing treatment-related events.</li> <li>· One severe TEAE (retinal vein occlusion, aripiprazole lauroxil group) and 1 serious TEAE (drug abuse, placebo group) were reported. Two subjects, both in the aripiprazole lauroxil group, discontinued the study due to TEAEs (akathisia, blood creatine phosphokinase increased) that were at least possibly related to study drug. No deaths occurred during the study.</li> <li>· In the aripiprazole lauroxil group, 27.5% of subjects experienced injection site reactions, compared to 7.7% of subjects in the placebo group. Injection site pain was the most commonly reported injection site reaction. In the aripiprazole lauroxil group, 19 events of injection site pain were considered related to study drug in 10 subjects (25.0%), whereas 1 event of injection site pain was considered related in 1 subject in the placebo group. The vast majority of injection site reactions within both treatment arms were reported to be of mild severity and resolved within 1 week.</li> <li>· Changes in laboratory parameters, vital signs measurements, and ECGs were generally small, and the majority were not clinically significant.</li> <li>· Based on C-SSRS responses, no subjects reported suicidal behavior. There were 5 instances of suicidal ideation by 3 subjects in each treatment group. None of the positive responses for suicidal ideation was considered by the investigator to be clinically significant, and thus they were not considered to be AEs.</li> <li>· As expected in previously stabilized patients, PANSS, and CGI-S scores changed little over the course of the study for aripiprazole lauroxil and placebo groups. The changes were similar between the 2 groups, were numerically small, and were not clinically meaningful.</li> </ul>	

### Conclusion

The majority of subjects in this study experienced at least 1 TEAE (approximately 77% in the placebo group and 80% in the aripiprazole lauroxil group), with similar proportions experiencing treatment-related adverse events in each treatment group. The vast majority of TEAEs were mild or moderate in severity. One serious TEAE was reported, and 2 subjects discontinued due to a TEAE. There were no deaths.

In conclusion, deltoid administration of 300 mg aripiprazole equivalents of aripiprazole lauroxil was safe and well tolerated, with no unexpected adverse events. Adverse events were consistent with the published systemic safety profile of aripiprazole. None of the injection site reactions was severe. The incidence, symptoms, and severity of local injection-site reactions were comparable to that of other established safe and well-tolerated depot atypical antipsychotics.

An IM injection of aripiprazole lauroxil to the deltoid muscle once monthly for 4 months was safe and well tolerated in adults with chronic, stable schizophrenia.

### Comments

The Office of Clinical Pharmacology has reviewed the study report and agrees with the sponsors analysis.

Multi-dose administration (4 monthly injections of 441 mg aripiprazole lauroxil) to deltoid injection site was safe and tolerated. There was no evidence of dose dumping in any subjects since exposures generally rose very gradually (i.e. BLLQ on day 1, below 5 ng/mL on day 7 and below 20 ng/mL on day 14) with no abnormally high C<sub>max</sub> in any subject.

Additionally, since only sparse PK sampling was performed in this study, the C<sub>max</sub> after 4<sup>th</sup> dose (deltoid injection) was compared to the C<sub>max</sub> after 4<sup>th</sup> dose (gluteal injection) in an alternate study.

Cross study C<sub>max</sub> comparison of ARIPIPRAZOLE concentrations in subjects at 441 mg AL

Study #	Dose (of AL)	Site of injection	C <sub>max</sub> in ng/mL (after 4th dose)	
			Mean	SD

Study ALKS9072-002	441 mg	Gluteal	133	46	
Study ALKS9072-102	441 mg	Deltoid	146	58	

AL= Aripiprazole lauroxil

Therefore, the steady state exposures of aripiprazole from the 2 different injection sites (compared across studies) are generally similar with levels <10% higher for deltoid site.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

PRAVEEN BALIMANE  
06/10/2015

HAO ZHU  
06/10/2015

### Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

<b>Application Number</b>	NDA 207533
<b>Drug Name</b>	Aripiprazole Lauroxil
<b>Proposed Indication</b>	Schizophrenia
<b>Clinical Division</b>	DCP1
<b>PBPK Consult request</b>	Praveen Balimane , PhD
<b>Primary PBPK Reviewer</b>	Ping Zhao, PhD and Xiaofeng Wang, PhD
<b>Secondary PBPK Reviewer</b>	Kevin Krudys, PhD
<b>Sponsor</b>	Alkermes

<b>Physiological-based Pharmacokinetic Modeling Review</b> .....	1
<b>1. Objectives</b> .....	5
<b>2. Background</b> .....	5
Figure 1. Effect of other drugs on aripiprazole pharmacokinetics (Figure 1, reference [3]) .....	5
Table 1: Dose adjustment table for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers for greater than 2 weeks (Table 2 from reference [6]).....	6
<b>3. Methods</b> .....	7
<b>4. Results</b> .....	9
4.1. Can Aripiprazole PBPK Model Be Used to Predict The Effect of CYP3A Modulators on Aripiprazole Exposure After Oral Administration?.....	9
4.2. Does Aripiprazole PBPK Model Coupled with Skin Absorption Mechanism Sufficiently Describe Aripiprazole PK after Intramuscular Injection of Aripiprazole Lauroxil?.....	10
4.3. Can The Effect of CYP Modulators on Aripiprazole PK Be Predicted in Subjects with Specific CYP2D6 Phenotype Receiving Aripiprazole Lauroxil Intramuscular Injection?.....	10
Table 2. PBPK predicted geometric mean Cmax and AUC of aripiprazole after intramuscular injection of Aripiprazole Lauroxil in subjects with different CYP2D6 genotypes. Source Tables 16 and 17, reference [1]; minimum and maximum values can be found in Appendix Table 1. ....	10
Table 3. Fold changes of PBPK predicted plasma aripiprazole exposure (Cmax and AUC, geometric means) from EMs receiving the same dose of Aripiprazole Lauroxil without CYP modulator(s).....	11
Table 4. Calculation of fold-changes using EMs receiving 441 mg Aripiprazole Lauroxil alone as reference.....	13
Figure 2. Box-Whisker plots of PBPK simulated steady state aripiprazole C <sub>max,ss</sub> (upper) and C <sub>ave,ss</sub> (lower) under the influence of co-medication in subjects with different CYP2D6 genotypes (Refer to Table 4 for codes). Dashed horizontal lines represent targeted drug concentration range. ....	14
<b>5. Conclusion</b> .....	15
<b>6. Appendices</b> .....	16
6.1. Abbreviations .....	16

6.2. *Appendix Tables and Figures* ..... 17

Appendix Table 1. Input parameter for aripiprazole PBPK model (Simcyp 13.0, Table 2 of ref [1]) ..... 17

Appendix Table 2. Input parameters of Aripiprazole Lauroxil PBPK model..... 18

Appendix Table 3. Predicted geometric mean, minimum, and maximum values of aripiprazole exposure in CYP2D6 EMs, IMs, or PMs. Source data from Tables 16 and 17 [1]. ..... 18

Appendix Table 4: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of ketoconazole (see Methods for simulation study design). ..... 19

Appendix Table 5: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of quinidine (see Methods for simulation study design). ..... 20

Appendix Table 6: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of both ketoconazole and quinidine (see Methods for simulation study design). ..... 21

Appendix Table 7: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of carbamazepine (see Methods for simulation study design). ..... 22

Appendix Figure 1: Simulated (lines) and observed (circles; Boulton et al., 2008, [15]) mean plasma concentration-time profiles of aripiprazole following a single oral dose of 5 mg aripiprazole (left, profile of 0-576 hours; right, profile of 0-6 hours)..... 23

Appendix Figure 2: Simulated (lines) and observed (circles; Clinical Study 98-206 Vol 69-79) mean plasma concentration-time profiles of aripiprazole after a single oral dose of 15 mg administered alone (left) and on the 2nd day of 14 days of dosing of ketoconazole (200 mg q.d.) (right). ..... 24

Appendix Figure 3: Simulated (lines) and observed (circles; Clinical Study 98-207 Vol 80-83) mean plasma concentration-time profiles of aripiprazole after a single oral dose of 10 mg to healthy CYP2D6 PMs ..... 24

Appendix Figure 4: Simulated (lines) and observed (circles; Clinical Study 98-207 Vol 80-83) mean plasma concentration-time profiles of aripiprazole after a single oral dose of 10 mg alone (left) or administered on the 1st day of 13 days of dosing of quinidine (166 mg q.d.) (right)..... 26

Appendix Figure 5: PBPK simulated geometric mean AUC ratio of aripiprazole under different steady-state carbamazepine trough concentrations ( $C_{\text{trough}}$ ) achieved under different carbamazepine dose regimens..... 26

Appendix Figure 6: Simulated (lines) and observed (circles; Clinical Study ALK9072-001, [16]) mean plasma concentration-time profiles of aripiprazole following a single intramuscular injection of 150 mg (upper panel), 300 mg (middle panel), or 400 mg (lower panel) Aripiprazole Lauroxil. .... 27

Appendix Figure 7. Simulated (lines) and observed (circles; Clinical Study ALK9072-002, [17]) mean plasma concentration-time profiles of aripiprazole following intramuscular injections of 300 mg (upper panel), 450 mg (middle panel), or 600 mg (lower panel) Aripiprazole Lauroxil administered every 28 days (4 in total). .... 28

Appendix Figure 8: Simulated (lines) and observed (circles and square; Clinical Study ALK9072-102, [17]) mean plasma concentrations of aripiprazole in CYP2D6 EMs (upper panel, n=25), IMs (middle panel, n=12) and PM subjects (lower panel, n=3) following IM injections of 300 mg Aripiprazole Lauroxil administered on days 1, 29, 57 and 85. .... 29

*References* ..... 30

### 1. Objectives

The main objective of this review is to evaluate the adequacy of sponsor’s conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) models to predict the drug-drug interaction (DDI) potential of aripiprazole as a victim in patients receiving Aripiprazole Lauroxil intramuscular injection. To support its conclusions the sponsor provided the following PBPK modeling and simulation report:

Quantitative prediction of the systemic exposure of aripiprazole after administration of Aripiprazole Lauroxil using prior in vitro and in vivo data: potential for drug-drug interactions as a victim [1]

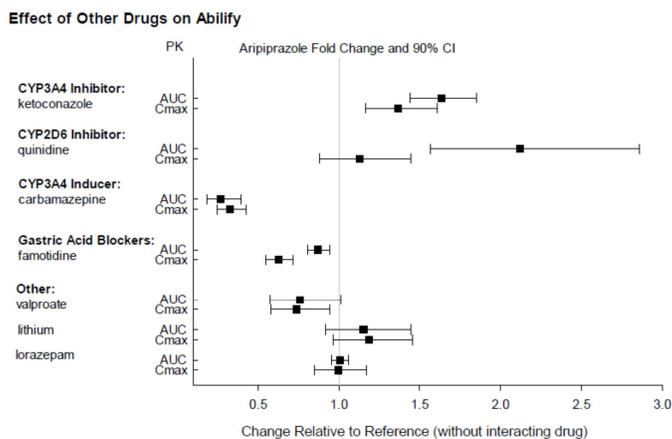
### 2. Background

ARISTADA (Aripiprazole Lauroxil) is a covalently bonded form of antipsychotic agent aripiprazole. The drug is formulated as an extended-release suspension for intramuscular injection. The conversion of Aripiprazole Lauroxil to aripiprazole is mediated by dissolution, enzymatic hydrolysis, and water mediated hydrolysis. Three doses are available 441, 662 or 882 mg (equivalent aripiprazole doses of 300, 450, and 600 mg, respectively) [2].

Aripiprazole is metabolized by CYP3A and CYP2D6 [3]. Multiple clinical studies have been conducted to evaluate the effect of co-medications on the pharmacokinetics (PK) of aripiprazole after oral administration (Figure 1, [4]). Of note, strong CYP3A inhibitor ketoconazole and strong CYP2D6 inhibitor quinidine increased plasma aripiprazole AUC (area-under-the-concentration-time-curve) by approximately 1.5 and 2.1-fold, respectively; strong CYP3A inducer carbamazepine decreased plasma aripiprazole AUC by more than 75%. In addition, subjects classified as poor metabolizers of CYP2D6 (PMs) have about 80% higher aripiprazole exposure compared to extensive metabolizers (EMs).

The product label of Abilify® recommended reducing usual dose by 2 fold in patients taking aripiprazole with a strong CYP3A inhibitor, in patients taking aripiprazole with a strong CYP2D6 inhibitor, or in CYP2D6 PMs; reducing usual dose to one quarter in CYP2D6 PMs taking a strong CYP3A inhibitor, or in patients taking both a strong CYP3A inhibitor and a strong CYP2D6 inhibitor; and doubling usual dose in patients taking a strong CYP3A inducer over 1 to 2 weeks [3].

Figure 1. Effect of other drugs on aripiprazole pharmacokinetics (Figure 1, reference [3])



Abilify Maintena® is an extended-release injectable suspension of aripiprazole for intramuscular use. The recommended starting and maintenance dose is 400 mg monthly as a single injection. For patients taking CYP3A or CYP2D6 modulators (inhibitor or inducer) for greater than 14 days, Abilify Maintena® product label recommends dose reduction to 300 mg monthly in patients taking a strong CYP3A inhibitor, patients taking a strong CYP2D6 inhibitor, or in CYP2D6 PMs; dose reduction to 200 mg in patients taking both CYP2D6 and CYP3A inhibitors, or in CYP2D6 PMs taking CYP3A inhibitors; and avoidance of the co-administration with strong CYP3A inducer [4]. These recommendations were based on simulation results using population pharmacokinetic modeling [5].

In current NDA submission, sponsor developed a PBPK model of Aripiprazole Lauroxil to simulate effect of CYP modulators on aripiprazole PK in CYP2D6 EM, intermediate metabolizer (IM) or PMs who receive ARISTADA intramuscular injection [1]. Simulation results were used to support dosing strategy proposed in draft product label, as summarized in **Table 1** [6].

**Table 1: Dose adjustment table**

(b) (4)

(Table (b) (4) from reference [6])

(b) (4)

This review evaluates the adequacy of sponsor's aripiprazole and Aripiprazole Lauroxil PBPK model to support the drug-drug interaction (DDI) claims in the product label of ARISTADA.

### 3. Methods

A population based PBPK software Simcyp® (V13, release 1, Sheffield, UK) [7, 8] were used by the sponsor to develop PBPK models of aripiprazole (**Appendix Table 1**) and Aripiprazole Lauroxil (**Appendix Table 2**). Unless otherwise stated, all simulations were conducted in Software's built-in "Sim-Healthy volunteer" population and ten trials of varying number of subjects were simulated for each dosing regimen. The default mean (Coefficient of variation, CV) enzyme abundance of CYP2D6 in EMs was 8 (61%) pmol/mg microsomal protein. This value was set to zero (0) in CYP2D6 PMs. In the absence of such data for CYP2D6 IM phenotype, a mean (CV) of 4 (61%) pmol/mg protein was applied by the sponsor. Perpetrator models for ketoconazole (Sim-ketoconazole 200 mg BID.cmp) and carbamazepine (SV-carbamazepine.cmp) and its metabolite (SV-Carbamazepine-10,11-epoxide.cmp) from the software's drug model library were directly used. Model for quinidine (Sim-quinidine.cmp) was modified by the sponsor to include an unbound reversible inhibition constant (K<sub>i</sub>) value for CYP3A of 3.4 μM (mean of 5.3 μM and 2.25 μM (half of IC<sub>50</sub> of 4.5 μM) from references [10] and [11], respectively).

Construction of aripiprazole PBPK models was done in two stages. In the first stage, sponsor used human PK data from several studies to develop aripiprazole PBPK model. A first order absorption rate constant (K<sub>a</sub>) was set to 1.5 h<sup>-1</sup> to allow recovery of observed t<sub>max</sub> and C<sub>max</sub> values [12]. The volume of distribution at steady state (V<sub>d,ss</sub>) of aripiprazole was optimized to 2.7 L/kg based on oral aripiprazole PK [12], and minimal PBPK distribution model was assumed [7]. Hepatic intrinsic clearance (CL<sub>int</sub>) was estimated from intravenous PK [10] using retrograde methods [7]. Clinical interaction study using ketoconazole (a strong CYP3A inhibitor) and PK study in CYP2D6 PM subjects were used to determine the contribution of CYP3A (fractional metabolism by CYP enzyme, f<sub>m,CYP3A</sub>=0.45), CYP2D6 (f<sub>m,CYP2D6</sub>=0.41) and an unspecified metabolic pathway (fraction of 0.14) in aripiprazole PBPK model for a CYP2D6 EM subject (**Appendix Table 1**).

Simulations were conducted by the sponsor for the following clinical trials to verify aripiprazole model:

- Effect of quinidine in CYP2D6 EMs (10 trials, 12 EM subjects per trial (50% female) aged 18 to 45 years old) [13]
- Plasma PK in EM, IM and PM healthy subjects (10 trials with 12 subjects per trial (50% female) aged 18 to 45 years old) [14]
- Plasma PK in patients taking oral 10 mg aripiprazole daily for 5 days (10 trials of 40 subjects in each trial (30% female; 65% EM, 32.5% IM, 2.5% PM) aged 21 to 55 years old) (Sponsor's study ALK9072-001, oral dosing cohort)

Simulations were conducted by FDA reviewer for the effect of carbamazepine on aripiprazole PK according to Citrome et al [15]. In this simulation, FDA reviewer modified sponsor's workspace file for the effect of enzyme modulator on steady state PK of orally administered aripiprazole by using carbamazepine as a perpetrator. Because CYP2D6 genetic status and the exact dose amount of carbamazepine were not available [15], simulations were conducted in 20 trials with 6 healthy CYP2D6 EM subjects in each trial, and various carbamazepine doses were tested. Oral aripiprazole was given once daily (q.d.) for 44 days. Oral carbamazepine was given between day 15 and day 44 under different regimens to achieve varying steady state trough concentrations of carbamazepine. These regimens are 200 mg twice daily (b.i.d.), 400 mg b.i.d., 600 mg b.i.d., or 600 mg every 8 hours.

In the second stage, sponsor extended aripiprazole model to develop PBPK model of Aripiprazole Lauroxil by incorporating the systemic absorption of aripiprazole after intramuscular injection of Aripiprazole Lauroxil. Because the software does not allow simulation of intramuscular injection,

sponsor used a skin absorption model to mimic intramuscular input. The model assumed that aripiprazole was applied on the thigh in a dermal patch formulation with an area of application of 4 cm<sup>2</sup>. In this model, the appearance of aripiprazole in blood stream is governed by drug release from the formulation, followed by permeation and diffusion through different skin compartments (stratum corneum, viable epidermis, and dermis). The first order release rate constant and the partition coefficient for the stratum corneum/viable epidermis of the drug were optimized using sensitivity analyses according to aripiprazole plasma PK data after intramuscular injection of Aripiprazole Lauroxil for formulation 1 (Clinical Study ALK9072-001 [16], 150 mg aripiprazole equivalent, single dose) and formulation 2 (Clinical Study ALK9072-002 [17], 300 mg aripiprazole equivalent every 28 days). Parameter values are summarized in **Appendix Table 2**.

Simulations of aripiprazole plasma PK in patients receiving IM injection of Aripiprazole Lauroxil were conducted according to Clinical studies ALK9072-001 and 002:

- Study 001, formulation 1. Ten trials with varying numbers of subjects in each trial for each single intramuscular dose (150 mg aripiprazole dose equivalent, 10 subjects, 26-52 years old, 20% female, 50% CYP2D6 IM and 50% CYP2D6 EMs; 300 mg aripiprazole dose equivalent, 8 subjects, 34-52 years old, 50% female, 25% CYP2D6 IM and 75% EMs; 400 mg aripiprazole dose equivalent, 8 subjects, 21-55 years old, 38% female, 37.5% CYP2D6 IM and 62.5% EMs).
- Study 002, formulation 2. Aripiprazole Lauroxil was given on days 34, 62, 90, and 118, with PK samples collected for the last dose. Ten trials with varying numbers of subjects in each trial for each intramuscular dose (441 mg, 23 subjects, 22-55 years old, 21% female, 8% CYP2D6 PM, 25% IM and 67% EM; 662 mg, 11 subjects, 23-54 years old, 25% female, 27% IM and 73% EM; 882 mg, 11 subjects, 21-55 years old, 21% female, 9% PM, 36% IM and 55% EM. Aripiprazole equivalent doses were 300, 450, and 600 mg, respectively).

Simulations of aripiprazole plasma PK in EM, IM, and PM subjects were conducted according to Study ALK9072-102 to verify Aripiprazole Lauroxil model. Patients received 441 mg intramuscular doses on days 1, 29, 57, and 85. Ten virtual trials of varying numbers of subjects in each CYP2D6 phenotype group were simulated (25 EM subjects, 25-44 years old, 20% female; 12 IM subjects, 31-54 years old, 42% female; 3 PMs, 42-50 years old, 33% female). Simulations were compared to observed data.

Finally, sponsor used Aripiprazole Lauroxil model to predict the following:

1. Pharmacogenetic effect: ten trials of 20 CYP2D6 EM, IM, or PM subjects aged 21 to 55 years (21% female) receiving 6 doses of 441, 662, and 882 mg Aripiprazole Lauroxil by intramuscular injection, each dose administered every 28 days
2. Effect of strong CYP3A inhibitor ketoconazole in CYP2D6 PMs: ten virtual trials of 20 CYP2D6 PM subjects aged 21 to 55 years (21% female) receiving 441, 662, and 882 mg Aripiprazole Lauroxil by intramuscular injection every 28 days (day 1, 29, 57, 85, 113, 141 and 169; 7 doses) coadministered with 200 mg BID ketoconazole for 1, 2, 3 or 4 weeks starting on day 169
3. Effect of strong CYP3A inducer carbamazepine in CYP2D6 PMs: ten virtual trials of 15 CYP2D6 PM subjects aged 21 to 55 years (21% female) receiving 441, 662, and 882 mg Aripiprazole Lauroxil via intramuscular injection every 28 days (day 1, 29, 57, 85, 113, 141 and 169; 7 doses) co-administered with 400 mg BID carbamazepine for 1, 2, 3 or 4 weeks starting on day 169

4. Effect of strong CYP3A inhibitor ketoconazole in CYP2D6 IMs: except for CYP2D6 genotype, demographics and design are the same as 2
5. Effect of strong CYP2D6 inhibitor quinidine in CYP2D6 IMs: except for CYP2D6 genotype, demographics and design are the same as 2
6. Effect of strong CYP3A inhibitor ketoconazole and strong CYP2D6 inhibitor quinidine in CYP2D6 IMs: except for CYP2D6 genotype, demographics and design are the same as 2
7. Effect of strong CYP3A inducer carbamazepine in CYP2D6 IMs: except for CYP2D6 genotype, demographics and design are the same as 3
8. Effect of strong CYP3A inhibitor ketoconazole in CYP2D6 EMs: except for CYP2D6 genotype, demographics and design are the same as 2
9. Effect of strong CYP2D6 inhibitor quinidine in CYP2D6 EMs: except for CYP2D6 genotype, demographics and design are the same as 2
10. Effect of strong CYP3A inhibitor ketoconazole and strong CYP2D6 inhibitor quinidine in CYP2D6 EMs: except for CYP2D6 genotype, demographics and design are the same as 2
11. Effect of strong CYP3A inducer carbamazepine in CYP2D6 EMs: except for CYP2D6 genotype, demographics and design are the same as 3

#### 4. Results

##### 4.1. Can Aripiprazole PBPK Model Be Used to Predict The Effect of CYP3A Modulators on Aripiprazole Exposure After Oral Administration?

Yes. Two major factors are critical for a substrate PBPK model to be used for predicting the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumptions of  $f_{m,CYP3A}$  and  $f_{m,CYP2D6}$  for aripiprazole), and capability of the model to describe PK profiles under different dosing regimens.

Aripiprazole model reasonably describes the observed PK profiles that were used for model development, including studies of the effects of CYP2D6 PM status or CYP3A inhibitor ketoconazole on plasma PK of aripiprazole (**Appendix Figures 1-3**). With regard to verification dataset (not used for model development), the model was able to describe the effect of CYP2D6 inhibitor quinidine in CYP2D6 EMs (**Appendix Figure 4**) and the PK of aripiprazole in CYP2D6 IMs or EMs after multiple oral dosing (data not shown). Additionally, FDA reviewer used sponsor's aripiprazole PBPK model to simulate the effect of carbamazepine on aripiprazole PK in CYP2D6 EMs taking aripiprazole orally. Because information on CYP2D6 genotype and exact doses of carbamazepine were not available [15], a sensitivity analysis was conducted by the FDA reviewer to evaluate the effect of different carbamazepine doses on the exposure of aripiprazole. **Appendix Figure 5** shows that the effect of carbamazepine on aripiprazole PK is dependent on the dosing regimen of carbamazepine. When predicted steady state trough concentration of carbamazepine falls within the range (8-12 mg/mL) targeted by Citrome et al [15] to ensure strong CYP3A induction, the simulated aripiprazole AUC ratio is comparable to the observed values (0.3 versus 0.3, respectively). Together, these simulation results support further use of aripiprazole PBPK model to predict the effect of CYP modulators under other clinical situations.

#### 4.2. Does Aripiprazole PBPK Model Coupled with Skin Absorption Mechanism Sufficiently Describe Aripiprazole PK after Intramuscular Injection of Aripiprazole Lauroxil?

Yes. In order to mimic the slow appearance of aripiprazole after intramuscular injection of Aripiprazole Lauroxil, sponsor updated aripiprazole PBPK model described above by incorporating a skin absorption component (See *Methods*). **Appendix Figures 6 and 7** show the simulated and observed aripiprazole PK profiles in subjects receiving intramuscular injection of Aripiprazole Lauroxil after single dose or multiple doses (once every 4 weeks). For single 441 mg dose level (300 mg aripiprazole equivalent, as reported in [1]), the model under-predicts aripiprazole exposure during early time points; for multiple dose conditions, the model under-predicts aripiprazole exposure after the first three doses for all dose levels. Sponsor stated that “This was not considered to be an issue as the main application of the model was for predictions of exposure of aripiprazole at steady state.”

**Appendix Figure 8** shows that for each CYP2D6 genotype (EMs, IMs, or PMs), the aripiprazole model with skin absorption mechanism reasonably captured the observed aripiprazole PK.

#### 4.3. Can The Effect of CYP Modulators on Aripiprazole PK Be Predicted in Subjects with Specific CYP2D6 Phenotype Receiving Aripiprazole Lauroxil Intramuscular Injection?

Model performance demonstrated in 4.1 and 4.2 is deemed adequate for Aripiprazole Lauroxil model to be used to predict the effect of CYP modulators on aripiprazole PK in subjects with various CYP2D6 genotypes receiving intramuscular injection the drug.

Predicted geometric mean Cmax and steady state AUC of aripiprazole in subjects with different CYP2D6 genotypes (EMs, IMs, or PMs) are summarized in **Table 2**. At each dose compared with CYP2D6 EMs, aripiprazole exposure values (Cmax and steady state AUC) are 30% and 90% higher in IMs and PMs, respectively.

**Table 2. PBPK predicted geometric mean Cmax and AUC of aripiprazole after intramuscular injection of Aripiprazole Lauroxil in subjects with different CYP2D6 genotypes. Source Tables 16 and 17, reference [1]; minimum and maximum values can be found in Appendix Table 1.**

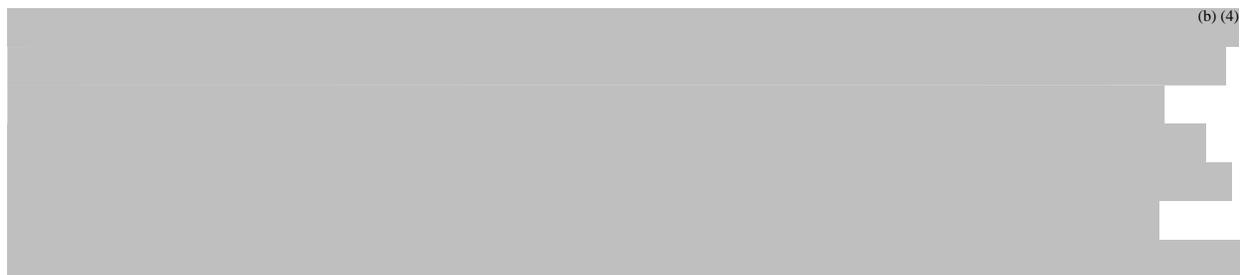
	441 mg		662 mg		882 mg		Fold-change from EM <sup>b</sup>	
	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax	AUC
EMs	103	2721	154	4081	206	5442	1	1
IMs	132	3503	198	5254	264	7006	1.3	1.3
PMs	192	5126	287	7688	383	10251	1.9	1.9

<sup>a</sup>AUC calculated as steady state AUC divided by 24 (28 hr interval, [1])

<sup>b</sup>Fold-changes were calculated using geometric mean value (Cmax or AUC) in EMs as denominator for IMs or PMs. Fold change values for IM/EM and PM/EM remain the same for all doses.

Effects of CYP modulators on the PK of aripiprazole in subjects receiving intramuscular injection of Aripiprazole Lauroxil are summarized in **Table 3**. For each condition, fold-change in geometric mean exposure (Cmax and AUC) was calculated separately for each dose in CYP2D6 EMs, IMs, or PMs, using the value in EMs without enzyme modulator(s) as reference. Of note, fold-changes remain the same for

each condition across different doses of Aripiprazole Lauroxil because aripiprazole models assume linear pharmacokinetics.



The simulated aripiprazole C<sub>max</sub> and average concentrations (C<sub>ave,ss</sub>) for conditions 1 to 11, overlaid with targeted concentration range (See Pharmacometrics review), are shown in **Figure 2**. Median C<sub>max</sub> values for conditions 1, 4, 7, and 10 are higher than the upper bound of the targeted concentration range.

**Table 3. Fold changes of PBPK predicted plasma aripiprazole exposure (C<sub>max</sub> and AUC, geometric means) from EMs receiving the same dose of Aripiprazole Lauroxil without CYP modulator(s).**

	Dosing of perpetrator(s)										Source data
	No inhibitor		1 week		2 weeks		3 weeks		4 weeks		
	C <sub>max</sub>	AUC	C <sub>max</sub>	AUC	C <sub>max</sub>	AUC	C <sub>max</sub>	AUC	C <sub>max</sub>	AUC	
EM 441 mg	1.0	1.0									Calculated from Table 1
EM 662 mg	1.5	1.5									
EM 882 mg	2.0	2.0									
Ketoconazole											Appendix Table 4
EM	1.0	1.0	1.3	1.1	1.4	1.2	1.5	1.4	1.6	1.5	
IM	1.3	1.3	1.8	1.5	2.0	1.7	2.3	2.0	2.3	2.1	
PM	1.9	1.9	3.0	2.3	3.8	2.9	4.5	3.5	4.8	3.9	
Quinidine											Appendix Table 5
EM	1.0	1.0	1.4	1.2	1.6	1.3	1.7	1.5	1.8	1.6	
IM	1.3	1.3	1.5	1.4	1.7	1.5	1.8	1.7	1.8	1.7	
PM	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	
Ketoconazole and Quinidine											Appendix Table 6
EM	1.0	1.0	2.4	1.5	3.3	2.1	4.1	2.9	4.5	3.3	
IM	1.3	1.3	2.5	1.8	3.5	2.4	4.2	3.1	4.6	3.5	
PM	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	
Carbamazepine											Appendix Table 7
EM	1.0	1.0	1.0	0.9	1.0	0.8	1.0	0.8	1.0	0.8	
IM	1.3	1.3	1.3	1.1	1.2	1.0	1.2	0.9	1.2	0.9	
PM	1.8	1.9	1.8	1.6	1.8	1.4	1.8	1.2	1.8	1.2	

<sup>a</sup>AUC was calculated as steady state AUC divided by 24 (28 hr interval)

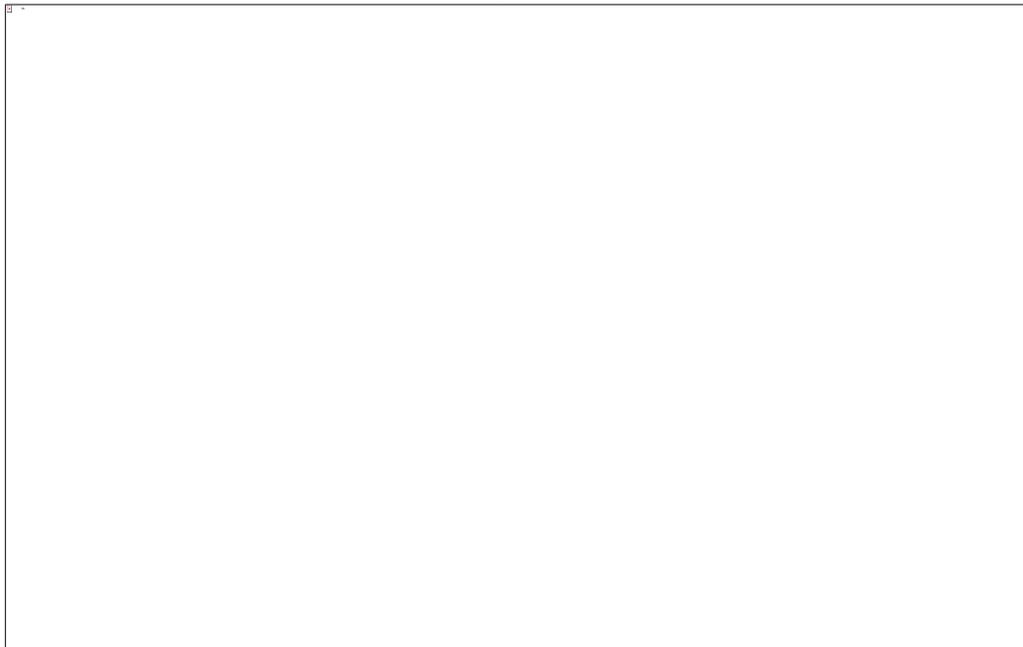
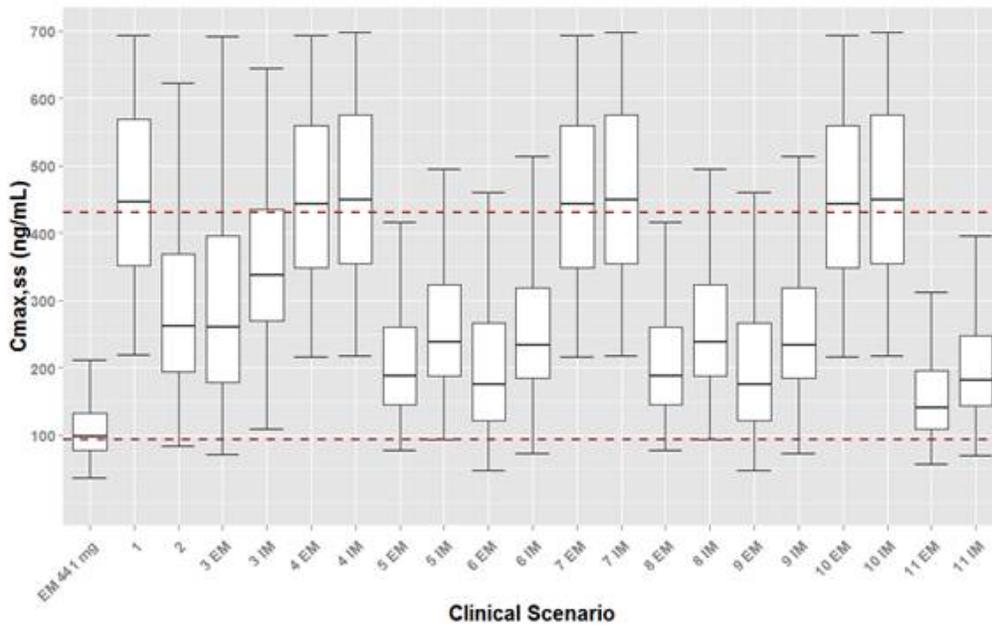
<sup>b</sup>NC: not calculated

**Table 4. Calculation of fold-changes using EMs receiving 441 mg Aripiprazole Lauroxil alone as reference.**

441, 662 or 882 mg Monthly Dosing (300, 450, and 600 mg aripiprazole)	Conditions	Sponsor's dosing proposal	Fold-change under sponsor's dosing proposal, using EMs receiving 441 mg without CYP modulator as reference (modulator for 4 weeks)
(b) (4)			

**Figure 2. Box-Whisker plots of PBPK simulated steady state aripiprazole  $C_{max,ss}$  (upper) and  $C_{ave,ss}$  (lower) under the influence of co-medication in subjects with different CYP2D6 genotypes (Refer to Table 4 for codes). Dashed horizontal lines represent targeted drug concentration range.**

$C_{ave,ss}$  = steady state AUC/28 days; See Methods for simulated sample size for each condition. Whiskers represent 1.5 times the length of the box away from the box [1.5\*Inter-quantile-range] or the minimum and maximum values if they are within the range of 1.5 \*Inter-quantile-range.



Appears this way on original

### **5. Conclusion**

Sponsor's PBPK models of aripiprazole and Aripiprazole Lauroxil are considered adequate to predict aripiprazole plasma PK in patients receiving intramuscular injection of Aripiprazole Lauroxil and CYP modulators. Based on targeted aripiprazole concentration ranges (See Pharmacometrics Review), it appears that sponsor's proposed doses of Aripiprazole Lauroxil co-administered with CYP modulators in subjects with different CYP2D6 genotypes are reasonable.

## 6. Appendices

### 6.1. Abbreviations

ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; B/P, blood to plasma ratio;  $C_{ave,ss}$ , average concentration at steady state;  $C_{max}$ , maximal concentration in plasma;  $C_{maxR}$ , the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance;  $CL_{int}$ , intrinsic clearance;  $CL_R$ , renal clearance; DDI: drug-drug interaction; F, bioavailability;  $F_a$ , fraction absorbed;  $f_{mj}$ , fraction of total clearance mediated by j CYP isoform;  $f_p$ , fraction unbound in plasma; GI: gastrointestinal;  $k_a$ , first order absorption rate constant;  $K_i$ , reversible inhibition constant;  $K_m$ , Michaelis-Menten Constant; LogP, logarithm of the octanol-water partition coefficient; NA, not applicable; NC, not calculated; ND, not determined; NDA: new drug application;  $P_{app}$ , apparent passive permeability; PBPK: Physiological-based Pharmacokinetic; q.d., once daily dosing;  $Q_{gut}$ , a hypothetical flow term for the intestine absorption model;  $T_{max}$ : time at maximal concentration in plasma;  $V_{d,ss}$ , volume of distribution at steady state.

## 6.2. Appendix Tables and Figures

**Appendix Table 1. Input parameter for aripiprazole PBPK model (Simcyp 13.0, Table 2 of ref [1])**

Parameter (unit)	Values	Notes	Reviewer's notes
MW	448.4		
log P	4.5	<a href="http://www.drugbank.ca/drugs/DB01238">http://www.drugbank.ca/drugs/DB01238</a>	
pKa	7.6	<a href="http://www.drugbank.ca/drugs/DB01238">http://www.drugbank.ca/drugs/DB01238</a>	
Compound type	Basic		
B/P	0.61	FDA CDER review: NDA # 021-436	
F <sub>D</sub>	0.01	FDA CDER review: NDA # 021-436	
f <sub>a</sub>	1	Assumed	
k <sub>a</sub> (h <sup>-1</sup> )	1.5	Derived from in vivo data from Boulton et al., 2008	
Q <sub>gut</sub>	10.3	Predicted from Caco-2 data;	
P <sub>app</sub> Caco-2 data (10 <sup>-6</sup> cm/s)	4.7	FDA CDER review: NDA # 021-436	
Metoprolol calibrator (10 <sup>-6</sup> cm/s)	7.1		
V <sub>ss</sub> (L/kg)	2.7	Derived using in vivo data from Boulton et al., 2008	Minimal PBPK. Sponsor initially used V <sub>ss</sub> from intravenous study (4.7 L/kg), which tended to underestimate observed C <sub>max</sub>
CL <sub>R</sub> (L/h)	0.003	FDA CDER review: NDA # 021-436	
CL <sub>u,int</sub> (μL/min per mg protein)	101.4	Derived using in vivo data from Boulton et al., 2008	Retrograde method in SimCYP was used by the sponsor based on systemic clearance after intravenous administration of aripiprazole (3.52 L/h, Boulton, 2008).
% contribution of hepatic metabolism			Initially 38 and 62% contribution values were assigned to CYP3A4 and CYP2D6 based on the results of clinical DDI study with ketoconazole. Contributions were further defined for CYP2D6 and an unspecified pathway (via human liver microsomes HLM)
CYP2D6	50.7		Calculation based on CYP2D6 PM PK
CYP3A4	38.5		Calculation based on in vivo DDI study with ketoconazole
Undefined enzyme(s)	12.2		

**Appendix Table 2. Input parameters of Aripiprazole Lauroxil PBPK model**

	Value		Reference	Reviewer notes
	Formulation 1	Formulation 2		
<u>Permeability related</u>				
<u>Partition coefficient</u>				
Viable epidermis - stratum corneum	400	450	User input via sensitivity analysis	
Blood - viable epidermis	2.85	2.85	Predicted according to <a href="#">Shatkin and Brown (1991) [18]</a>	
<u>Permeability constant (cm/h)</u>				
Stratum corneum	0.0123	0.0123	Predicted using <a href="#">Lien and Gao (1995) [19]</a>	
Viable epidermis	1.23	1.23	Predicted using <a href="#">Chinery &amp; Gleeson (1993) [20]</a>	
<u>Diffusion coefficients (cm<sup>2</sup>/h)</u>				
Stratum corneum	1.0 x 10 <sup>-6</sup>	1.0 x 10 <sup>-6</sup>	Predicted using <a href="#">Shatkin and Brown (1991) [18]</a>	
Viable epidermis	4.8 x 10 <sup>-5</sup>	4.8 x 10 <sup>-5</sup>	Predicted using <a href="#">Guy (1982) [21]</a>	
<u>Formulation related</u>				
First order release rate constant (1/h)	0.003	0.0075	User input via sensitivity analysis	The value of 0.007 1/h was used by the sponsor for formulation 2 and DDI simulations

**Appendix Table 3. Predicted geometric mean, minimum, and maximum values of aripiprazole exposure in CYP2D6 EMs, IMs, or PMs. Source data from Tables 16 and 17 [1].**

		300 mg		450 mg		600 mg	
		Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)
EMs	Geometric mean	103	2721	154	4081	206	5442
	Minimum	37.1	1001	55.6	1501	74.1	2001
	Maximum	334.3	9110	501.4	13664	668.6	18219
IMs	Geometric mean	132	3503	198	5254	264	7006
	Minimum	47	1253	70	1880	93	2506
	Maximum	439	12082	658	18122	878	24163
PMs	Geometric mean	192	5126	287	7688	383	10251
	Minimum	56.6	1520	85	2280	113	3040
	Maximum	658	18116	987	27173	1316	36232

<sup>a</sup>AUC calculated as steady state AUC divided by 24 (28 hr interval)

**Appendix Table 4: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of ketoconazole (see Methods for simulation study design).**

		Inhibitor dosing: Ketoconazole									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
		Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)
EMs											
300 mg	Geo Mean	103	2733	131	3056	149	3409	158	3771	160	3986
	Min	38	1045	38	1060	39	1076	40	1092	41	1104
	max	334	9115	403	10244	458	11306	505	12217	532	12586
450 mg	Geo Mean	155	4099	196	4584	223	5113	237	5657	240	5979
	Min	58	1567	58	1591	59	1614	61	1637	61	1655
	max	502	13672	604	15365	686	16960	757	18326	798	18879
600 mg	Geo Mean	206	5466	261	6113	297	6818	316	7542	319	7972
	Min	77	2090	77	2121	79	2151	81	2183	81	2207
	max	669	18230	806	20487	915	22613	1010	24434	1064	25172
IMs											
300 mg	Geo Mean	132	3519	183	4081	207	4533	235	5386	240	5759
	Min	47	1256	68	1638	70	1860	72	1928	73	1962
	max	439	12113	530	13454	593	14643	699	16485	756	17027
450 mg	Geo Mean	199	5278	274	6122	311	6800	352	8079	360	8638
	Min	70	1884	102	2458	105	2791	109	2892	109	2943
	max	659	18169	796	20181	890	21964	1048	24727	1134	25541
600 mg	Geo Mean	265	7037	366	8162	414	9067	469.3	10772	479	11518
	Min	93.5	2512	136.4	3277	139.4	3721	144.8	3856	146	3924
	max	879	24225	1061	26908	1186.9	29285	1398	32969	1511.8	34054
PMs											
300 mg	Geo Mean	192	5151	306	6417	393	8002	459	9673	496	10572
	Min	57	1524	137	2219	174	3327	205	4447	219	4693
	max	662	18305	763	19926	926	22253	1100	24584	1212	25477

		Inhibitor dosing: Ketoconazole									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
450 mg	Geo Mean	288	7726	459	9626	590	12004	689	14509	744	15857
	Min	85	2286	206	3328	261	4990	307	6671	329	7040
	max	993	27458	1145	29890	1390	33380	1650	36875	1212	38215
600 mg	Geo Mean	385	10301	612	12835	787	16005	919	19346	992	21143
	Min	113	3048	275	4437	348	6653	409	8894	438	9387
	max	1325	36610	1526	39853	1853	44507	2200	49167	2424	50953

<sup>a</sup>AUC calculated as steady state AUC divided by 24 (28 hr interval)

Source data: EM 300 mg, 450 mg, and 600 mg Tables 54, 55, and 56, respectively; IM 300 mg, 450 mg, and 600 mg, Tables 30, 31, and 32, respectively; PM 300 mg, 450 mg, and 600 mg, Tables 18, 19, and 20, respectively [1]

**Appendix Table 5: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of quinidine (see Methods for simulation study design).**

		Inhibitor dosing: Quinidine									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
		Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)
EMs											
300 mg	Geo Mean	103	2733	142	3173	165	3648	178	4134	180	4404
	Min	38	1045	43	1115	45	1156	47	1200	47	1237
	max	334	9115	448	10774	540	12050	597	13540	615	14200
450 mg	Geo Mean	155	4099	212	4759	247	5472	267	6201	271	6607
	Min	58	1567	64	1672	68	1734	70	1800	70	1856
	max	502	13672	671	16162	810	18076	896	20311	923	21300
600 mg	Geo Mean	206	5466	283	6345	330	7296	356	8268	361	8809
	Min	77	2090	85	2230	91	2312	94	2400	94	2474
	max	669	18230	895	21549	1080	24101	1194	27081	1230	28400
IMs											
300 mg	Geo Mean	132	3519	188 °	3870	175	4221	187	4566	189	4741
	Min	46.8	1256	34.1	1284	50	1313	52	1344	52	1369
	max	439	12113	545	13338	568	14125	614	14824	628	15236
450 mg	Geo Mean	199	5278	233	5805	262	6332	280	6848	284	7112

		Inhibitor dosing: Quinidine									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
	Min	70	1884	71	1927	74	1970	77	2016	77	2054
	max	659	18169	742	20007	851	21187	921	22236	942	22854
600 mg	Geo Mean	265	7037	311	7740	349	8442	374	9131	378	9483
	Min	94	2512	95	2569	99	2627	103	2688	103	2739
	max	879	24225	990	26676	1135	28249	1229	29647	1256	30471
PMs	NA <sup>b</sup>										

<sup>a</sup>AUC calculated as steady state AUC divided by 24 (28 hr interval); <sup>b</sup>NA: not applicable; <sup>c</sup> corrected to be 155 ng/mL for further calculation based on raw simulation data

Source data: EM 300 mg, 450 mg, and 600 mg Tables 60, 61, and 62, respectively; IM 300 mg, 450 mg, and 600 mg, Tables 36, 37, and 38, respectively [1]

**Appendix Table 6: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of both ketoconazole and quinidine (see Methods for simulation study design).**

		Inhibitor dosing: Ketoconazole and Quinidine									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
		Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)
EMs											
300 mg	Geo Mean	104	2745	245	4057	346	5850	421	7951	464	9111
	Min	38	1045	117	1745	156	2868	191	3870	217	4174
	max	334	9115	559	12515	828	15655	1031	19787	1118	21756
450 mg	Geo Mean	155	4118	368	6085	519	5850 <sup>c</sup>	632	11927	696	13667
	Min	58	1567	175	2618	235	2868	287	5804	325	6261
	max	502	13672	839	18772	1242	15655	1547	29681	1676	32634
600 mg	Geo Mean	207	5490	490	8114	692	11700	842	15902	928	18222
	Min	77	2090	234	3491	313	5736	382	7739	433	8348
	max	669	18230	1119	25029	1656	31311	2062	39574	2235	43512
IMs											
300 mg	Geo Mean	133	3526	265	4857	362	6598	435	8556	476	9603
	Min	47	1256	125	1940	164	3063	197	4113	218	4389
	max	439	12113	615	15089	863	18111	1056	21023	1137	22883
450 mg	Geo Mean	199	5290	397	7286	543	9898	652	12835	714	14404

		Inhibitor dosing: Ketoconazole and Quinidine									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
	Min	70	1884	188	2909	246	4594	296	6169	327	6584
	max	659	18169	922	22633	1294	27166	1585	31535	1705	34325
600 mg	Geo Mean	265	7053	530	9714	724	13197	870	17113	952	19206
	Min	94	2512	251	3879	327	6125	395	8226	436	8778
	max	879	24225	1230	30177	1726	36222	2113	42046	2273	45766
PMs	NA <sup>b</sup>										

<sup>a</sup>AUC calculated as steady state AUC divided by 24 (28 hr interval); <sup>b</sup>NA: not applicable; <sup>c</sup> corrected to be 8775 ng/mL h for further calculation based on raw simulation data

Source data: EM 300 mg, 450 mg, and 600 mg Tables 66, 67, and 68, respectively; IM 300 mg, 450 mg, and 600 mg, Tables 42, 43, 44 respectively [1]

**Appendix Table 7: PBPK predicted plasma Cmax and AUC of aripiprazole (geometric mean (GeoMean), minimum (Min) and maximum (Max)) in subjects receiving intramuscular injection of Aripiprazole Lauroxil with and without co-administration of carbamazepine (see Methods for simulation study design).**

		Inhibitor dosing: Carbamazepine									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
		Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)
EMs											
300 mg	Geo Mean	104	2745	102	2477	100	2282	99	2119	99	2061
	Min	39	1069	39	1020	39	982	38	948	38	935
	max	322	8566	314	7337	314	6644	314	6092	314	5927
450 mg	Geo Mean	156	4117	154	3715	151	3423	148	3178	148	3092
	Min	59	1604	59	1530	58	1474	58	1422	58	1402
	max	484	12848	472	11005	472	9966	472	9138	472	8891
600 mg	Geo Mean	208	5490	205	4953	201	4564	197	4238	197	4123
	Min	78	2139	78	2040	78	1965	77	1896	77	1870
	max	645	17131	629	14673	629	13289	629	12185	629	11855
IMs											
300 mg	Geo Mean	133	3521	131	3093	128	2803	127	2570	127	2493
	Min	49	1285	49	1232	48	1181	46	1123	46	1069
	max	442	11895	433	9947	433	8800	433	7984	433	7762

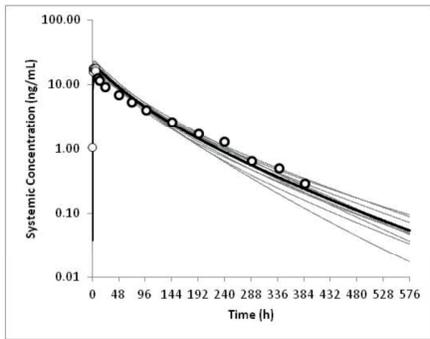
		Inhibitor dosing: Carbamazepine									
		No inhibitor		1 week		2 weeks		3 weeks		4 weeks	
450 mg	Geo Mean	199	5281	196	4640	192	4205	191	3855	191	3739
	Min	73	1928	73	1847	72	1772	69	1684	69	1604
	max	664	17843	650	14921	650	13201	650	11977	650	11643
600 mg	Geo Mean	266	7041	261	6187	257	5606	254	5140	254	4985
	Min	98	2571	98	2463	95	2362	92	2245	92	2139
	max	885	23790	867	19895	867	17600	867	15969	867	15523
PMs											
300 mg	Geo Mean	191	5108	188	4266	186	3762	185	3391	185	3279
	Min	59	1551	59	1470	57	1397	56	1269	56	1204
	max	763	20831	756	15889	756	13565	756	12204	756	11877
450 mg	Geo Mean	287	7662	282	6398	278	5644	277	5087	277	4919
	Min	88	2326	88	2206	86	2096	84	1903	84	1805
	max	1145	31245	1135	23833	1135	20347	1135	18306	1135	17816
600 mg	Geo Mean	382	10216	375	8531	371	7525	370	6782	370	6559
	Min	118	3101	117	2941	114	2794	112	2538	112	2407
	max	1527	41661	1513	31778	1513	27130	1513	24408	1513	23754

<sup>a</sup> AUC calculated as steady state AUC divided by 24 (28 hr interval); <sup>b</sup>NA: not applicable

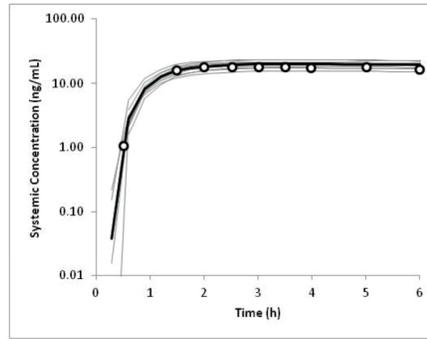
Source data: EM 300 mg, 450 mg, and 600 mg Tables 66, 67, and 68, respectively; IM 300 mg, 450 mg, and 600 mg, Tables 42, 43, 44 respectively [1]

**Appendix Figure 1: Simulated (lines) and observed (circles; Boulton et al., 2008, [15]) mean plasma concentration-time profiles of aripiprazole following a single oral dose of 5 mg aripiprazole (left, profile of 0-576 hours; right, profile of 0-6 hours).**

Figures 5 and 6 of reference [1]



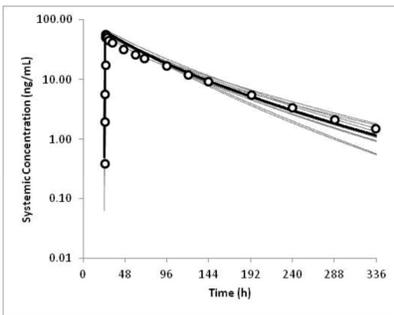
The grey lines represent the outcomes of simulated individual trials ( $10 \times 14$ ) and the solid black line is the mean data for the simulated population ( $n=140$ ).



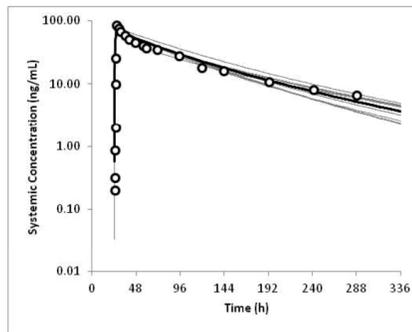
The grey lines represent the outcomes of simulated individual trials ( $10 \times 14$ ) and the solid black line is the mean data for the simulated population ( $n=140$ ).

**Appendix Figure 2: Simulated (lines) and observed (circles; Clinical Study 98-206 Vol 69-79) mean plasma concentration-time profiles of aripiprazole after a single oral dose of 15 mg administered alone (left) and on the 2nd day of 14 days of dosing of ketoconazole (200 mg q.d.) (right).**

Source Figures 7 and 8 of [1].



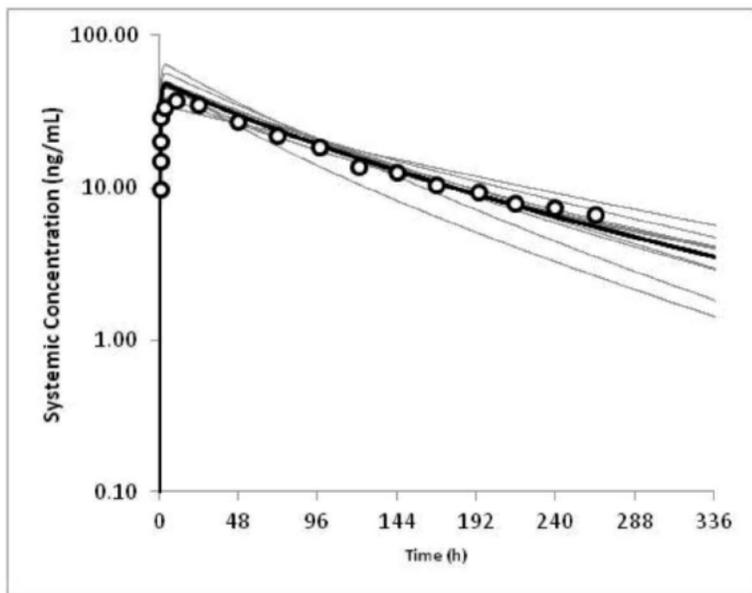
The grey lines represent the outcomes of simulated individual trials ( $10 \times 16$ ) and the solid black line is the mean data for the simulated population ( $n=160$ ).



The grey lines represent the outcomes of simulated individual trials ( $10 \times 16$ ) and the solid black line is the mean data for the simulated population ( $n=160$ ).

**Appendix Figure 3: Simulated (lines) and observed (circles; Clinical Study 98-207 Vol 80-83) mean plasma concentration-time profiles of aripiprazole after a single oral dose of 10 mg to healthy CYP2D6 PMs.**

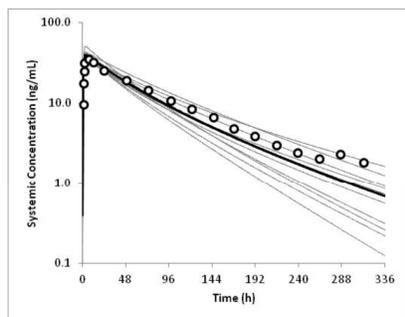
Source Figure 9 of [1].



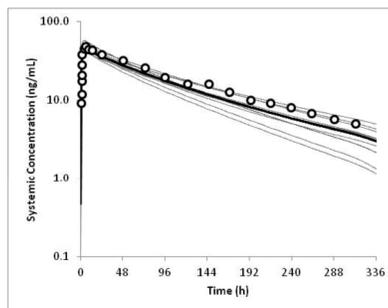
The grey lines represent the outcomes of simulated individual trials ( $10 \times 5$ ) and the solid black line is the mean data for the simulated population ( $n=50$ ).

**Appendix Figure 4: Simulated (lines) and observed (circles; Clinical Study 98-207 Vol 80-83) mean plasma concentration–time profiles of aripiprazole after a single oral dose of 10 mg alone (left) or administered on the 1st day of 13 days of dosing of quinidine (166 mg q.d.) (right).**

Source, Figures 10 and 11 of reference [1].



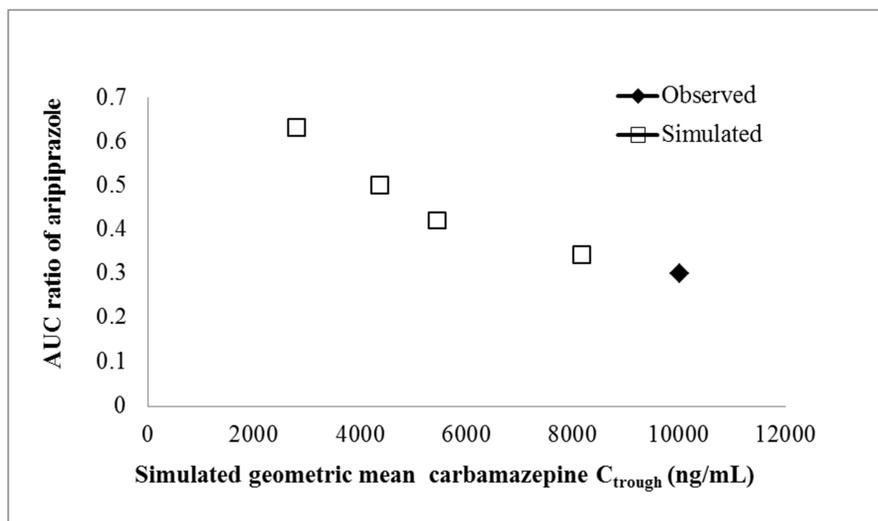
The grey lines represent the outcomes of simulated individual trials ( $10 \times 16$ ) and the solid black line is the mean data for the simulated population ( $n=160$ ).



The grey lines represent the outcomes of simulated individual trials ( $10 \times 16$ ) and the solid black line is the mean data for the simulated population ( $n=160$ ).

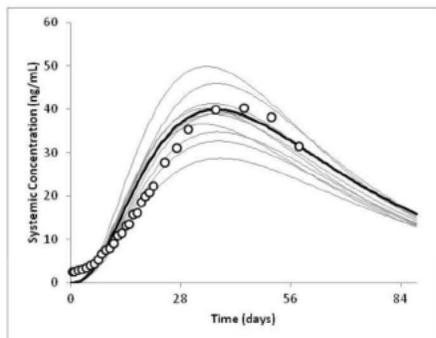
**Appendix Figure 5: PBPK simulated geometric mean AUC ratio of aripiprazole under different steady-state carbamazepine trough concentrations ( $C_{trough}$ ) achieved under different carbamazepine dose regimens.**

Simulation was conducted in 6 virtual healthy CYP2D6 EM subjects Carbamazepine dosing regimens (day 15 to day 44) are 200 mg b.i.d., 400 mg b.i.d., 600 mg b.i.d., and 600 mg every 8 hours for low to high  $C_{trough}$  values; aripiprazole is given 30 mg q.d. (day 1 to day 44). Observed  $C_{trough}$  of 10 mg/L represents mid-point of range of 8-12 mg/L reported in reference [15]

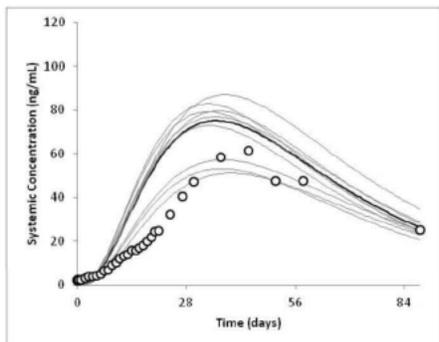


**Appendix Figure 6: Simulated (lines) and observed (circles; Clinical Study ALK9072-001, [16]) mean plasma concentration-time profiles of aripiprazole following a single intramuscular injection of 150 mg (upper panel), 300 mg (middle panel), or 400 mg (lower panel) Aripiprazole Lauroxil.**

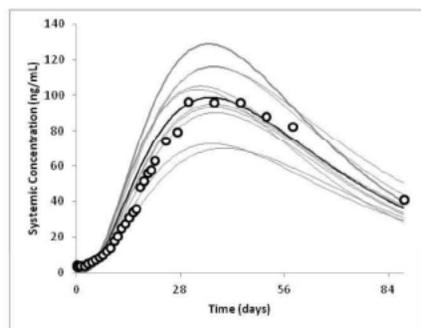
*Doses are aripiprazole equivalent doses. Source, Figures 14-16, Reference [1]*



The grey lines represent the outcomes of simulated individual trials ( $10 \times 10$ ) and the solid black line is the mean data for the simulated population ( $n=100$ ).



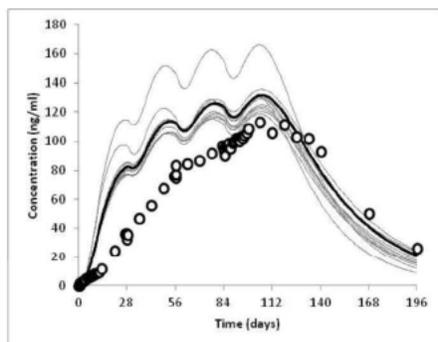
The grey lines represent the outcomes of simulated individual trials ( $10 \times 8$ ) and the solid black line is the mean data for the simulated population ( $n=80$ ).



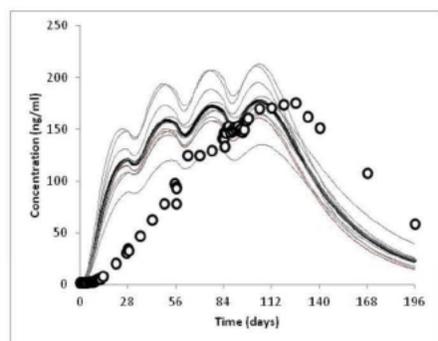
The grey lines represent the outcomes of simulated individual trials ( $10 \times 8$ ) and the solid black line is the mean data for the simulated population ( $n=80$ ).

**Appendix Figure 7. Simulated (lines) and observed (circles; Clinical Study ALK9072-002, [17]) mean plasma concentration-time profiles of aripiprazole following intramuscular injections of 300 mg (upper panel), 450 mg (middle panel), or 600 mg (lower panel) Aripiprazole Lauroxil administered every 28 days (4 in total).**

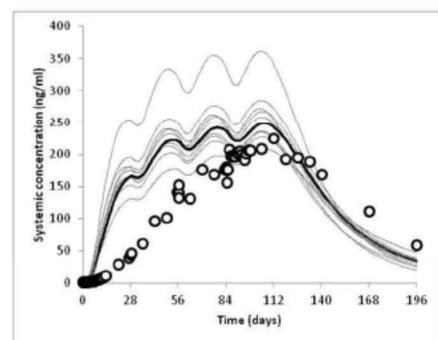
*Doses are aripiprazole equivalent doses. Source, Figures 17-19, Reference [1]*



The grey lines represent the outcomes of simulated individual trials (10 × 23) and the solid black line is the mean data for the simulated population (n=230).



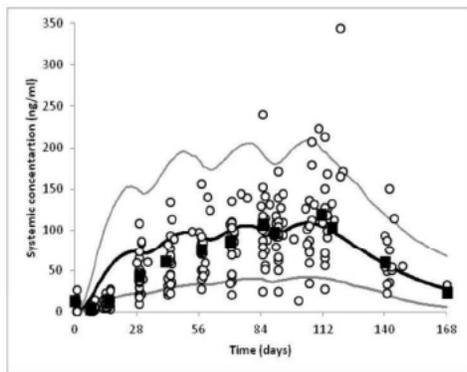
The grey lines represent the outcomes of simulated individual trials (10 × 11) and the solid black line is the mean data for the simulated population (n=110).



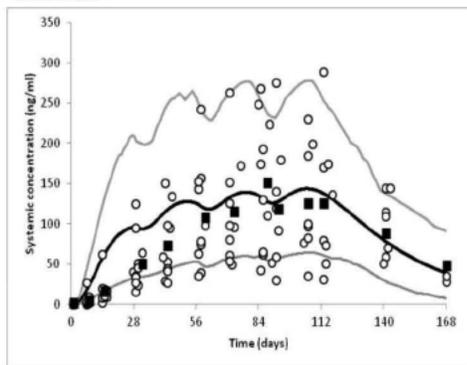
The grey lines represent the outcomes of simulated individual trials (10 × 11) and the solid black line is the mean data for the simulated population (n=110).

**Appendix Figure 8: Simulated (lines) and observed (circles and square; Clinical Study ALK9072-102, [17]) mean plasma concentrations of aripiprazole in CYP2D6 EMs (upper panel, n=25), IMs (middle panel, n=12) and PM subjects (lower panel, n=3) following IM injections of 300 mg Aripiprazole Lauroxil administered on days 1, 29, 57 and 85.**

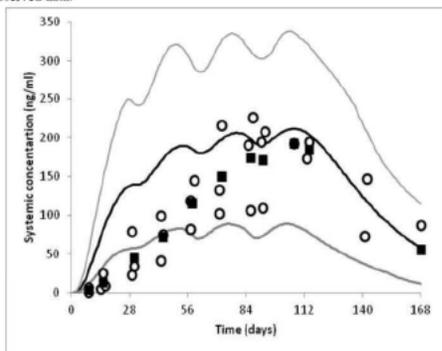
*Doses are aripiprazole equivalent doses. Source Figures 20-22 of reference [1].*



The solid black line is the mean data and the grey lines are the 5th and 95th percentiles for the simulated population data (n=250). The circles represent individual observed data and the squares are the mean of the observed data.



The solid black line is the mean data and the dashed lines are the 5th and 95th percentiles for the simulated population data (n=120). The circles represent individual observed data and the squares are the mean of the observed data.



The solid black line is the mean data and the dashed lines are the 5th and 95th percentiles for the simulated population data (n=30). The circles represent individual observed data and the squares are the mean of the observed data.

## References

1. Alkermes ALK9072-052: (b) (6) Quantitative prediction of the systemic exposure of aripiprazole after administration of aripiprazole lauroxil using prior in vitro and in vivo data: potential for drug-drug interactions as a victim.
2. Alkermes : NDA Submission 2.7.2 Summary of Clinical Pharmacology Studies
3. ABILIFY® (aripiprazole). Product Label December 12, 2014 update:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf)
4. ABILIFY MAINTENA® (aripiprazole) for extended-release injectable suspension, for intramuscular use Product Label December 05, 2014 update:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/202971s003lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202971s003lbl.pdf)
5. ABILIFY MAINTENA® (aripiprazole) Clinical Pharmacology Review:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2013/202971Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202971Orig1s000ClinPharmR.pdf)
6. Draft Label of ARISTADA submitted in NDA207533
7. Simcyp manual: A Guide for IVIVE and PBPK/PD Modeling using the Simcyp Population-based Simulator version 12, CERTARA™ 2013.
8. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp population-based ADME simulator. *Expert Opin Drug Metab Toxicol* 2009 5(2):211-23.
9. Edwards, D.J., Lavoie, R., Beckman, H., Blevins, R., Rubenfire, M. The effect of coadministration of verapamil on the pharmacokinetics and metabolism of quinidine. *Clin Pharmacol Ther* 1987; 41: 68-73.
10. Galetin A, Clarke SE and Houston JB. Quinidine and haloperidol as modifiers of CYP3A4 activity: multisite kinetic approach. *Drug Metab Dispos* 2002; 30: 1512-1522
11. Englund G, Lindquist P, Skogastierna C et al. Cytochrome P450 properties of common efflux transporter inhibitors. *Drug Metab Dispos* 2014; 42: 441-447.
12. Boulton DW, Kollia G, Mallikaarjun S, Komoroski B, Sharma A, Kovalick LJ and Reeves R. Pharmacokinetics and tolerability of intramuscular, oral and intravenous aripiprazole in healthy subjects and in patients with schizophrenia. *Clin Pharmacokinet* 2008; 47(7):475-485.
13. Otsuka Pharmaceuticals. NDA 21-436—Aripiprazole—Abilify™—Clinical Pharmacology and Biopharmaceutics Review. <[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2002/21-436\\_Abilify.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-436_Abilify.cfm)> (2002).
14. Hendset M, Hermann M, Lunde H, Refsum H and Molden E. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. *Eur J Clin Pharmacol* 2007; 63:1147-1151.

15. Citrome L, Macher JP, Salazar DE, Mallikaarjun S, Boulton DW (2007) Pharmacokinetics of aripiprazole and concomitant carbamazepine. *J Clin Psychopharmacol.* 27(3):279-83.
16. Clinical Study Protocol ALK9072-101 - A phase 1, randomized, open label, single-dose study to evaluate the safety, tolerability, and pharmacokinetics of aripiprazole lauroxil following administration to the deltoid or gluteal muscle in subjects with chronic stable schizophrenia.
17. Clinical Study Protocol ALK9072-102 - A phase 1, randomized, double-blind, placebocontrolled, multiple-dose study to evaluate the safety and tolerability of aripiprazole lauroxil following deltoid administration in subjects with chronic stable schizophrenia.
18. Shatkin JA, Brown HS. 1991. Pharmacokinetics of the dermal route of exposure to volatile organic chemicals in water: A computer simulation model. *Environ Res.* 1991; 56: 90-108.
19. Lien EJ, Gao H. QSAR analysis of skin permeability of various drugs in man as compared to in vivo and in vitro studies in rodents. *Pharm Res* 1995; 12(4):583-587.
20. Chinery RL, Gleason AK. 1993. A compartmental model for the prediction of breath concentration and absorbed dose of chloroform after exposure while showering. *Risk Anal* 13(1):51-62.
21. Guy RH, Maibach HI. Rapid radial transport of methyl nicotinate in the dermis. *Arch Dermatol Res* 1982; 273(1-2):91-95.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

PING ZHAO  
04/27/2015

XIAOFENG WANG  
04/27/2015

KEVIN M KRUDYS  
04/29/2015

## OFFICE OF CLINICAL PHARMACOLOGY:

### PHARMACOMETRIC REVIEW

#### 1 SUMMARY OF FINDINGS

##### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

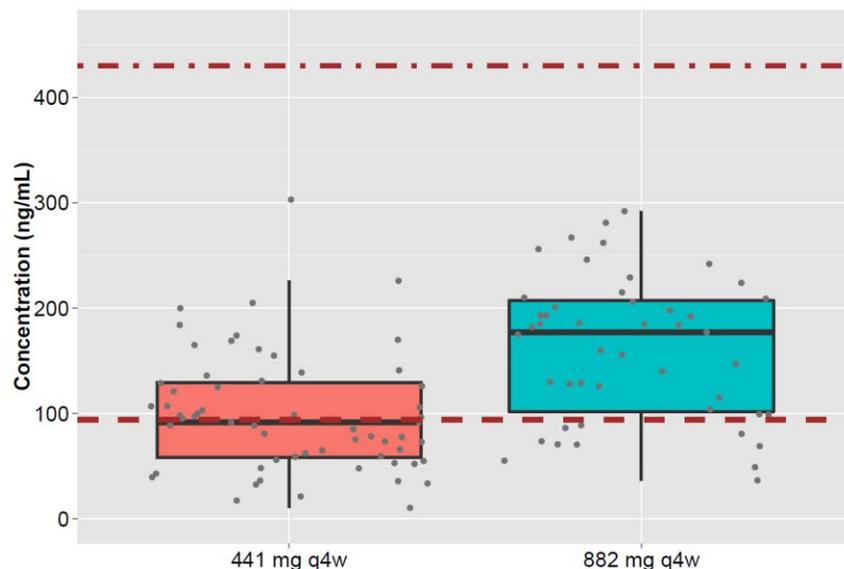
##### 1.1.1 Is there sufficient evidence of effectiveness for aripiprazole lauroxil IM injection in adult patients with schizophrenia?

Yes.

Study ALK9072-003 was a global, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of treatment with once monthly IM aripiprazole lauroxil (441 mg and 882 mg) as compared with placebo over a period of 12 weeks in subjects with schizophrenia experiencing an acute exacerbation episode. In this pivotal study, subjects in the two aripiprazole lauroxil treatment groups received 21 days of concomitant oral aripiprazole doses, while subjects in the placebo control group received 21 days of oral placebo. The results showed statistically significant and clinically meaningful improvement in Positive and Negative Syndrome Scale (PANSS) total score in both treatment groups compared with the placebo group (for details, please see Section 3.1).

However, additional evidence is needed to demonstrate the efficacy contribution from aripiprazole lauroxil IM injection alone and to rule out the possibility that 21 days of concomitant oral aripiprazole doses contributed most of or all the efficacy. Given the fact that efficacy is known to be driven by aripiprazole exposures, the effectiveness of aripiprazole lauroxil injection alone could be demonstrated from a PK perspective. The observed steady state concentration levels of approved oral aripiprazole doses (10 mg to 30 mg QD) could be used to establish a range of aripiprazole concentrations within which aripiprazole concentrations are considered both tolerable and effective. The lower boundary of this concentration window, 93.3 ng/mL, is defined as the observed mean steady state C<sub>min</sub> following 10 mg daily oral doses; the upper boundary, 427 ng/mL, is defined as the observed mean steady state C<sub>max</sub> following 30 mg daily oral doses. The observed median aripiprazole concentrations on day 85 of subjects from the two treatment groups in Study ALK9072-003 are within this concentration window as shown in Figure 1. Moreover, aripiprazole exposures on day 85 can be solely attributed to aripiprazole lauroxil IM injection since exposures due to oral doses has been completely washed out by day 85 given the oral half-life of approximately 3 days. Therefore, the effectiveness of aripiprazole lauroxil IM injection can be confirmed.

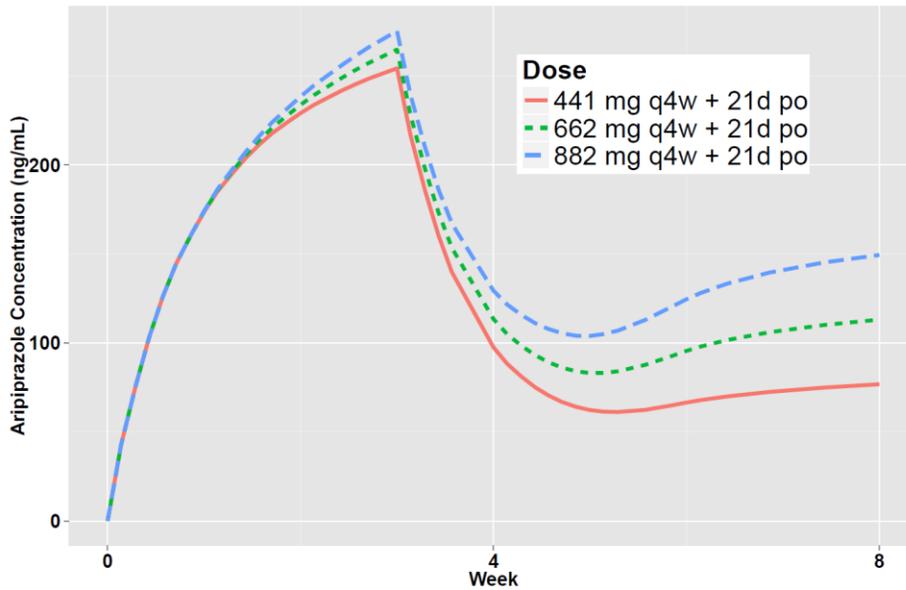
**Figure 1. Observed Aripiprazole Exposure on Day 85 for the 2 Dose Levels.**



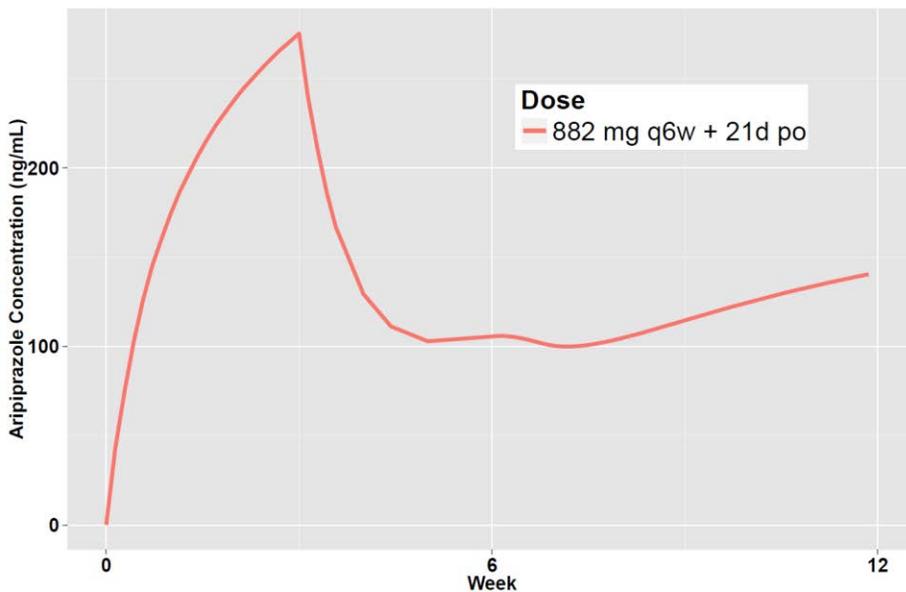
### **1.1.2 Is the proposed treatment initiation approach acceptable?**

Yes. The sponsor's proposed aripiprazole lauroxil treatment initiation regimen with 21 consecutive days of oral aripiprazole supplementation along with the first injection is considered acceptable. Due to slow dissolution and absorption of aripiprazole lauroxil, aripiprazole concentration rises very slowly following the first intramuscular (IM) injection, which may result in delayed treatment effect. Supplemental oral aripiprazole doses are able to elevate aripiprazole concentrations quickly to reach therapeutic levels. This treatment initiation approach was evaluated by independent PK simulation by the reviewer. The simulated mean aripiprazole concentration time profiles for the first and second IM injections along with 21 days of concurrent 15 mg oral aripiprazole administration at three monthly aripiprazole lauroxil doses (441 mg, 662 mg, and 882 mg monthly) and at 882 mg every six weeks are shown in Figure 2 and Figure 3, respectively. The results show that aripiprazole concentrations are able to rise and reach therapeutic levels during the first dosing interval due to the supplemental oral aripiprazole doses. This initiation approach, oral supplementation for the first 21 days, was performed during the pivotal trial (Study ALK9072-003). No tolerability issues or lack of efficacy during this phase were observed. Therefore, the proposed treatment initiation approach is acceptable.

**Figure 2. Simulated Mean Aripiprazole Concentration Time Profiles for the 1st and 2nd monthly Aripiprazole Lauroxil Doses with 21 days of Concurrent Oral ABILIFY (15 mg) Administration**



**Figure 3. Simulated Mean Aripiprazole Concentration Time Profiles for the 1st and 2nd 882 mg every six weeks Aripiprazole Lauroxil Dose with 21 days of Concurrent Oral ABILIFY (15 mg) Administration**

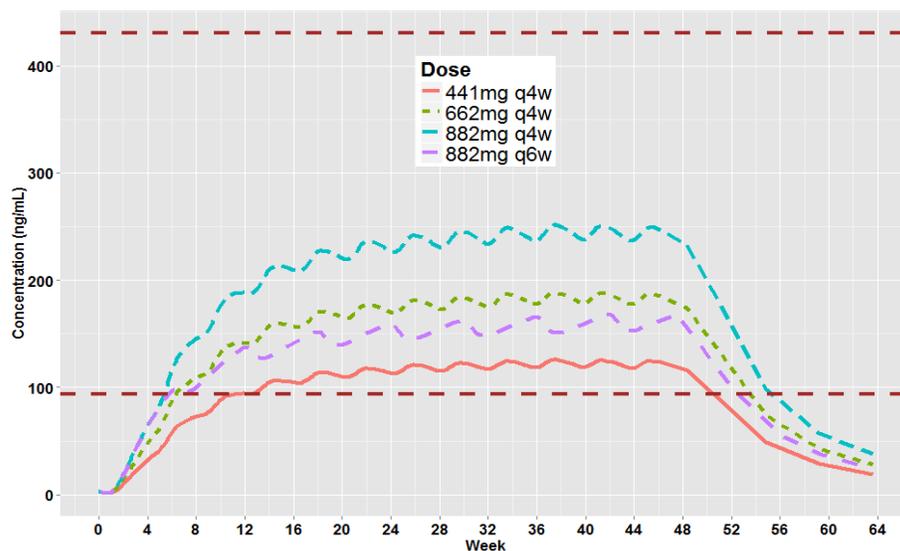


**1.1.3 Are the two unstudied doses/dosing regimens (662 mg monthly and 882 mg every 6 weeks) acceptable?**

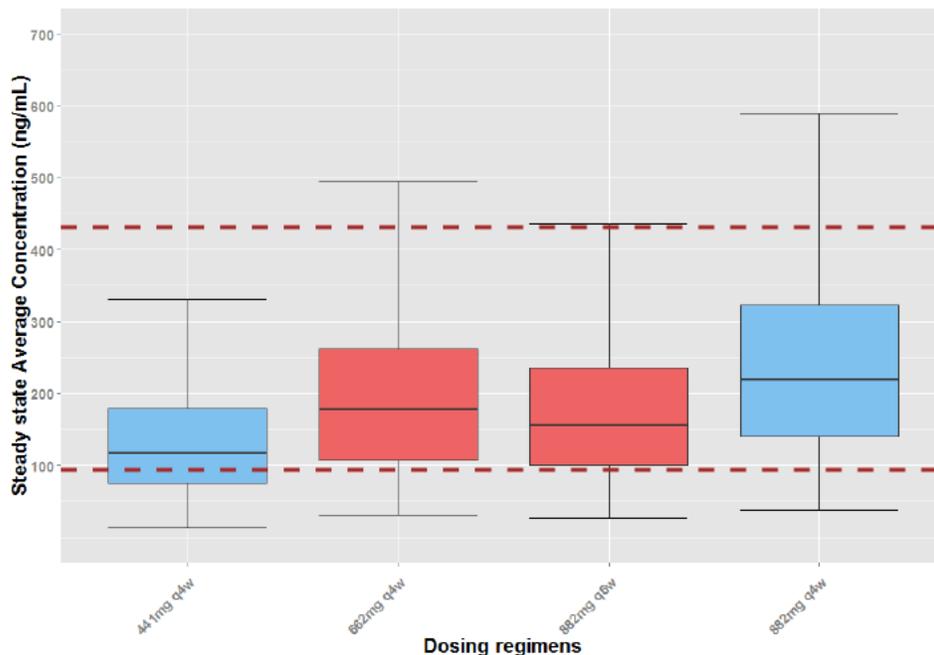
Yes. The sponsor’s proposed doses and dosing regimens include 441 mg, 662 mg and 882 mg monthly and 882 mg every 6 weeks. 441 mg and 882 mg monthly doses were

evaluated in the pivotal efficacy trial and have been demonstrated to be both efficacious and well tolerated. For the two unstudied doses, 662 mg monthly and 882 mg every 6 weeks, PK simulations were conducted. Steady-state mean aripiprazole exposures following 662 mg monthly and 882 mg every 6 weeks doses are within the steady state mean exposures of 441 mg monthly and 882 mg monthly doses (Figure 4 and Figure 5). Moreover, simulated steady state average concentrations of all dosing regimens are within the observed exposures levels for the approved dose range (10 mg to 30 mg- QD) of oral aripiprazole (ABILIFY), which could be used to establish a range of steady state aripiprazole concentrations within which aripiprazole exposures are considered both tolerable and effective. Therefore, the two unstudied doses, 662 mg monthly and 882 mg every six weeks, are also acceptable from a PK perspective.

**Figure 4. Simulated Mean Aripiprazole Concentration Time Profiles following 441 mg, 662 mg , and 882 mg Monthly and 882 mg every 6 weeks doses up to Steady State.**



**Figure 5. Simulated Average Steady State Aripiprazole Concentrations for The Studied (441 mg and 882 mg monthly) and Two Unstudied (662 mg monthly and 882 mg every 6 weeks) doses/dosing regimens. The Lower Dash Line Represents the Observed Mean Steady State Cmin following 10 mg Daily Oral Doses and the Upper Dash Line Represents the Observed Mean Steady State Cmax following 30 mg Daily Oral Doses. Blue Boxes Represent Studied Dosing Regimens, while Red Boxes Represent Unstudied Dosing Regimens.**



#### 1.1.4 Is the proposed recommendation for missed doses acceptable?

##### 1.1.4.1 Is the sponsor's originally proposed recommendation for missed doses acceptable?

No.

The exposures of all doses/dosing regimens are generally at the lower end of the concentration window. Therefore, when recommendations for missed doses are assessed, we are more concerned with the concentrations dropping below the lower boundary of the concentration window than concentration rising above the upper boundary.

The sponsor's originally proposed recommendation for missed doses are as follow: When a dose is missed, administer the next injection of ARISTADA as soon as possible. If the time elapsed since the last ARISTADA injection exceeds the length of time noted in Table 1, (b) (4)

(b) (4) This recommendation is considered inappropriate because it does not cover all possible clinical scenarios. Specifically, full re-initiation, i.e. 21 days of oral aripiprazole supplementation with the next ARISTADA injection, would be needed if time since last ARISTADA injection was long enough. An extreme example is that if a patient on monthly 441 mg ARISTADA missed 10 or more injections, the drug level would probably be negligible at the time of ARISTADA re-initiation. In this case, 21 days, (b) (4) of oral aripiprazole supplementation would be appropriate for ARISTADA re-initiation. Therefore, this originally proposed recommendation is not acceptable and an information request asking the sponsor to propose the length of time elapsed since the last injection beyond which full re-initiation, i.e. initiation with 21 days of oral aripiprazole supplementation, is needed was sent out to the sponsor during the post-mid-cycle communication.

**Table 1. Sponsor Originally Proposed Recommendation for Re-initiation of Concomitant Oral Aripiprazole Supplementation**

(b) (4)



**1.1.4.2 Is the sponsor's currently proposed recommendation for missed doses acceptable?**

In general, the sponsor's updated recommendation for 662 mg monthly, 882 mg monthly, and 882 every 6 weeks doses appears reasonable. However, the recommendation for 441 mg monthly dose is considered unacceptable.

The sponsor modified the recommendation for missed doses in response to the information request which asked the sponsor to propose a set of cutoff time points beyond which full initiation with 21 days of oral supplementation is needed. The currently proposed recommendation is listed in Table 2. PK simulation was used to evaluate the currently proposed recommendation. Simulation results show that the re-initiation strategies for monthly 662 mg, monthly 882 mg, and 882 mg every 6 weeks doses would not result in exposures that are below the lower boundary of the acceptable concentration window. Therefore, the recommendations for missed doses for monthly 662 mg, monthly 882 mg, and 882 mg every 6 weeks doses are considered appropriate.

At the 441 mg monthly dose level, the cutoff time point of 6 weeks for no required oral supplementation is considered appropriate since it would not result in exposures below the lower boundary of the acceptable concentration window. However, the cutoff time point of (b) (4) weeks for full re-initiation with 21 days of oral supplementation is considered inappropriate. Simulation results demonstrate that the (b) (4) IM injection with partial re-initiation (7 days of oral supplementation) would result in (b) (4)

(Figure 6). In contrast, full re-initiation with 21 days of oral supplementation would be appropriate (b) (4)

(Figure 7). Moreover, partial re-initiation with 7 days of oral supplementation is acceptable if time since last injection is >6 weeks but ≤7 weeks (Figure 8). Therefore, 7 weeks since last injection should be considered as the appropriate cutoff time point beyond which full re-initiation with 21 days of oral supplementation is needed at the 441 mg monthly dose level. Our recommendation for re-initiation following missed doses is presented in Table 3.

**Table 2. Sponsor Currently Proposed Recommendation for Re-initiation of Concomitant Oral Aripiprazole Supplementation following Missed Doses**

Dose of Patient's Last ARISTADA Injection	Length of Time Since Last Injection		
	No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole
Monthly 441 mg	≤ 6 weeks	> 6 and ≤ (b) (4) weeks	(b) (4) weeks
Monthly 662 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
Monthly 882 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg every 6 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks

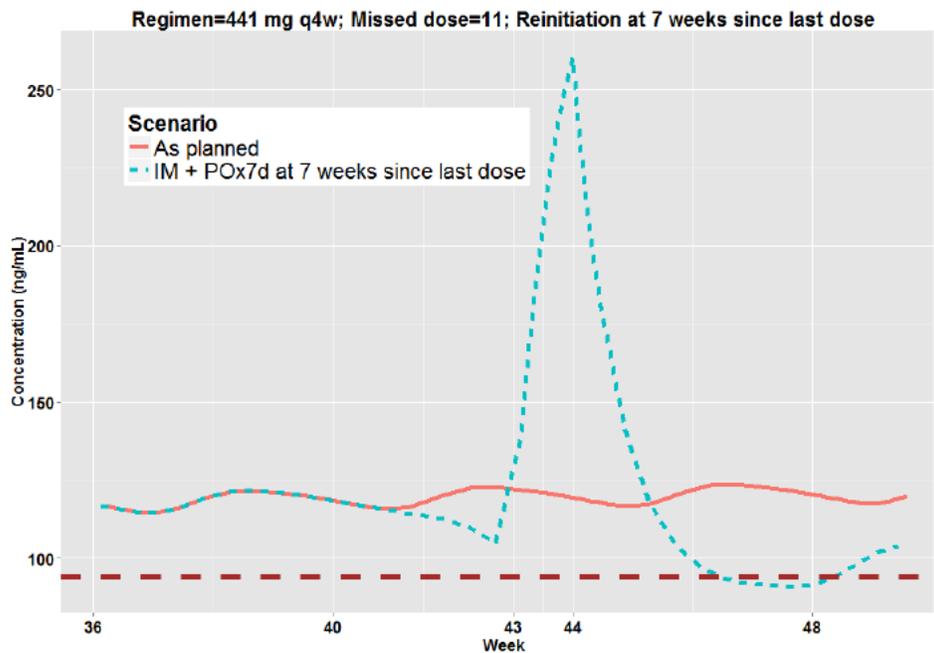
**Figure 6. Simulation for Re-initiation with IM Injection plus 7 days of Oral Doses (b) (4) Since Last Dose (b) (4) after Missing a Dose at Steady State at 441 mg Monthly Dose Level**



**Figure 7. Simulation for Re-initiation with IM Injection plus 21 days of Oral Doses**  
(b) (4) Since Last Dose (b) (4) after Missing a Dose at Steady State at 441 mg Monthly Dose Level



**Figure 8. Simulation for Re-initiation with IM Injection plus 7 days of Oral Doses at 7 Weeks Since Last Dose (Week 43) after Missing a Dose at Steady State at 441 mg Monthly Dose Level**



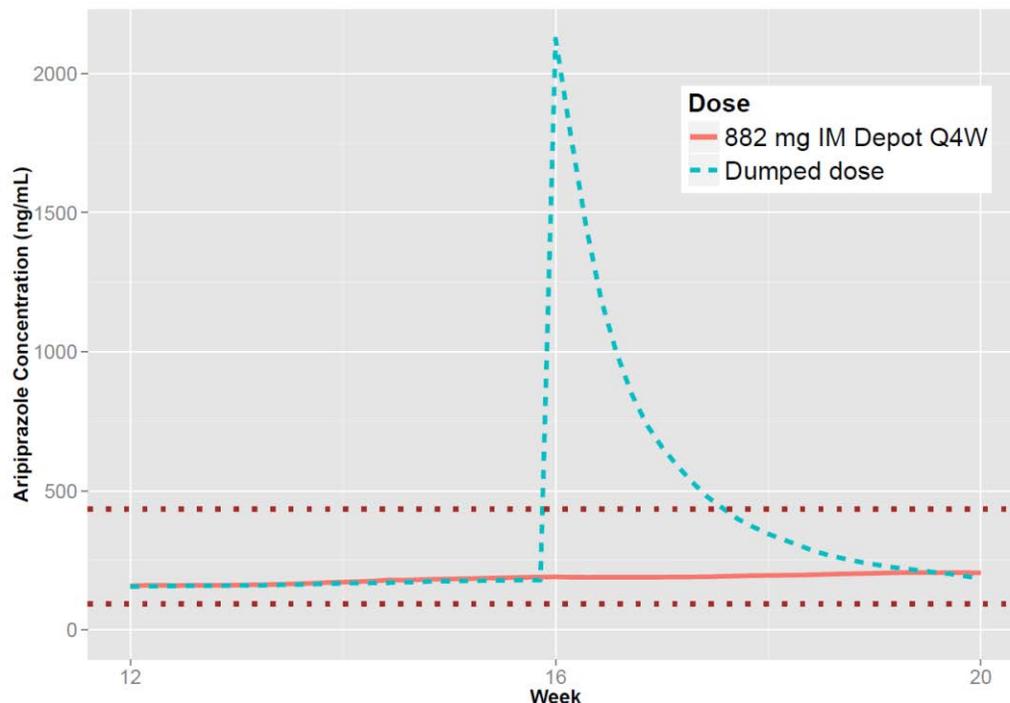
**Table 3. FDA Recommendation for Re-initiation of Concomitant Oral Aripiprazole Supplementation following Missed Doses**

Dose of Patient's Last ARISTADA Injection	Length of Time Since Last Injection		
	No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole
Monthly 441 mg	≤ 6 weeks	> 6 and ≤ 7 weeks	> 7 weeks
Monthly 662 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
Monthly 882 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg every 6 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks

**1.1.5 What is the impact of dose dumping on aripiprazole exposure?**

No evidence of dose dumping was observed in the clinical trials (four Phase 1 trials) as well as the pivotal trial (Study ALK9072-003) and four Phase I trials. Simulated aripiprazole concentrations following dose dumping at steady state (5<sup>th</sup> dose on week 16) of the highest dose level, 882 mg IM depot monthly, show a decline to concentrations normally observed following 882 mg IM depot within 2 weeks after the entire dumped dose enters the systemic circulation (Figure 9). The peak concentration would reach ~2200 ng/mL, but decline much faster than a typical aripiprazole lauroxil IM injection

**Figure 9. Simulated Mean Aripiprazole Concentrations vs. Time for Dose Dumping of 882 mg IM Depot. The upper horizontal dotted line represents observed mean steady-state C<sub>max</sub> at 30 mg QD oral dose and the lower horizontal dotted line represents observed mean steady-state C<sub>min</sub> at 10 mg QD oral dose.**



## 1.2 Recommendations

The Pharmacometrics reviewer finds this application acceptable in general. All proposed doses/dosing regimens including the two unstudied dosing regimens, 662 mg monthly and 882 mg every 6 weeks, are considered acceptable. Sponsor's updated recommendation for missed dose (in response to agency's information request) at 662 mg (monthly) and 882 mg (monthly and every 6 weeks) is considered appropriate. However, the recommendation for monthly 441 mg dose is considered inappropriate. The pharmacometrics reviewer recommends 7 weeks since last ARISTADA injection, rather than <sup>(b)</sup><sub>(4)</sub> weeks, as the cutoff for full re-initiation at the monthly 441 mg dose.

## 1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

## 2.3 Recommendation for Missed Doses

When a dose is missed, administer the next injection of ARISTADA as soon as possible. Consult [Table 1](#) for dosing recommendations regarding oral supplementation.

**Table 1: Recommendation for Concomitant Oral Aripiprazole Supplementation Following Missed Doses**

(b) (4)

<u>Dose of Patient's Last ARISTADA Injection</u>	<u>Length of Time Since Last Injection</u>		
	<u>No Oral Supplementation Required</u>	<u>Supplement with 7 Days Oral Aripiprazole</u>	<u>Supplement with 21 Days Oral Aripiprazole</u>
<u>Monthly 441 mg</u>	<u>≤ 6 weeks</u>	<u>&gt; 6 and ≤ 7 weeks</u>	<u>&gt; 7 weeks</u>
<u>Monthly 662 mg</u>	<u>≤ 8 weeks</u>	<u>&gt; 8 and ≤ 12 weeks</u>	<u>&gt; 12 weeks</u>
<u>Monthly 882 mg</u>	<u>≤ 8 weeks</u>	<u>&gt; 8 and ≤ 12 weeks</u>	<u>&gt; 12 weeks</u>
<u>882 mg every 6 weeks</u>	<u>≤ 8 weeks</u>	<u>&gt; 8 and ≤ 12 weeks</u>	<u>&gt; 12 weeks</u>

## 2 PERTINENT REGULATORY BACKGROUND

Aripiprazole lauroxil (ARISTADA™) is a non-ester covalent modification of aripiprazole which is an atypical antipsychotic approved in the US (November 2002, NDA 21436) as an oral form for multiple indications. Aripiprazole lauroxil has been classified as a new molecular entity and it has been studied as a long acting injection (LAI) for the treatment of schizophrenia in adult patients.

## 3 RESULTS OF SPONSOR'S ANALYSIS

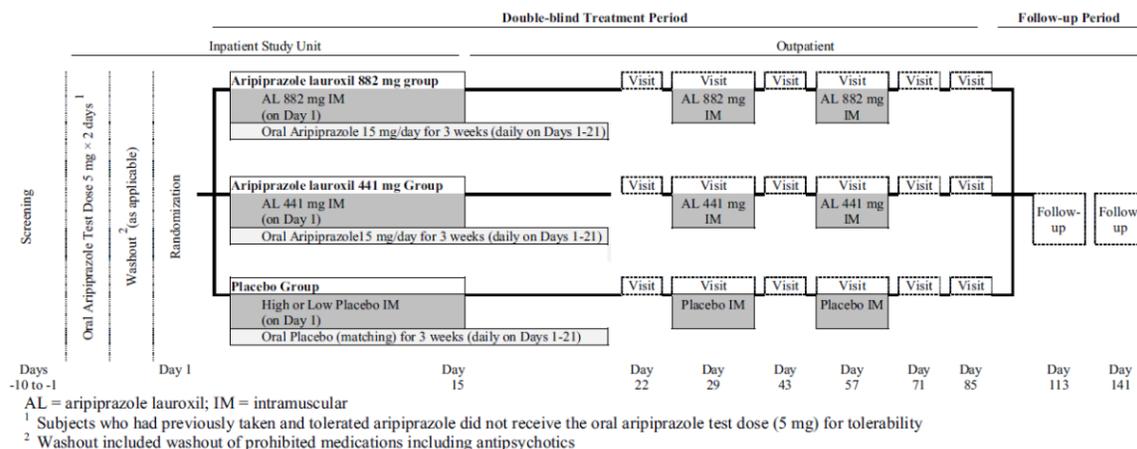
### 3.1 Summary of the Clinical Study Report: (ALK9072-003)

The pivotal efficacy trial, Trial ALK9072-003, was a 12-week, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of aripiprazole lauroxil in subjects with schizophrenia. The primary objective of the trial was to evaluate the efficacy of aripiprazole lauroxil compared with placebo, as measured by change from baseline in PANSS total score, in schizophrenia patients experiencing an acute exacerbation. The secondary objective was to determine the safety and tolerability of aripiprazole lauroxil. Subjects enrolled in this trial included male or female subjects, age 18 to 70 years with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision

(DSM-IV-TR) criteria and experiencing an acute exacerbation with onset less than 2 months prior to screening.

The study design is shown in Figure 10. After screening for eligibility, all subjects were required to discontinue their currently prescribed antipsychotics in an inpatient setting. The washout period was 2-5 days. For subjects who were naïve to aripiprazole, a test dose of oral aripiprazole 5 mg was administered by mouth daily for 2 days prior to randomization, to evaluate tolerability prior to proceeding to the long acting injectable study drug. Subjects who successfully passed screening and tolerated the oral test doses, or had a history of safe and well-tolerated exposure to aripiprazole, were randomized on day 1 in a 1:1:1 ratio to 1 of the 3 treatment groups: aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo. In addition to IM injection of the study drug, subjects also received supplemental oral study drug daily along with the first IM injection for 21 days weeks. Subjects randomized to the aripiprazole lauroxil treatment groups received oral aripiprazole supplemental doses, and subjects randomized to the placebo group received matching supplemental oral placebo. During the 12 week treatment period, efficacy, safety, tolerability and PK were assessed. The treatment period was followed by two monthly follow-up visits.

**Figure 10 Study Design Schematic**



Source: CSR ALK9072-003 page 30

A total of 623 subjects were randomized and 622 received at least 1 dose of IM study drug. One randomized subject was discontinued due to a protocol violation prior to receiving IM study drug. Among the 662 subjects, a total of 360 subjects (57.9%) completed the treatment period.

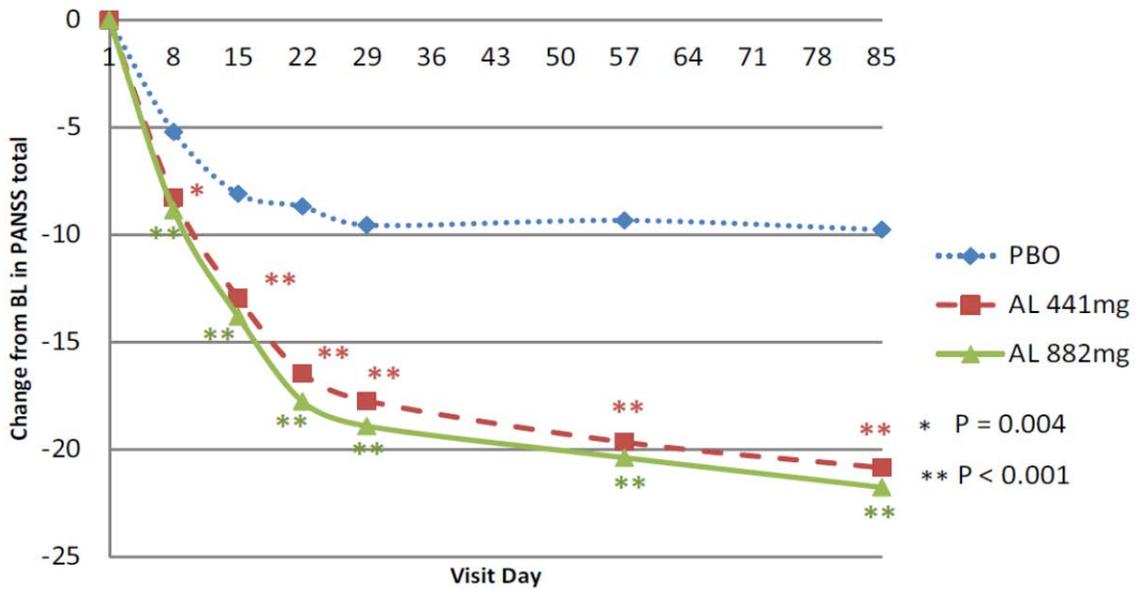
Blood samples for PK assessment were taken on Days 1, 2, 5, 8, 15, 22, 29, 43, 57, 71, 85, 113 and 141. Samples on Days 1, 29 and 57 were taken pre-dose. A single sample was also taken between Day -10 and Day -1. Plasma concentration of aripiprazole lauroxil, N-hydroxymethyl aripiprazole, aripiprazole, and dehydroaripiprazole were assessed. Relevant PK data were evaluated by using non-linear mixed effects modeling.

The primary efficacy endpoint was the PANSS total score change from baseline to Day 85. The primary analysis was an analysis of covariance (ANCOVA) model with last

observation carried forward (LOCF) imputation. Safety was monitored by the evaluation of adverse events.

The primary efficacy analysis included 596 randomized subjects. The ANCOVA results show that the mean change from baseline to Day 85 was -20.9 and -21.8 for the 441 mg and 883 mg groups and both are significantly greater than the mean change from baseline to Day 85 of -9.8 for the placebo group, as shown in Figure 11.

**Figure 11 Change from Baseline in PANSS Total Score by Visit by ANCOVA LOCF**



Source: CSR ALK9072-003 page 68

Table 4 presents an overall summary of adverse events, serious adverse events, and adverse events leading to discontinuation during the treatment period and the follow-up period. According to the sponsor, compared to placebo, aripiprazole lauroxil was well tolerated.

**Table 4. Summary of Adverse Events**

Category	Placebo (N=207) n (%)	Aripiprazole Lauroxil	
		441 mg (N=207) n (%)	882 mg (N=208) n (%)
<b>Treatment Period</b>			
Any Treatment Emergent Adverse Event (TEAE)	129 (62.3)	122 (58.9)	119 (57.2)
Any Related TEAE	72 (34.8)	80 (38.6)	77 (37.0)
Any Severe TEAE	12 (5.8)	9 (4.3)	9 (4.3)
Death	1 (0.5)	0	0
Any Serious Adverse Event (SAE)	4 (1.9)	3 (1.4)	4 (1.9)
Any SAE leading to Discontinuation	2 (1.0)	2 (1.0)	0
Any Related SAE	0	0	1 (0.5)
Any AE leading to Discontinuation	37 (17.9)	14 (6.8)	6 (2.9)
<b>Follow-up Period</b>			
Any Treatment Emergent Adverse Event (TEAE)	5 (2.5)	4 (8.2)	4 (11.4)
Any Related TEAE	1 (2.5)	0	0
Any Severe TEAE	0	0	1 (2.9)
Death	0	0	0
Any Serious Adverse Event (SAE)	0	0	1 (2.9)
Any SAE leading to Discontinuation	0	0	1 (2.9)
Any Related SAE	0	0	0
Any AE leading to Discontinuation	1 (2.5)	0	1 (2.9)

Source: CSR ALK9072-003 page 95

### 3.2 Summary of the Population PK Study Report: (ALK9072-050/ALK9072-051)

A population PK analysis was performed using aripiprazole and dehydro-aripiprazole data from four phase 1 trials (ALK9072-001, -002, -101, and -102) and the phase 3 trial ALK9072-003. The studies included in the popPK analysis are listed in Table 5. The final PK dataset included 10817 aripiprazole concentrations and 10803 dehydro-aripiprazole concentrations from 616 subjects. The structure of the PK model is shown in Figure 12. The sponsor's analysis showed aripiprazole and dehydro-aripiprazole concentration-time data was adequately described by a model containing depot compartments for each IM and oral administration and central and peripheral compartments for both aripiprazole and dehydro-aripiprazole. Conversion of IM aripiprazole lauroxil to aripiprazole was adequately described by a zero-order process with the duration (D1) of conversion estimated and the first-order absorption of aripiprazole from the dosing depot defined as 1/D1. Additionally, a lag time (ALAG) was applied to the IM depot to account for the delay in the appearance of aripiprazole in the central compartment after IM administration of aripiprazole lauroxil. Absorption of aripiprazole following oral dosing was described by a first-order process (Ka). Covariate analysis was performed to assess the effect of injection site, aripiprazole lauroxil formulation, body weight, and CYP2D6

polymorphism. The final model contained covariate effects that described higher relative bioavailability of IM injection and slower lag time for Formulation 1 of aripiprazole lauroxil (Formulation 2 is the intended commercial formulation), for VC/F to increase with body weight, and for lower CL/F in CYP2D6 poor metabolizers. The PK parameters of the final model are presented in Table 6..

The sponsor evaluated the final model by performing visual predictive checks (VPC). The model prediction appeared to be in good agreement with the PK observations. The VPC indicated that less than 9% of observed aripiprazole and less than 10% of observed dehydro-aripiprazole were outside the final popPK model-predicted 90% prediction intervals for all the studies (Figure 13 - Figure 17). The goodness of fit plots for aripiprazole and dehydro-aripiprazole are presented in Figure 18 and Figure 19, respectively.

*Reviewer's comments:*

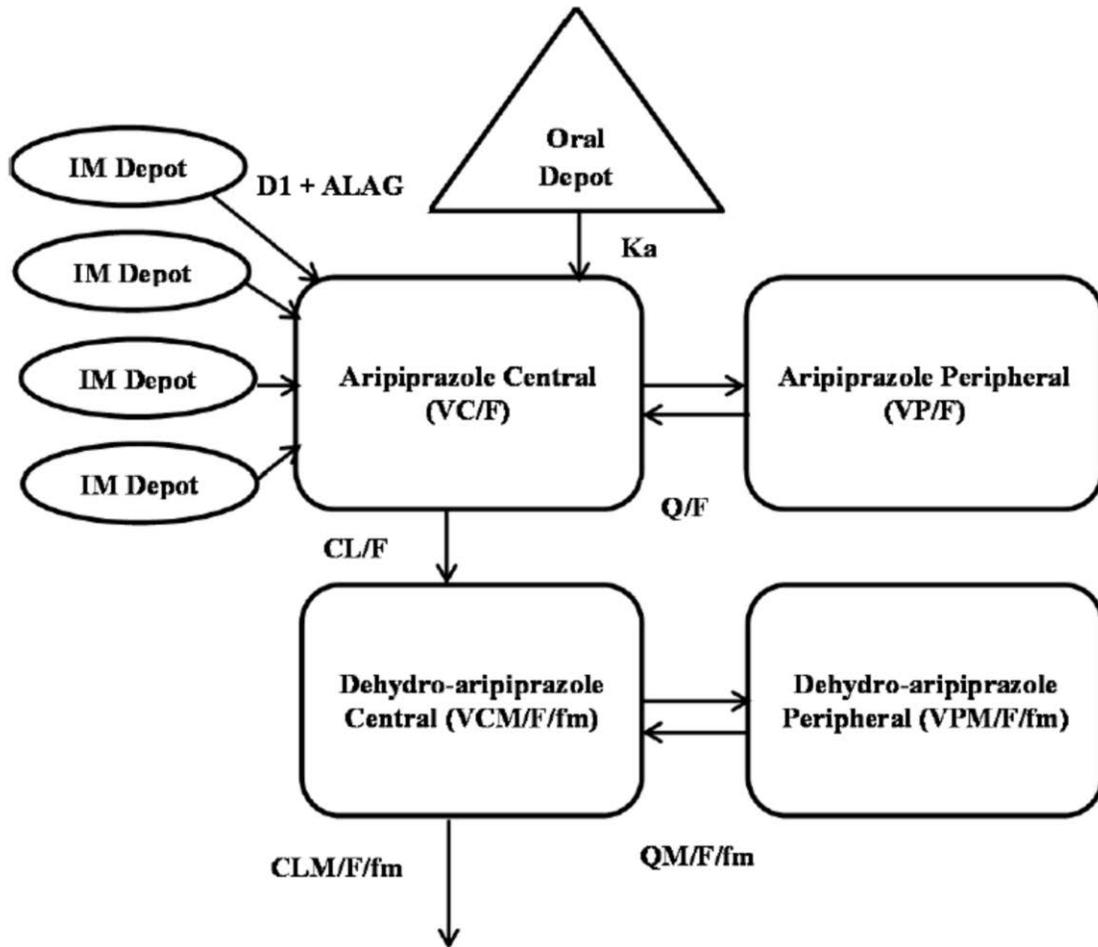
*The sponsor's population PK model adequately described both aripiprazole and dehydro-aripiprazole concentration-time data from all 5 studies.*

**Table 5. Summary of Studies Included in the PopPK Analysis**

Study	Population and Planned No. Subjects	Dose/Treatment Duration	Planned PK Data
ALK9072-001 (Phase 1) Gluteal injection site	<u>Population:</u> Up to 46 subjects male and female with chronic stable schizophrenic subjects dosed with oral aripiprazole. 32 subjects were to receive IM aripiprazole lauroxil or placebo.	Oral aripiprazole (Abilify® 10 mg) once daily for 5 days (Days 1 to 5). On Day 27, subjects were randomized to receive a single gluteal IM of aripiprazole lauroxil at dose levels of 221, 441 or 588 mg, or placebo.	PK samples were collected on Day 1 (first day of oral aripiprazole administration) and on Day 27 pre-dose and at 1, 4, 8, and 12 hr post-dose. Single PK samples were collected pre-dose on Days 2 through 6, and single samples taken on Days 24 and 25, Days 28 through 48, and Days 51, 54, 57, 64, 71, 78, 85, and 115.
ALK9072-002 (Phase 1) Gluteal injection site	<u>Population:</u> 48 male and female adults with chronic stable schizophrenia	Oral aripiprazole (Abilify® 10 mg) once daily for 5 days (Days 1 to 5). On Day 34, 62, 90, and 118 subjects received gluteal IM aripiprazole lauroxil, at dose levels of 441, 662 or 882 mg, or placebo.	PK samples were taken on Days 1, 34 and 118 within 1 hr of dosing and at 1, 4, 8, and 12 hr post-dose. On Days 62 and 90 samples were taken within 1 hr of dosing and at 1 and 4 hr post-dose. Single samples were taken pre-dose on Days 2, 3, 4 and 5 and single samples collected on Days -1, 8, 13, 24, 29, 30, 33, 35 through 47, 55, 61, 69, 76, 83, 89, 97, 104, 111, 117, 119 through 132, 139, 146, 153, 160, 167, 174, 202, and 230.
ALK9072-003 (Phase 3) Gluteal injection site	<u>Population:</u> 540 subjects with acute exacerbation of schizophrenia	Subjects received IM aripiprazole lauroxil 441 or 882 mg, or placebo with doses administered on Days 1, 29 and 57. In addition to IM study drug, subjects received oral study drug daily for the first 3 weeks after randomization.	PK samples were taken on Days 1, 2, 5, 8, 15, 22, 29, 43, 57, 71, 85, 113 and 141. Samples on Days 1, 29 and 57 were taken pre-dose. A single sample was also taken between Day -10 and Day -1.
ALK9072-101 (Phase 1) Deltoid and gluteal injection site	<u>Population:</u> 46 male and female adults with chronic stable schizophrenia	On Day 1 subjects received gluteal IM 441 mg aripiprazole lauroxil or placebo in the deltoid muscle or the gluteal muscle. 2 subjects were administered (221 mg aripiprazole lauroxil in the deltoid muscle.	PK samples were taken pre-dose and 1, 4, 8, and 12 hr post-dose. Single samples were drawn on Days 2-7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 28, 31, 38, 45, 52, 59, 70, 80 and 89.
ALK9072-102 (Phase 1) Deltoid injection site	<u>Population:</u> 52 male and female adults with chronic stable schizophrenia	On Day 1 subjects received IM 441 mg aripiprazole lauroxil or placebo in the deltoid muscle. Subjects then received 3 additional monthly IM injections administered alternately between the left and right arms and were followed until 84 days after the fourth injection.	PK samples were taken on Day 1 4-8 hours post-dose. On other dosing days (Days 29, 57, and 85), PK samples were collected pre-dose. On non-dosing days, PK samples could have been collected at any time.

Source: CSR ALK9072-050-ALK9072-051 page 24

Figure 12 Final PopPK Model Structure



Source: CSR ALK9072-050-ALK9072-051 page 65

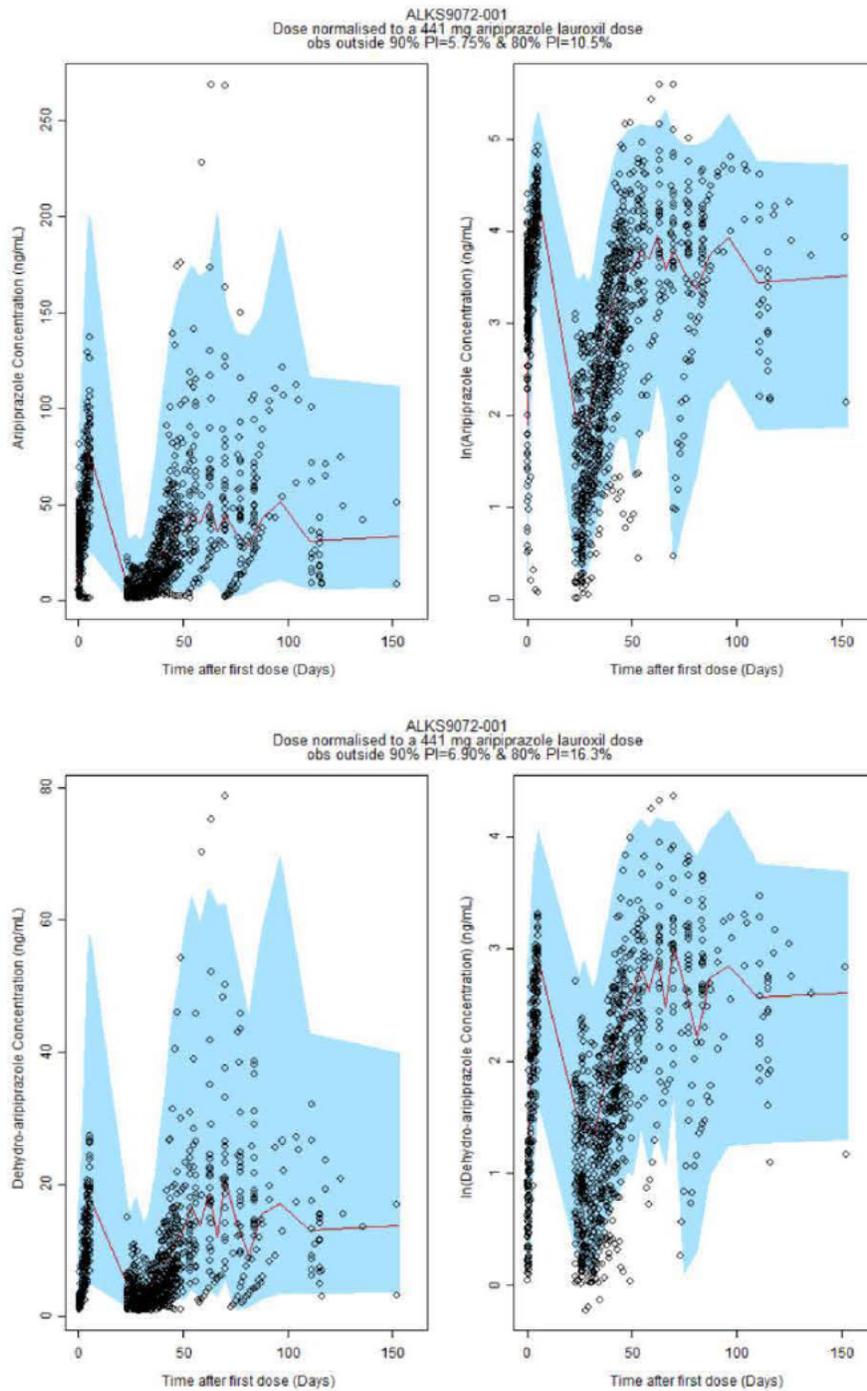
**Table 6. Final PK Model Parameter Estimates**

Parameter [Units]	NONMEM Estimates			CV%
	Point Estimate	%RSE	95% CI	
Ka (hr <sup>-1</sup> )	0.574	24.3	0.440-0.748	
FPO**	1.00	-	-	
FIM FORM2 <sup>(1)</sup>	0.581	6.30	0.543-0.621	
FIM FORM1 <sup>(2)</sup>	1.57	21.6	1.29-1.89	
D1 (hr)	854	0.387	812-898	
ALAG (hr) FORM2	129	1.17	116-144	
ALAG FORM1 <sup>(3)</sup>	0.247	12.3	0.176-0.346	
CL/F (L/hr) Non-PM*	2.02	4.02	1.91-2.14	
CL/F PMs* <sup>(4)</sup>	0.767	22.7	0.682-0.863	
VC/F (L)	268	0.537	252-284	
WT ON VC/F <sup>(5)</sup>	1.00	-	-	
Q/F (L/hr)	0.423	7.37	0.374-0.479	
VP/F (L)	2122	1.21	1772-2540	
CLM/F/fm (L/hr)	5.16	1.84	4.85-5.47	
VCM/F/fm (L)	354	0.756	324-388	
QM/F/fm (L/hr)	0.868	74.6	0.705-1.07	
VPM/F/fm (L)	351	1.86	284-433	
Ari(0) (ng/mL)	0.915	134	0.725-1.15	
Deh(0) (ng/mL)	0.188	7.07	0.150-0.237	
<b>Inter-individual variability</b>				
Ka	4.36	9.08	3.58-5.14	209%
FPO	0.0	-	-	-
FIM	0.394	9.72	0.319-0.469	62.8%
D1	0.247	8.38	0.206-0.288	49.7%
ALAG	0.866	7.69	0.735-0.997	93.1%
CL/F	0.329	7.42	0.281-0.377	57.4%
VC/F	0.396	9.77	0.320-0.472	62.9%
QP/F	1.16	8.88	0.958-1.36	108%
VP/F	1.74	11.6	1.34-2.14	132%
CLM/F/fm	0.389	7.02	0.335-0.443	62.4%
VCM/F/fm	0.685	7.91	0.579-0.791	82.8%
QM/F/fm	3.06	11.2	2.39-3.73	175%
VPM/F/fm	0.938	18.1	0.605-1.27	96.9%
Ari(0)	2.55	11.3	1.99-3.11	160%
Deh(0)	2.16	12.5	1.63-2.69	147%
<b>Residual variability</b>				
$\sigma^2_{prop}$ Aripiprazole	0.261	1.01	0.256-0.266	26.1
$\sigma^2_{prop}$ Dehydro-	0.221	1.17	0.216-0.226	22.1

\* Refers to CYP2D6 phenotype, \*\*Fixed at 1.00, <sup>(1)</sup> in reference to FPO, <sup>(2)</sup> in reference to FIM FORM2, <sup>(3)</sup> in reference to ALAG FORM2, <sup>(4)</sup> in reference CL/F Non-PM, <sup>(5)</sup> power effect = VC/F\*(WT/70)<sup>1.0</sup>

Source: CSR ALK9072-050-ALK9072-051 page 67

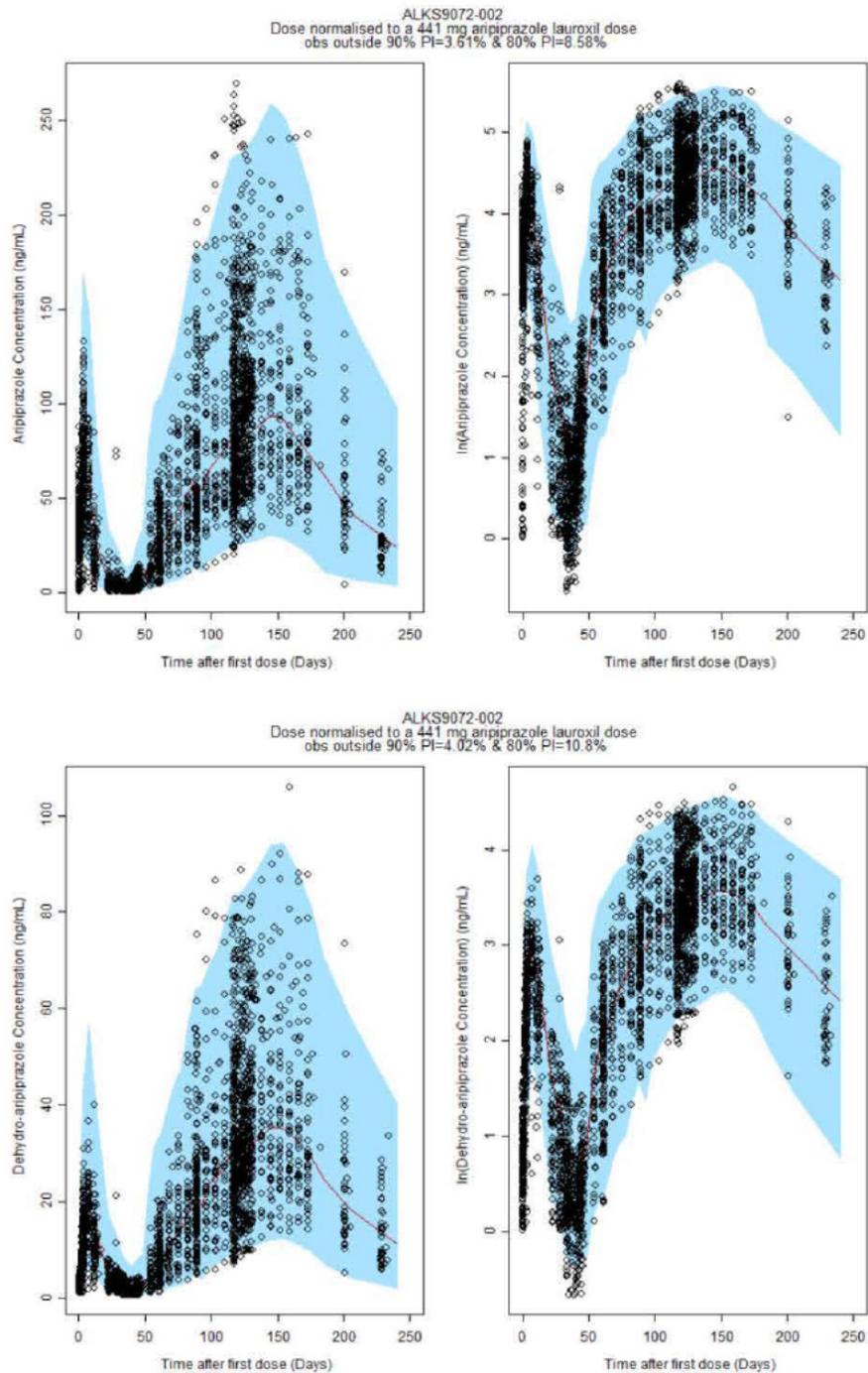
**Figure 13. VPC for the Final Model for Study ALK9071-001**



Open Circle: Observed concentration; Solid Line: Median of predictions; Shaded Region: 90% prediction interval.

Source: CSR ALK9072-050-ALK9072-051 page 76

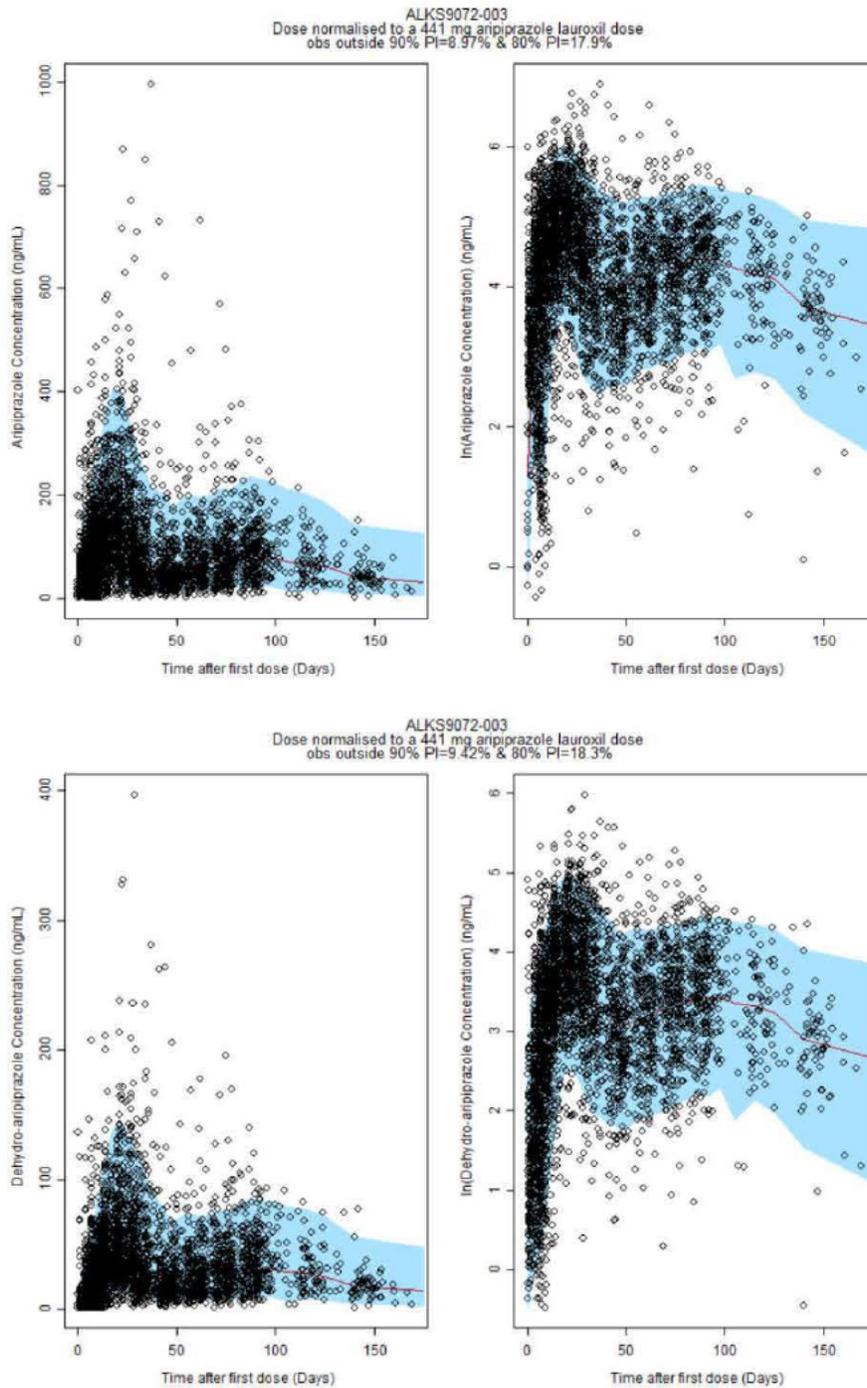
**Figure 14. VPC for the Final Model for Study ALK9071-002**



Open Circle: Observed concentration: Solid Line: Median of predictions: Shaded Region: 90% prediction interval.

Source: CSR ALK9072-050-ALK9072-051 page 77

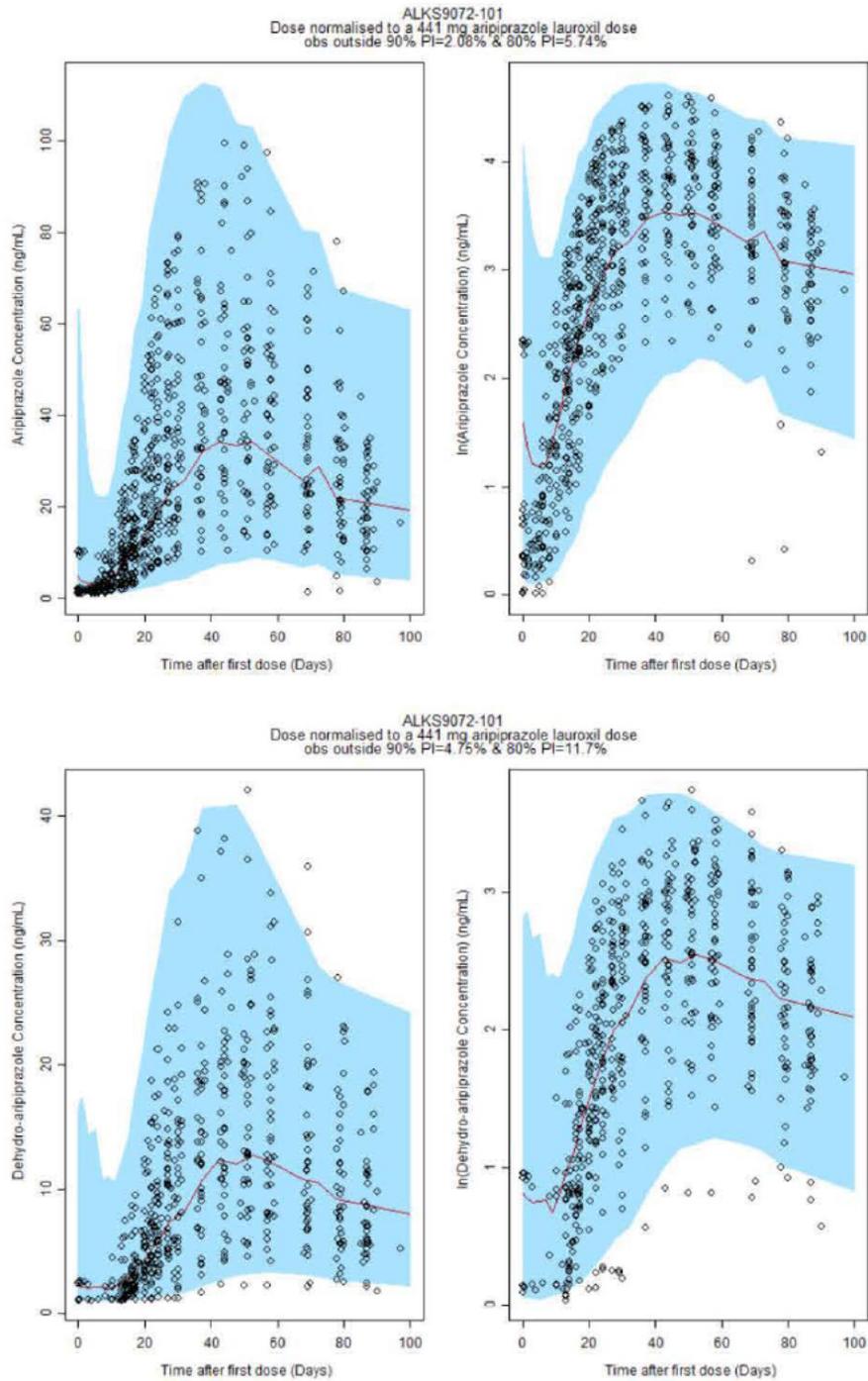
**Figure 15. VPC for the Final Model for Study ALK9071-003**



Open Circle: Observed concentration; Solid Line: Median of predictions; Shaded Region: 90% prediction interval.

Source: CSR ALK9072-050-ALK9072-051 page 78

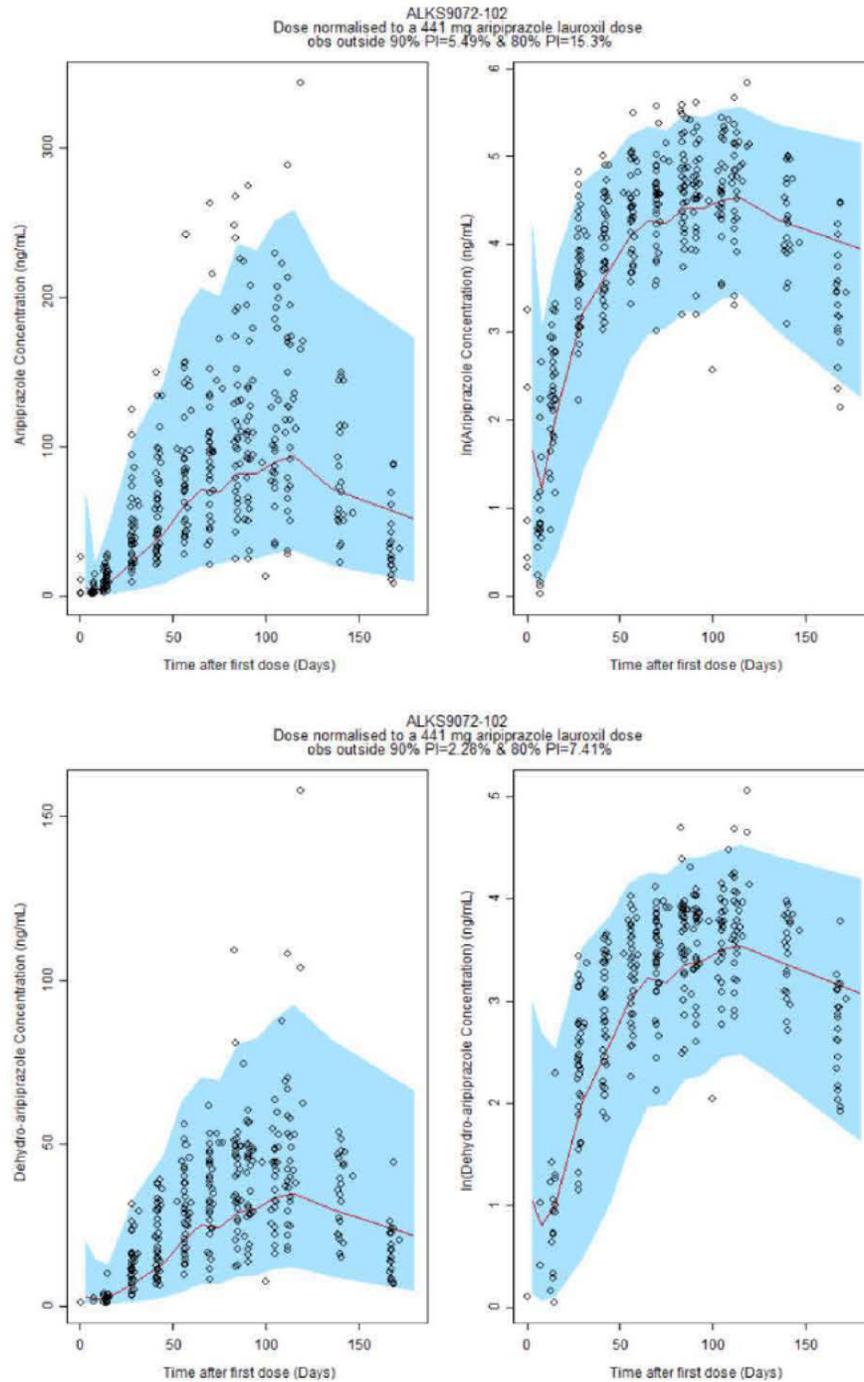
**Figure 16. VPC for the Final Model for Study ALK9071-101**



Open Circle: Observed concentration; Solid Line: Median of predictions; Shaded Region: 90% prediction interval.

Source: CSR ALK9072-050-ALK9072-051 page 79

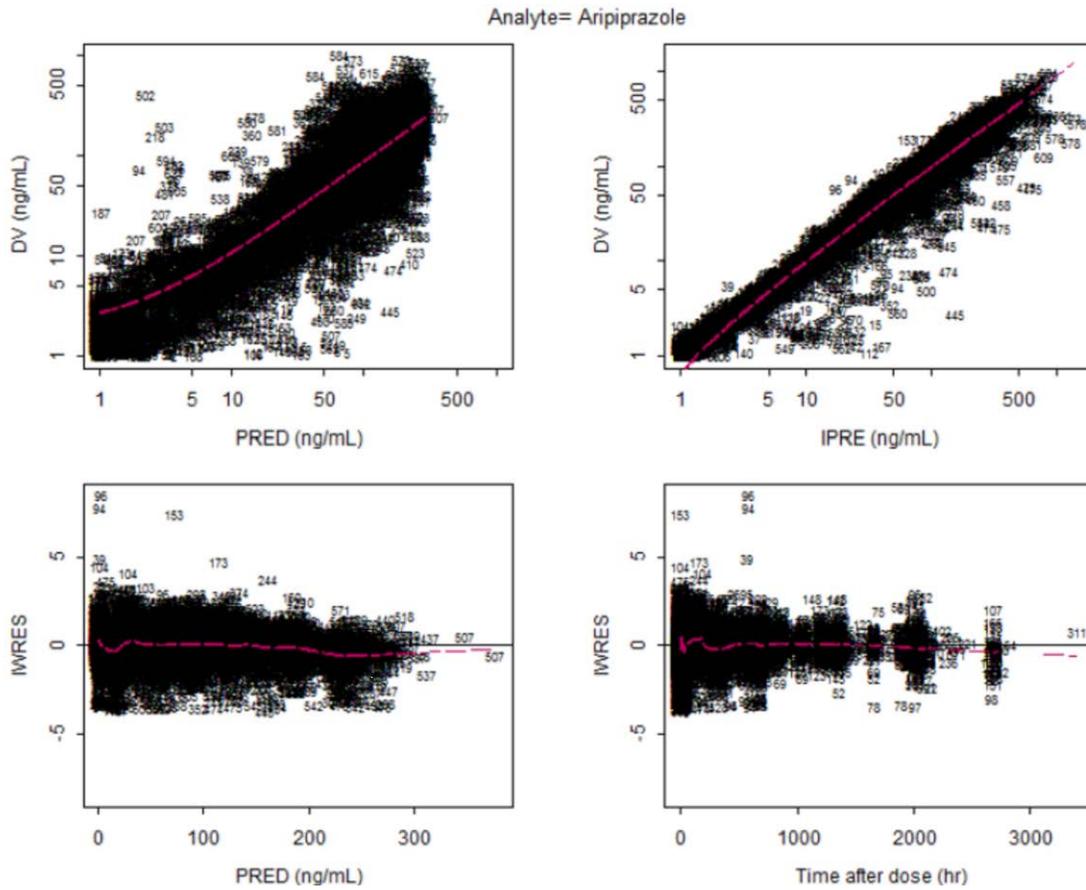
**Figure 17. VPC for the Final Model for Study ALK9071-102**



Open Circle: Observed concentration; Solid Line: Median of predictions; Shaded Region: 90% prediction interval.

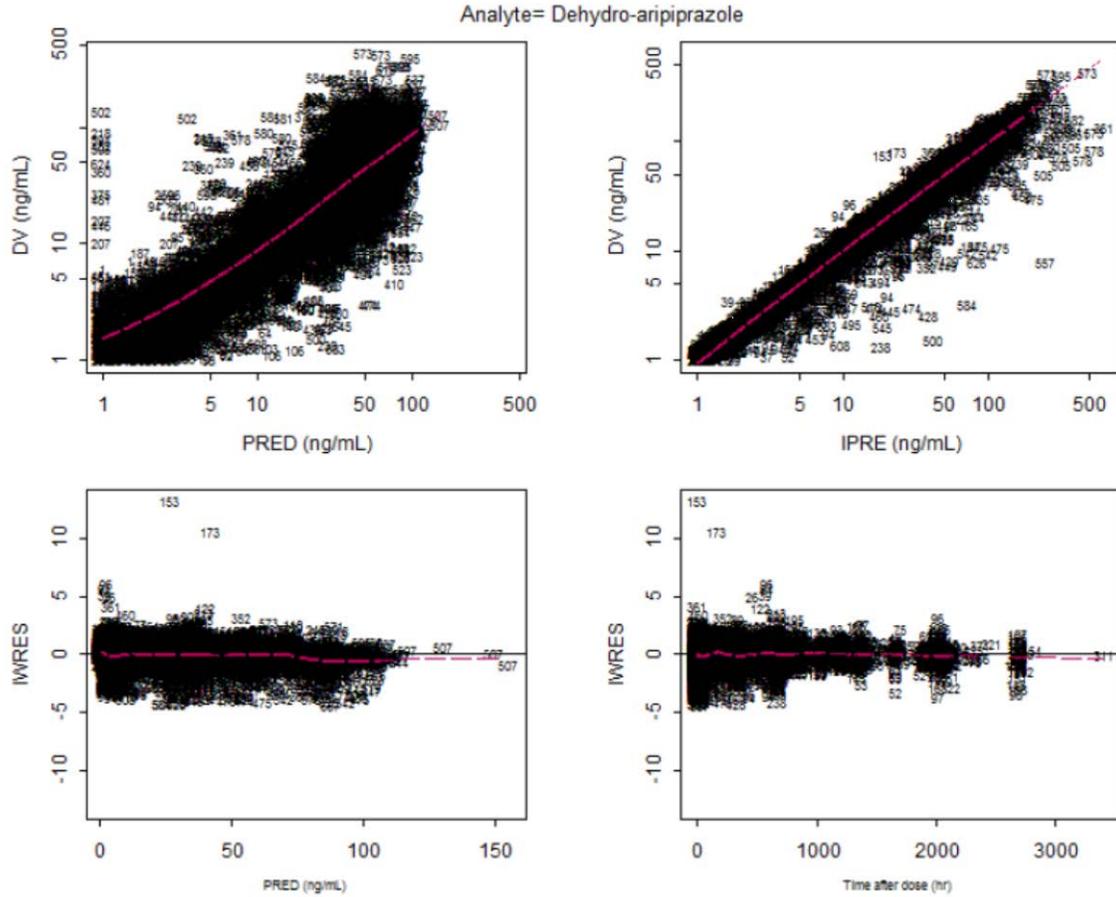
Source: CSR ALK9072-050-ALK9072-051 page 80

Figure 18. Goodness-of-fit Plots for Aripiprazole from the Final Model



Source: CSR ALK9072-050-ALK9072-051 page 74

**Figure 19. Goodness-of-fit Plots for Dehydro-aripiprazole from the Final Model**



Source: CSR ALK9072-050-ALK9072-051 page 74

### 3.3 Summary of the Population PK Simulation Results

In the population PK report, the sponsor submitted PK simulation results to evaluate the following aspects of the dosing strategy for aripiprazole lauroxil IM injection:

- IM treatment initiation
- Impact of early IM aripiprazole lauroxil doses
- Impact of delayed IM aripiprazole lauroxil doses
- Recovery from delayed IM aripiprazole lauroxil doses
- Impact of dose dumping

#### 3.3.1 IM dose initiation

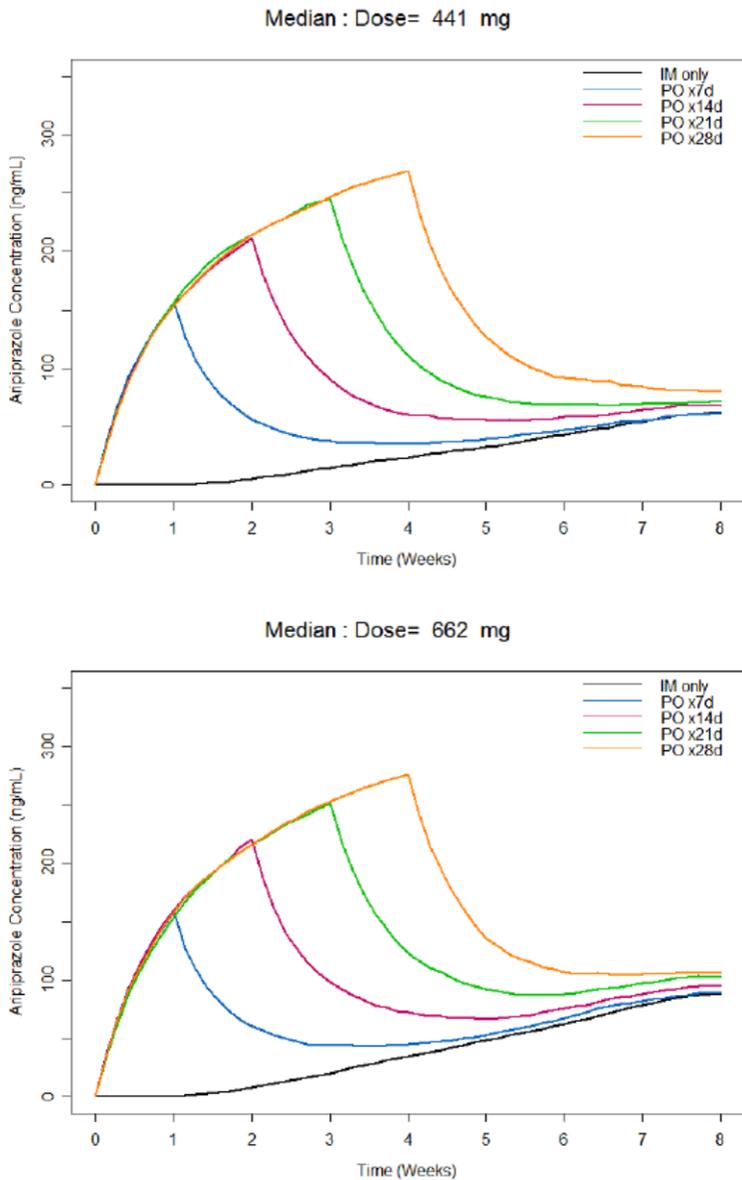
PK simulations of aripiprazole concentration time profiles using various oral supplementation schemes were performed to determine a treatment initiation strategy for the three monthly IM injection regimens. The following scenarios were simulated:

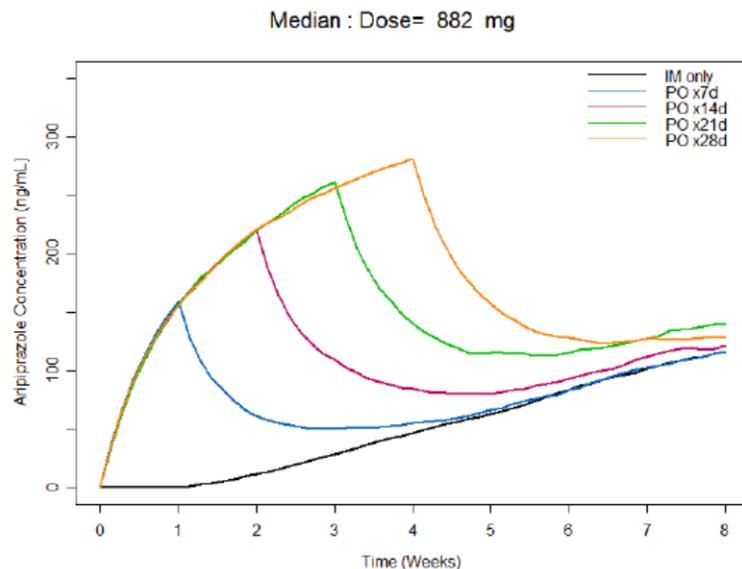
- No oral supplementations with monthly IM aripiprazole lauroxil administration.

- 7, 14, 21, or 28 days of daily oral dosing (15 mg) with the initial IM injection followed by monthly IM aripiprazole lauroxil administration.

The simulations for the first 2 IM injections are shown in Figure 20. The sponsor claims that daily oral dosing with 15 mg aripiprazole for 21 days was predicted to be sufficient to maintain aripiprazole concentrations above 94 ng/mL (the lower boundary of the therapeutic range) during the first month of therapy for all three doses of aripiprazole lauroxil.

**Figure 20. Median Aripiprazole Concentration Time Profiles for the 1st and 2nd Monthly Aripiprazole Lauroxil Doses with Concurrent Oral Aripiprazole Administration**





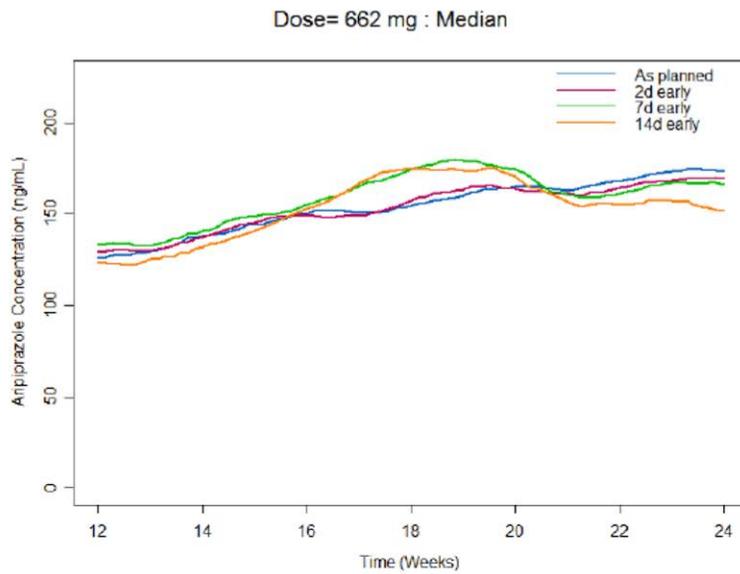
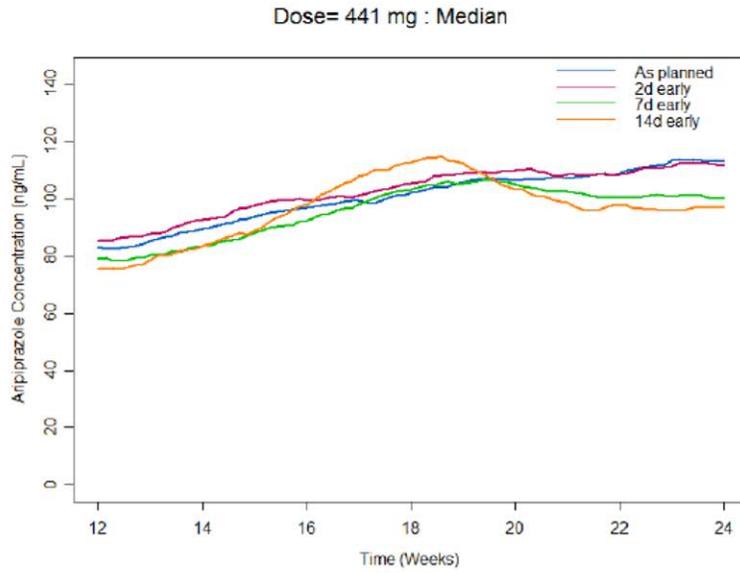
Source: CSR ALK9072-050-ALK9072-051 page 88

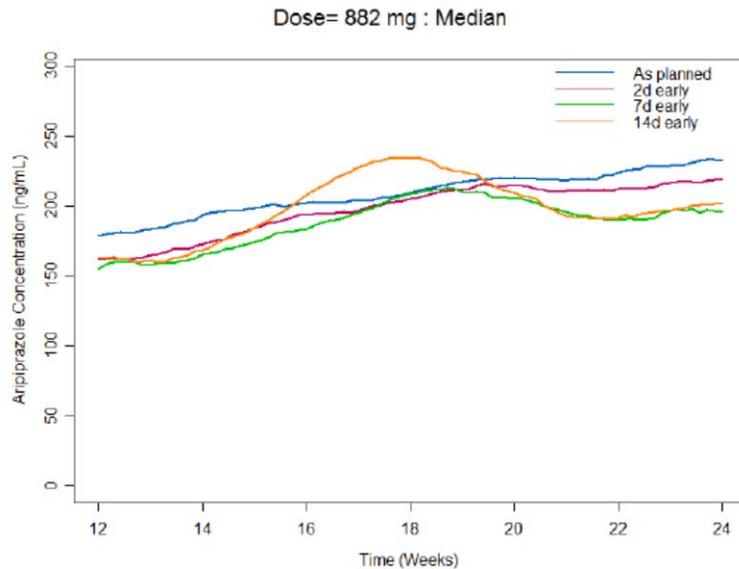
*Reviewer's comments: Simulation results demonstrate that treatment initiation with 21 days of oral supplemental doses is able to maintain aripiprazole concentration above the lower boundary of the concentration window during the first two months at 662 mg and 882 mg dose levels. At 441 mg dose, although such initiation approach would result in exposures that are below the lower boundary of the concentration window during the second dosing interval, efficacy is not likely to be compromised because efficacy of both 441 mg and 882 mg monthly doses with such dose initiation approach has been demonstrated in the pivotal study ALK9072-002. Therefore, the proposed treatment initiation with 21 days of concurrent oral aripiprazole doses is considered acceptable.*

### 3.3.2 Impact of early IM aripiprazole lauroxil doses

PK simulations were performed to describe the impact of an early monthly IM dose on the aripiprazole concentration-time profiles. For monthly IM doses of 441, 662, and 882 mg aripiprazole lauroxil, concentration-time profiles were simulated whereby the 5<sup>th</sup> dose was administered 2, 7, or 14 days early. Median aripiprazole concentration-time profiles describing the impact of dosing 2-14 days early following 4<sup>th</sup>, 5<sup>th</sup> (early dose), and 6<sup>th</sup> doses are presented in Figure 21. The sponsor claims that little impact on median aripiprazole concentrations was noted for doses administered up to 14 days early. Doses administered 7 to 14 days early resulted in slightly higher peaks and lower median trough concentrations as subsequent doses were simulated to occur at the originally planned time. The increase in  $C_{max,ss}$  resulting from a dose administered 14 days early was less than the upper threshold of the therapeutic window previously defined for oral aripiprazole.

**Figure 21. Median Aripiprazole Concentration Time Profiles for Early Aripiprazole Lauroxil Administration at Steady State**





Source: CSR ALK9072-050-ALK9072-051 page 97

Reviewer's comments: The sponsor conducted PK simulations of early dose scenarios up to 14 days early for all 3 monthly doses. Results show that an early dose of up to 14 days at steady state could change the PK profiles. However, such changes are not expected have clinically significant impact on safety and efficacy.

### 3.3.3 Impact of delayed IM aripiprazole lauroxil doses

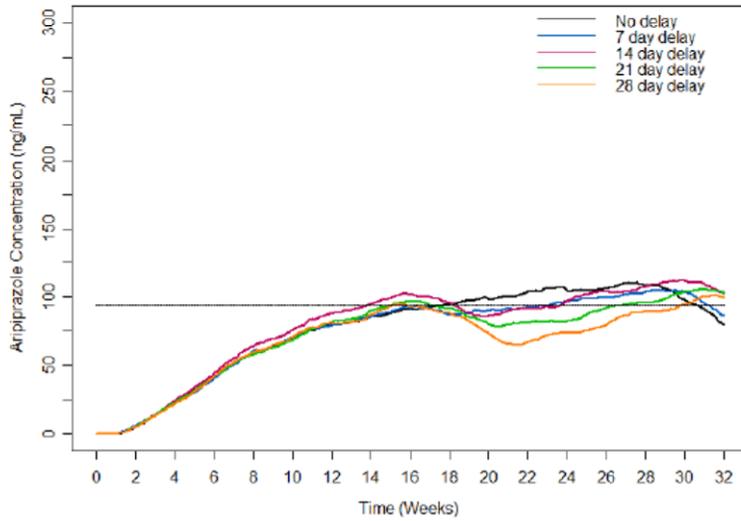
Simulations were conducted to describe the impact of delayed IM dose on the aripiprazole concentration-time profiles before (2<sup>nd</sup> and 3<sup>rd</sup> doses) and at steady state (5<sup>th</sup> dose). The following delayed scenarios were simulated:

- Dose delayed by 7 days.
- Dose delayed by 14 days.
- Dose delayed by 21 days.
- Dose delayed by 28 days.

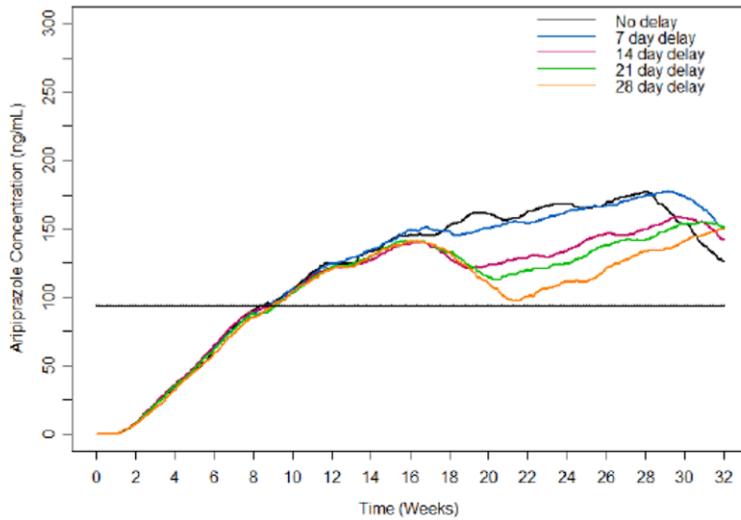
The results of delay scenarios for the monthly regimens with varying delays after the 5<sup>th</sup> (steady-state) dose are shown in Figure 22.

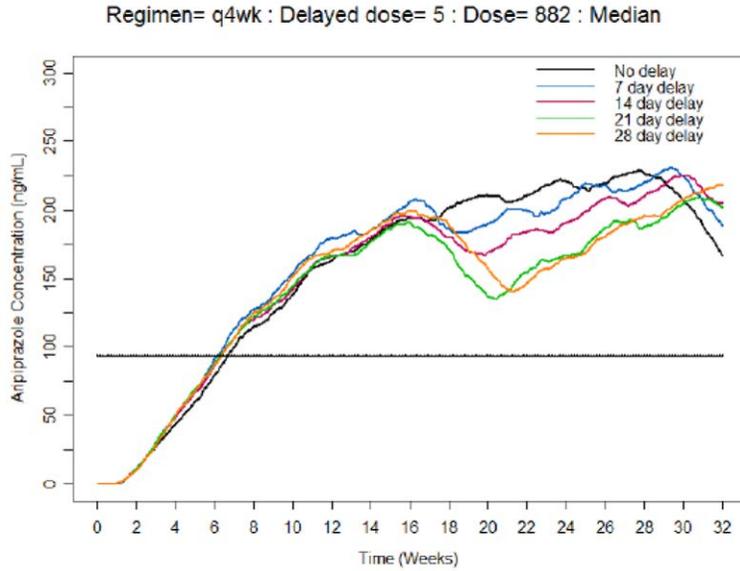
**Figure 22. Median Aripiprazole Concentration Time Profiles after Delayed Aripiprazole Lauroxil Dosing at Steady State**

Regimen= q4wk : Delayed dose= 5 : Dose= 441 : Median



Regimen= q4wk : Delayed dose= 5 : Dose= 662 : Median



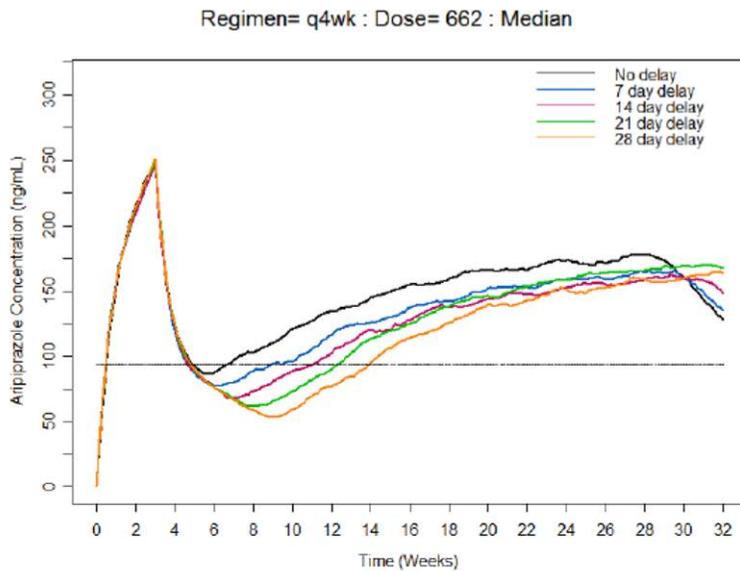
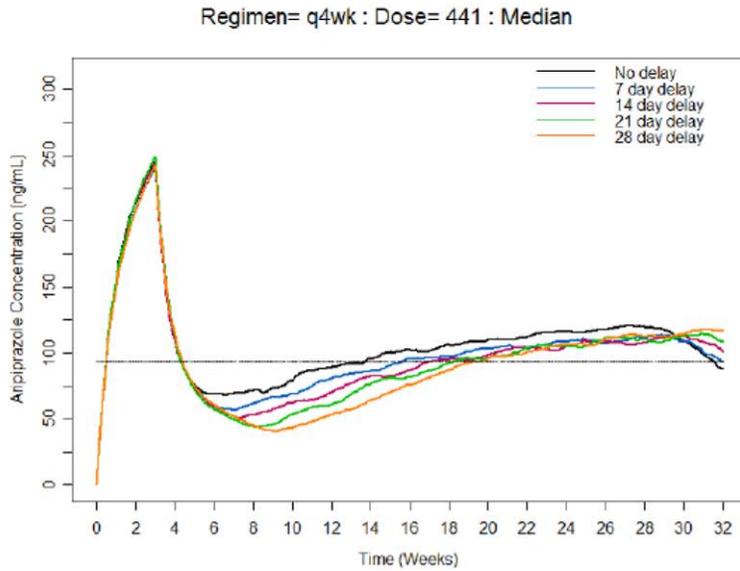


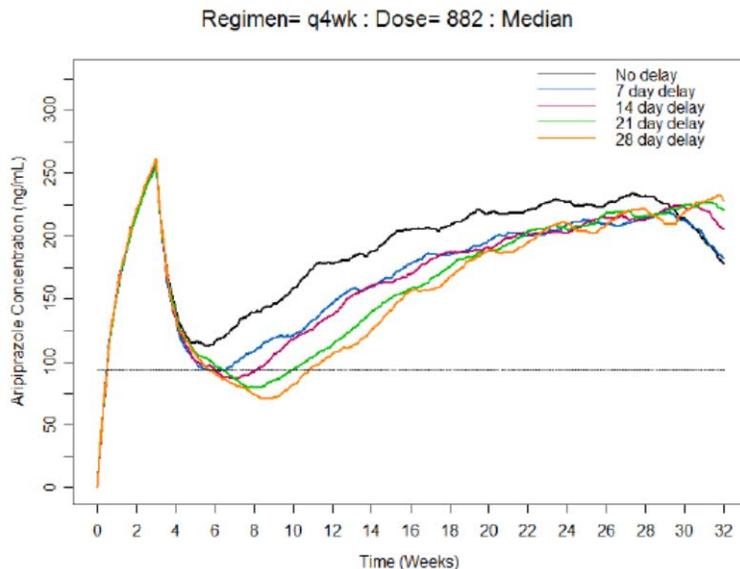
Source: CSR ALK9072-050-ALK9072-051 page 91 & 540

The sponsor claims that all delays of 7 days or more in the 441 mg monthly regimen resulted in excursions of the median aripiprazole concentration below the 94 ng/mL threshold. The excursions below the 94 ng/mL threshold for the 7 and 14-day delays in the 441 mg monthly regimen were marginal. No excursions were noted for either the 662 or 882 mg monthly regimens.

Because initiation of IM dosing is expected to include supplemental oral dosing, additional simulations were performed to assess the impact of delays in the timing of the 2<sup>nd</sup> IM dose after initiation with a first dose with concurrent oral dosing (15 mg PO aripiprazole QD for 21 days). The results of delay scenarios for the monthly regimens with varying delays after the 2<sup>nd</sup> dose with concurrent oral dosing are shown in Figure 23.

**Figure 23. Median Aripiprazole Concentration Time Profiles after Delayed 2nd Aripiprazole Lauroxil Dose Following a 21-Day Oral Aripiprazole Lead-In Administered Concurrently with the First Aripiprazole Lauroxil Dose**





Source: CSR ALK9072-050-ALK9072-051 page 93

The sponsor claims that delays in the 2<sup>nd</sup> dose of the 441 or 662 mg monthly regimen prolonged the time during which the median aripiprazole concentration remained below the 94 ng/mL lower threshold. Delays of 14 days or more in the 882 mg monthly regimen resulted in excursions of the median aripiprazole concentration below the 94 ng/mL lower threshold when the 2<sup>nd</sup> dose was delayed.

*Reviewer's comments: The impact of delayed doses both before and at steady state was adequately demonstrated by the sponsor's PK simulations. The results show that delays of 7 days or more could significantly change the aripiprazole PK profiles, especially at 441 mg dose level. Therefore, appropriate treatment re-initiation approach would be needed to make sure that efficacy would not be compromised due to delayed doses.*

### 3.3.4 Recovery from delayed IM aripiprazole lauroxil doses

The purpose of these simulations was to describe the impact on the aripiprazole concentration-time profiles of delays in IM dose with supplemental oral aripiprazole recovery. Simulations were performed whereby the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> or 5<sup>th</sup> aripiprazole lauroxil dose was delayed before commencing recovery 7, 14, 21 and 28 days following the delayed dose with IM only or, IM and oral treatment regimens. The following recovery scenarios were simulated:

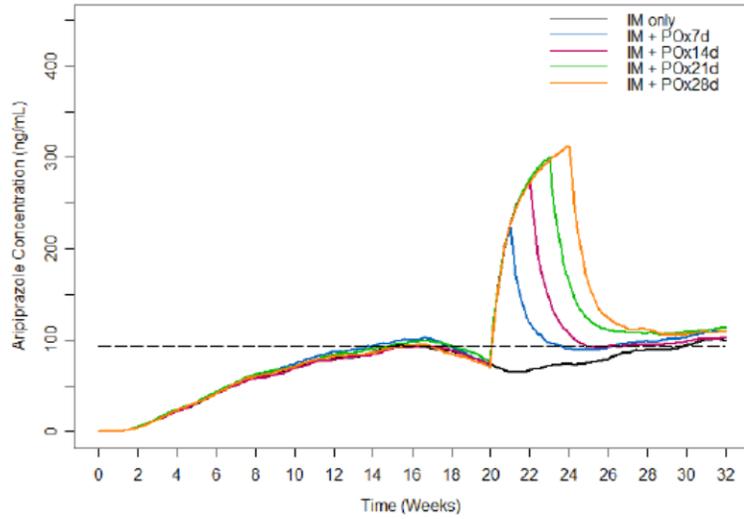
- Recovery by IM alone.
- IM and 7 days of oral dosing post-recovery IM injection.
- IM and 14 days of oral dosing post-recovery IM injection.
- IM and 21 days of oral dosing post-recovery IM injection.
- IM and 28 days of oral dosing post-recovery IM injection.

The worst cases of 28-day delay for monthly regimens at steady state (5<sup>th</sup> dose) are presented in Figure 24. The sponsor claims that for the 441 mg monthly regimen, 7 daily doses of 15 mg oral aripiprazole returned median concentrations to the therapeutic range

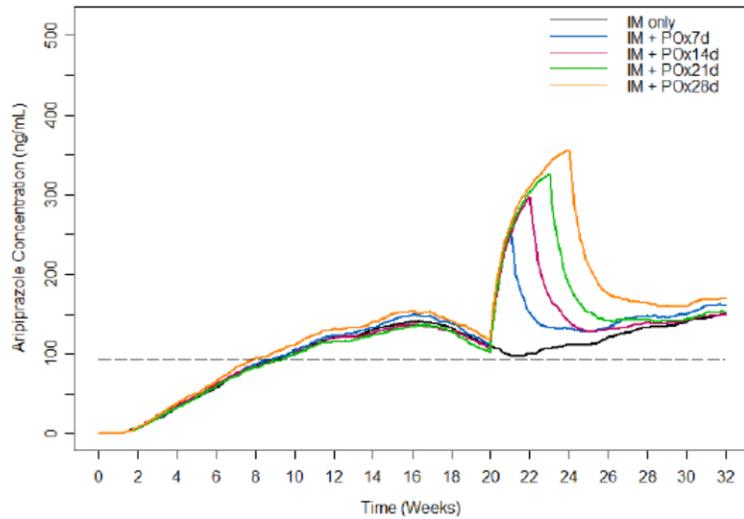
within days of the initiation of recovery treatment. Median aripiprazole concentrations remained above 94 ng/mL after a 28-day delay in a steady-state dose at the 662 and 882 mg monthly regimens without supplementation with oral aripiprazole.

**Figure 24. Median Aripiprazole Concentration Time Profiles after Recovery from Delayed Aripiprazole Lauroxil Dosing With and Without Oral Aripiprazole Supplementation**

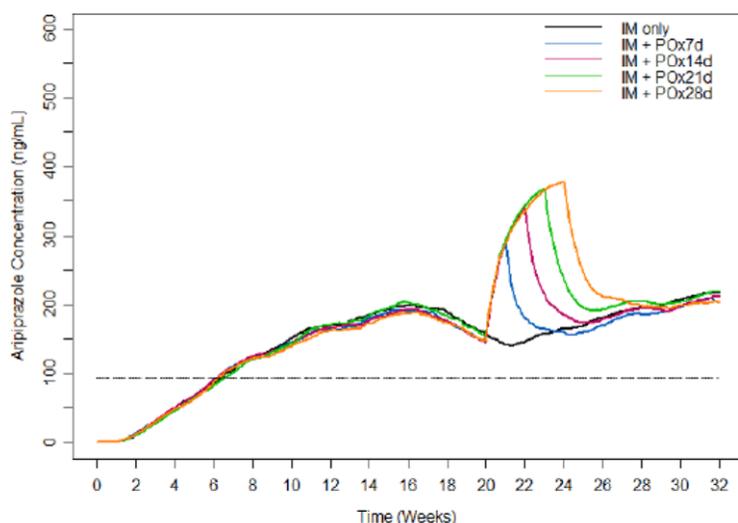
Regimen= q4wk : Delay dose= 5 : Recovery starts=28 days : Dose= 441 : Median



Regimen= q4wk : Delay dose= 5 : Recovery starts=28 days : Dose= 662 : Median



Regimen= q4wk : Delay dose= 5 : Recovery starts=28 days : Dose= 882 : Median



Source: CSR ALK9072-050-ALK9072-051 page 95

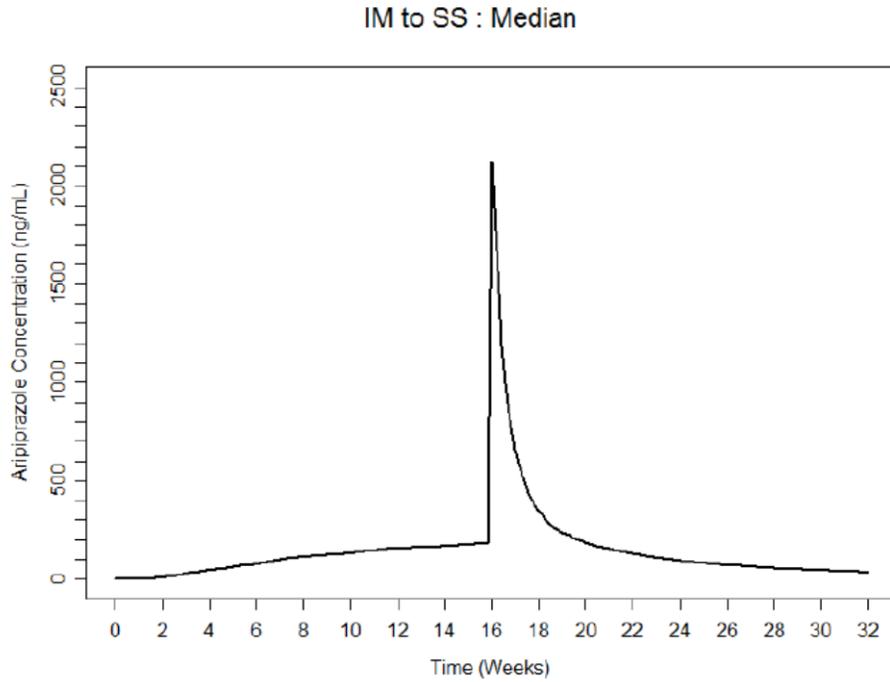
Reviewer's comments: PK simulations were conducted for various missed dose scenarios with different delayed time and different treatment re-initiation approaches. And the simulated PK profiles were compared with the lower boundary of the concentration window to determine the appropriateness of the treatment re-initiation approach. Overall, this idea of utilizing PK simulation to support recommendations for missed dose is appropriate.

However, the pharmacometrics reviewer has the following concern. (b) (4)  
simulated time since last ARISTATDA injection, which is considered inadequate. Clinical scenarios with longer time since last injection, e.g. 12 or more weeks, should be evaluated. Without evaluating clinical scenarios with longer time since last injection, the necessity of full re-initiation approach with 21 days of oral supplemental doses would be neglected.

### 3.3.5 Impact of dose dumping

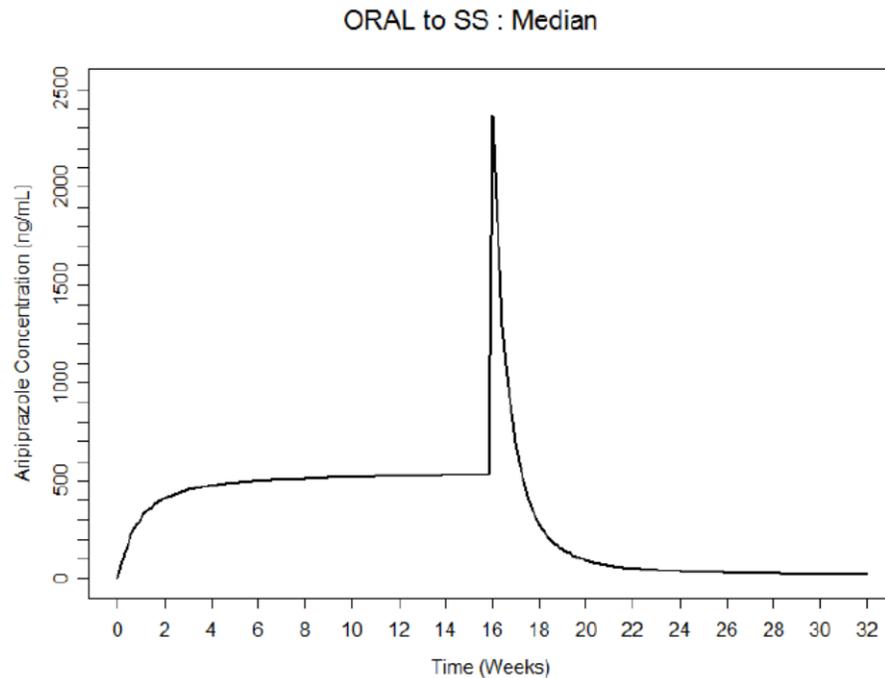
PK simulations were performed to describe dose dumping scenarios, where an IM dose converts from aripiprazole lauroxil to aripiprazole immediately upon administration. Two simulations were performed, one whereby a 882 mg aripiprazole lauroxil dose releases immediately upon first administration in combination with 3 weeks of 30 mg oral aripiprazole already at steady-state, and one where the same 882 mg aripiprazole lauroxil dose releases immediately at steady-state following 882 mg once-monthly IM aripiprazole lauroxil dosing. IV bolus model was used to mimic the dose dumping. The median concentration-time profiles are presented in Figure 25 and Figure 26. The sponsor claims that simulated aripiprazole concentrations following dose dumping show a decline to concentrations normally observed following administration of 882 mg monthly within ~2 weeks after the entire dose enters the systemic circulation. The peak would reach ~2200 ng/mL, 5-6 times higher than the upper end of the aripiprazole therapeutic window, but descend rapidly.

**Figure 25. Median Aripiprazole Concentration Time Profiles for an Aripiprazole Lauroxil Dose Dump Following Administration of 882 mg Monthly to Steady-State**



Source: CSR ALK9072-050-ALK9072-051 page 98

**Figure 26. Median Aripiprazole Concentration Time Profiles for an Aripiprazole Lauroxil Dose Dump Following Administration of 30 mg Oral Aripiprazole Daily to Steady-State**



Source: CSR ALK9072-050-ALK9072-051 page 99

*Reviewer's comments: the sponsor's simulations for possible dose dumping seem to cover the worse clinical scenarios. The impact of possible dose dumping was adequately characterized by the simulations.*

*In addition, the reviewer checked signals of dose dumping in the phase 3 trial. 4 subjects with high concentration levels were identified (subject 537, 571 and 584 from 441 mg dose group; and subject 573 from 882 mg dose group). However, the high concentrations in these 4 subjects are unlikely due to dose dumping because of the following reasons. 1) The highest observed concentration is ~1000 ng/mL which is much lower than the simulated peak concentration of ~2200 ng/mL following dose dumping. 2) No sudden increase in concentration is observed. 3) Some high concentrations observed during the first 22 days may be attributed to concomitant oral aripiprazole administration. Therefore, no evidence of dose dumping in the phase 3 study was concluded.*

## 4 REVIEWER'S ANALYSIS

### 4.1 Introduction

Independent PK simulations were conducted to verify the sponsor's simulation results. Additional simulations were performed to address the reviewer's following concerns. 1) The sponsor simulated multiple-dose PK profiles up to 32 weeks (following 8 aripiprazole lauroxil monthly doses or 6 every-6-weeks doses). From the sponsor's simulation results, it's not clear that whether true steady state has been reached by week 32 because it appears aripiprazole concentrations are still increasing by week 32.

Therefore, to address this issue, PK profiles following more than 10 aripiprazole lauroxil injections were simulated for each dose/dosing regimen to characterize the true steady state aripiprazole exposure levels. 2) The sponsor's simulations for recovery from delayed/missed doses did not cover all possible clinical scenarios. Therefore, independent simulations for unevaluated clinical scenarios, i.e. missed dose scenarios with longer time since last injection, were conducted to aid the establishment of optimal treatment re-initiation strategy following missed doses.

## 4.2 Objectives

Analysis objectives are:

1. To evaluate the concentration-time profiles of the two unstudied dosing regimens (662 mg monthly and 882 mg every 6 weeks).
2. To evaluate the steady state exposure levels for all doses.
3. To evaluate the dosing recommendations for treatment initiation.
4. To evaluate the dosing recommendations for missed/delayed doses.
5. To evaluate the impact of dose dumping.

## 4.3 Methods

Simulations, using the sponsor's population PK model and oral aripiprazole population PK model (from oral aripiprazole [ABILIFY] submission NDA21436), were performed for the following scenarios:

- Steady state concentration-time profiles for the aripiprazole lauroxil doses/dosing regimens (441, 662, 882 mg monthly and 882 mg every 6 weeks) and oral doses (10, 15, 20, and 30 mg)
- Treatment initiation with different number of supplemental oral doses at all dose levels.
- Treatment re-initiation with various re-initiation schemes at different time since last injection after missed dose at all dose levels.
- Dose dumping at steady state of monthly 882 mg doses

In addition, to assess the proposed dose recommendations, simulated PK profiles were compared with an aripiprazole concentration window which was established using observed data following approved oral aripiprazole doses (10-30 mg daily). The observed mean steady state C<sub>min</sub> of 93.3 ng/mL following 10 mg daily oral doses (the lowest approved oral dose) from study 00-231 in NDA21436 was defined as the lower boundary. The observed mean steady state C<sub>max</sub> of 427 ng/mL following 30 mg daily oral doses (the highest approved oral dose) from study 138-023 in NDA21436 was defined as the upper boundary.

### 4.3.1 Data Sets

Data sets used are summarized in 7.

**Table 7. Analysis Data Sets**

Study Number	Name	Link to sharedrive
	pk.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Aripiprazole Lauroxil_NDA207533_XW\PPK Analyses\Reviewer's analysis\Full model

### 4.3.2 Software

NONMEM 7.2 was used for population PK analysis and simulations and graphical analysis was performed via R 3.1.2.

### 4.3.3 Models

The reviewer utilized the sponsor's population PK model and final PK parameters and population PK model from oral aripiprazole (ABILIFY) submission to perform simulations.

## 4.4 Results

See Section 1 (Summary of Findings) of this report.

## 5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Link to sharedrive
	PK simulations	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Aripiprazole Lauroxil_NDA207533_XW\PPK Analyses\Reviewer's analysis\PK simulations
cn138-pop-pk.pdf	Oral aripiprazole popPK model	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Aripiprazole Lauroxil_NDA207533_XW\PPK Analyses

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

XIAOFENG WANG  
04/22/2015

KEVIN M KRUDYS  
04/22/2015

## Clinical Pharmacology Review

---

<b>NDA #:</b>	207533
<b>Proposed Brand Name:</b>	ARISTADA
<b>Generic Name:</b>	Aripiprazole Lauroxil
<b>Dosage Form:</b>	IM Injection (Extended-Release Suspension for IM Injection)
<b>Dosage Strength:</b>	441-mg, 662 mg, 882 mg- single use pre-filled syringe
<b>Indication:</b>	Treatment of Schizophrenia in adults
<b>Sponsor:</b>	Alkermes
<b>Submission Type:</b>	505(b)(2), NCE
<b>Submission Date:</b>	August 22 <sup>nd</sup> , 2014
<b>OCP Review Team:</b>	Praveen Balimane, Xiaofeng Wang, Kevin Krudys, Jeff Kraft, Christian Grimstein, Ping Zhao, Hao Zhu

---

OCP Required Inter-Division Briefing = April 15<sup>th</sup>, 2015

### Table of Contents

1	EXECUTIVE SUMMARY .....	2
1.1.	<i>Recommendation</i> .....	5
1.1.1	Labeling Recommendations.....	6
1.2.	<i>Phase IV Requirements/Commitments</i> .....	6
1.3.	<i>Summary of Clinical Pharmacology Findings</i> .....	6
2.	Question Based Review.....	7
2.1.	<i>Specific Questions</i> .....	7
2.1.1.	<i>Is there evidence of effectiveness for aripiprazole lauroxil IM injection in schizophrenic adult patients (prescribability)?</i> .....	7
2.1.2.	<i>Are the sponsor's proposed doses and dosing regimens appropriate for the general patient population?</i> .....	9
2.1.3.	<i>What are the projected steady state exposure levels of aripiprazole at all dose levels and regimens of Aripiprazole Lauroxil compared to steady state levels for oral ABILIFY?</i> .....	12

2.1.4. Can Aripiprazole Lauroxil be administered at both sites- gluteal muscle and deltoid muscle?.....	13
2.1.5. Was an adequate PBPK model built to predict Aripiprazole PK after IM injection of Aripiprazole Lauroxil?.....	15
2.1.6. Was the PBPK model able to predict Aripiprazole exposures for various CYP2D6 polymorphic subjects (EM, IM and PM's) and what is the recommended dose for patients who are CYP2D6 PM's?.....	16
2.1.7. What is the recommended dose for patients taking Aripiprazole Lauroxil injection concomitantly with CYP3A4 modulators and/or CYP2D6 inhibitors on a short-term or long-term basis?.....	18
2.1.8. What is the recommendation for missed IM doses? When should full re-initiation with 21 days of supplemental oral doses be needed after missed IM doses? .....	20
2.1.9. What is the scenario if there is a dose-dumping after injection of Aripiprazole Lauroxil injection?.....	23
2.1.10. What is the bioavailability of aripiprazole lauroxil IM injection product relative to the approved IR product? .....	25
2.1.11. What are the single-dose PK characteristics of Aripiprazole Lauroxil injection in adult patients? .....	25
2.1.12. What are the multiple-dose PK characteristics of Aripiprazole Lauroxil injection in adult patients? .....	27

## 1 EXECUTIVE SUMMARY

Alkermes is seeking approval of ARISTADA, an extended-release suspension of aripiprazole lauroxil for intramuscular (IM) injection, for the treatment of schizophrenia in adult patients. Aripiprazole lauroxil is a covalently bonded prodrug of aripiprazole, an atypical antipsychotic agent. It is formulated as an extended-release suspension in a pre-filled syringe to be administered via intramuscular (IM) injection into the deltoid (441 mg) muscle or gluteal (441, 662 or 882 mg) muscle. Aripiprazole lauroxil was submitted as a 505(b)(2) NDA relying on the Agency's previous findings of safety and efficacy for ABILIFY (NDA 21436). Since aripiprazole lauroxil contains a non-ester modification of aripiprazole (hydroxymethyl), it is considered as a NCE.

The efficacy of aripiprazole lauroxil extended release IM injection was established in a single Phase 3 efficacy study (ALK9072-003) that demonstrated the efficacy of two aripiprazole lauroxil dose levels (441 mg and 882 mg- given monthly) in subjects with schizophrenia. Statistically significant and clinically meaningful improvement over placebo was observed consistently across both doses, for the primary and secondary endpoints, across all three regions where the study was conducted, and across all study time points, starting with Day 8 through the end of the 12-week treatment period. Additionally, single dose and multiple dose pharmacokinetics of aripiprazole (and all relevant drug related moieties) were adequately characterized in patients with schizophrenia.

Our findings are summarized below:

- An adequate link between aripiprazole lauroxil IM injection and the marketed aripiprazole oral tablet has been established.
- Aripiprazole lauroxil IM injection is efficacious in treating patients with schizophrenia.
- The dose levels and the dosing regimens proposed by the sponsor are acceptable.
- The pharmacokinetic profile is sufficient to support a once monthly or once every 6 weeks dosing (for the 882 mg dose level). Due to significant low concentration of aripiprazole during the first 7-10 days post the first injection and the initial slow rising phase of aripiprazole concentration, it is reasonable to include oral aripiprazole as a supplement for 21 days at the time of initiation of therapy with IM injection.
- Aripiprazole lauroxil can be administered through deltoid muscle for the 441 mg dose and via the gluteal muscle for all 3 dose levels (441 mg, 662 mg and 882 mg).
- Dose adjustments in CYP2D6 poor metabolizers and in patients receiving CYP2D6 and/or CYP3A4 modulators are recommended in Table 1.
- No evidence of dose dumping was observed in pharmacokinetic data collected in the clinical trials (single dose, multiple dose or pivotal efficacy study).

**Table 1: Sponsor-Proposed and FDA-Recommended Dosing of Aripiprazole Lauroxil IM Depot**

Sponsor Proposed Dosing	FDA’s Assessment and Recommendations
<b>Dosing Initiation of Aripiprazole lauroxil</b>	
(b) (4)	<ul style="list-style-type: none"> <li>• To be administered by intramuscular injection in the deltoid (441 mg dose only) or gluteal (441 mg, 662 mg or 882 mg) muscle by a healthcare professional               <ul style="list-style-type: none"> <li>○ For patients who have never taken aripiprazole before: Establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA. Then treat with 15 mg oral aripiprazole for 21 consecutive days along with the first injection of ARISTADA at a dose of 441 mg . Based on efficacy and tolerability, increase dose to the next higher dose after 2 monthly dosing at a certain level.</li> <li>○ For patients on a stable dose of oral aripiprazole: Initiate ARISTADA but continue to treat with oral aripiprazole for 21 consecutive days with the first injection of ARISTADA. Use the following starting doses of ARISTADA to switch from oral aripiprazole:</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>▪ 10 mg oral aripiprazole= 441 mg ARISTADA</li> <li>▪ 15 mg oral aripiprazole= 662 mg ARISTADA</li> <li>▪ 20 mg or higher oral aripiprazole= 882 mg ARISTADA</li> </ul> <ul style="list-style-type: none"> <li>• ARISTADA can be given intra-muscularly at a dose of 441 mg, 662 mg or 882 mg administered monthly or 882 mg dose every 6 weeks</li> </ul>
--	---

**Dosing Interval and Re-initiation after Missed Doses**

	<p>(b) (4) Recommendation for Concomitant Oral Aripiprazole Supplementation Following Missed Doses</p> <table border="1" style="width: 100%;"> <thead> <tr> <th rowspan="2">Dose of Patients Last ARISTADA Injection</th> <th colspan="3">Length of Time Since Last Injection</th> </tr> <tr> <th>No Oral Supplementation Required</th> <th>Supplement with 7 Days Oral Aripiprazole</th> <th>Supplement with 21 Days Oral Aripiprazole</th> </tr> </thead> <tbody> <tr> <td>Monthly 441 mg</td> <td>≤6 weeks</td> <td>&gt; 6 and ≤7 weeks</td> <td>&gt;7weeks</td> </tr> <tr> <td>Monthly 662 mg</td> <td>≤8 weeks</td> <td>&gt; 8 and ≤12 weeks</td> <td>&gt;12 weeks</td> </tr> <tr> <td>Monthly 882 mg</td> <td>≤8 weeks</td> <td>&gt; 8 and ≤12 weeks</td> <td>&gt;12 weeks</td> </tr> <tr> <td>882 mg every 6 weeks</td> <td>≤8 weeks</td> <td>&gt; 8 and ≤12 weeks</td> <td>&gt;12 weeks</td> </tr> </tbody> </table>	Dose of Patients Last ARISTADA Injection	Length of Time Since Last Injection			No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole	Monthly 441 mg	≤6 weeks	> 6 and ≤7 weeks	>7weeks	Monthly 662 mg	≤8 weeks	> 8 and ≤12 weeks	>12 weeks	Monthly 882 mg	≤8 weeks	> 8 and ≤12 weeks	>12 weeks	882 mg every 6 weeks	≤8 weeks	> 8 and ≤12 weeks	>12 weeks
Dose of Patients Last ARISTADA Injection	Length of Time Since Last Injection																							
	No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole																					
Monthly 441 mg	≤6 weeks	> 6 and ≤7 weeks	>7weeks																					
Monthly 662 mg	≤8 weeks	> 8 and ≤12 weeks	>12 weeks																					
Monthly 882 mg	≤8 weeks	> 8 and ≤12 weeks	>12 weeks																					
882 mg every 6 weeks	≤8 weeks	> 8 and ≤12 weeks	>12 weeks																					

**Dosing Recommendations for Drug Interactions and CYP2D6 genotypes**

	<p>(b) (4)</p> <ul style="list-style-type: none"> <li>- No dosage changes recommended for Aripiprazole lauroxil, if CYP modulators are added for less than 2 weeks</li> <li>- Make the following dose changes to Aripiprazole lauroxil if CYP modulators added for greater than 2 weeks</li> </ul> <table border="1" style="width: 100%; margin-top: 10px;"> <thead> <tr> <th>Concomitant medicine</th> <th>Dose change for Aripiprazole lauroxil</th> </tr> </thead> <tbody> <tr> <td>Strong CYP3A4 inhibitor</td> <td>Reduce the dose of ARISTADA to the next lower strength. Patients on 441 mg ARISTADA can stay on, if tolerated.</td> </tr> </tbody> </table>	Concomitant medicine	Dose change for Aripiprazole lauroxil	Strong CYP3A4 inhibitor	Reduce the dose of ARISTADA to the next lower strength. Patients on 441 mg ARISTADA can stay on, if tolerated.
Concomitant medicine	Dose change for Aripiprazole lauroxil				
Strong CYP3A4 inhibitor	Reduce the dose of ARISTADA to the next lower strength. Patients on 441 mg ARISTADA can stay on, if tolerated.				

(b) (4)	Strong CYP2D6 inhibitor	Reduce the dose of ARISTADA to the next lower strength. Patients on 441 mg ARISTADA can stay on, if tolerated. No dose adjustment required for PM's of CYP2D6.
	Both Strong CYP3A4 inhibitor and Strong CYP2D6 inhibitor	Patients at 662 or 882 mg dose = Avoid use. However, if patients known to be PM's of CYP2D6, then reduce the dose of ARISTADA to the next lower strength.  Patient at 441 mg dose= Stay on, if tolerated.
	CYP3A4 inducers	No dose adjustment for 662 and 882 mg dose, increase the 441 mg dose to 662 mg

Dose adjustments as recommended in ABILIFY label should be used for the first 21 days of supplemental oral aripiprazole treatment.

**1.1. Recommendation**

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA package to support a recommendation of approval of aripiprazole lauroxil IM injection formulation. The acceptability of specific drug information is provided below.

<b>Decision</b>	<b>Acceptable to OCP?</b>	<b>Comment</b>
Overall	Yes	Pending labeling agreement with the sponsor
Evidence of effectiveness	Yes	One positive registration trial in adult patients
Proposed dose for adult patients	Yes	Refer to Table 1.
Labeling	Changes suggested	Pending satisfactory agreement with the

		sponsor
--	--	---------

### 1.1.1 Labeling Recommendations

The final labeling language is subject to change pending satisfactory agreement with the sponsor.

### 1.2. Phase IV Requirements/Commitments

No Phase IV study recommendation.

### 1.3. Summary of Clinical Pharmacology Findings

The key pharmacokinetic features of aripiprazole following the IM injection of aripiprazole lauroxil are summarized as follows:

- Aripiprazole lauroxil is formulated as an extended-release suspension in a pre-filled syringe to be administered via intramuscular (IM) injection into the deltoid or gluteal muscle. In vivo conversion of aripiprazole lauroxil to aripiprazole is governed by dissolution of the drug (b) (4) followed by enzyme-mediated hydrolysis, generating lauric acid and *N*-hydroxymethyl aripiprazole. The covalently bonded *N*-hydroxymethyl aripiprazole is then converted to aripiprazole following hydrolysis releasing aripiprazole and formaldehyde.
- The bioavailability of aripiprazole lauroxil IM injection product relative to the approved IR product was predicted to be 58%. It was derived utilizing a PopPK model which simulated steady-state exposures of aripiprazole and dehydro-aripiprazole.
- Aripiprazole lauroxil concentrations were BLQ in plasma across all clinical studies. The appearance of aripiprazole in plasma is gradual and prolonged following IM administration of aripiprazole lauroxil due to the slow dissolution properties of the drug from the injection site. Following a single IM dose, the typical lag time of appearance of aripiprazole in plasma was 4.8 to 6 days and the T<sub>max</sub> was 37-48 days. At steady-state the terminal T<sub>1/2</sub> of aripiprazole was estimated to be 27-35 days.
- Due to the slow appearance of aripiprazole in systemic circulation after the IM injection, when initiating treatment with aripiprazole lauroxil, the first dose of aripiprazole lauroxil should be administered concurrently with oral aripiprazole for 21 days. This ensures adequate aripiprazole concentrations within the therapeutic range during the first month of therapy.
- Increases in total systemic exposure following repeated monthly administration of aripiprazole lauroxil were dose proportional over the studied dose range of 441 to 882 mg.

- Following four doses of aripiprazole lauroxil, aripiprazole concentrations increased by 9-13-fold when compared to the first dose. The exposure levels for all moieties (parent and metabolites) appear to approach steady state in 4 doses.
- Aripiprazole is extensively metabolized, mainly by CYP3A4 and CYP2D6. Dehydro-aripiprazole, an active metabolite of aripiprazole, circulates at a level about ~ 38% of the parent at steady state. This ratio of metabolite/parent remains similar in both oral ABILIFY, and aripiprazole lauroxil IM injections.
- Aripiprazole exposure was similar for deltoid and gluteal IM injections of 441 mg aripiprazole lauroxil, thus for this dose, the deltoid and gluteal administration sites can be used interchangeably. Only gluteal site injection is recommended for 662 and 882 mg injections.
- The physiochemical properties of aripiprazole lauroxil and aripiprazole (b) (4) make it very unlikely that dose dumping into the systemic circulation would occur. Moreover, no evidence of dose dumping was observed in the clinical trials (single dose, multiple dose or pivotal efficacy study).

## 2. QUESTION BASED REVIEW

### 2.1. Specific Questions

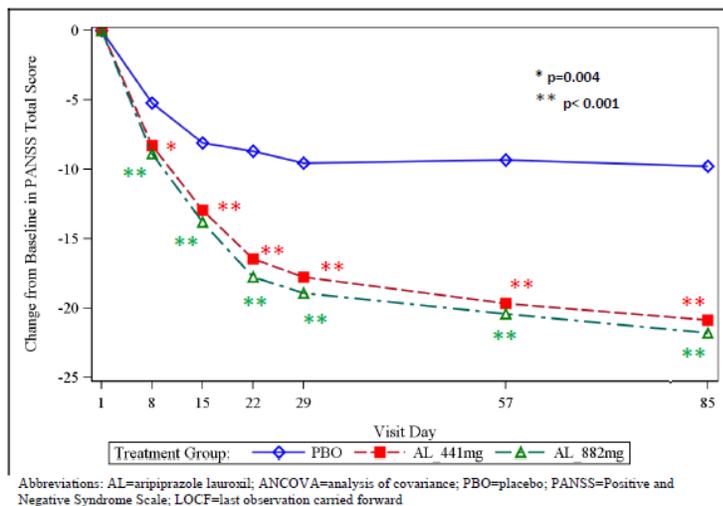
#### 2.1.1. *Is there evidence of effectiveness for aripiprazole lauroxil IM injection in schizophrenic adult patients (prescribability)?*

Yes. The efficacy of aripiprazole lauroxil was demonstrated in the pivotal efficacy study ALK9072-003.

Study ALK9072-003 was a global, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of treatment with once monthly IM aripiprazole lauroxil (441 mg and 882 mg) as compared with placebo over a period of 12 weeks in subjects with schizophrenia experiencing an acute exacerbation episode. Statistically significant and clinically meaningful improvement over placebo was observed consistently across both doses, for the primary and secondary endpoints, across all three regions where the study was conducted, and across all study time points, starting with Day 8 through the end of the 12-week treatment period (Figure 1). A total of 623 subjects were randomized and 622 received at least one injection of IM study drug (aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo). A total of 360 subjects (58%) completed the 12-week treatment period. Clinically meaningful and statistically significant differences compared with placebo were seen in the primary efficacy endpoint, change from baseline to Day 85 in the Positive and Negative Syndrome Scale (PANSS) total score (least square [LS] mean difference from placebo -10.9 and -11.9 for the 441 mg and 882 mg groups, respectively with  $p < 0.001$  for each group, using an analysis of

covariance with last observation carried forward approach (i.e., analysis of covariance [ANCOVA], last observation carried forward [LOCF])

**Figure 1: Efficacy of Aripiprazole lauroxil: Change from Baseline in PANSS Total Score by Visit by ANCOVA LOCF**



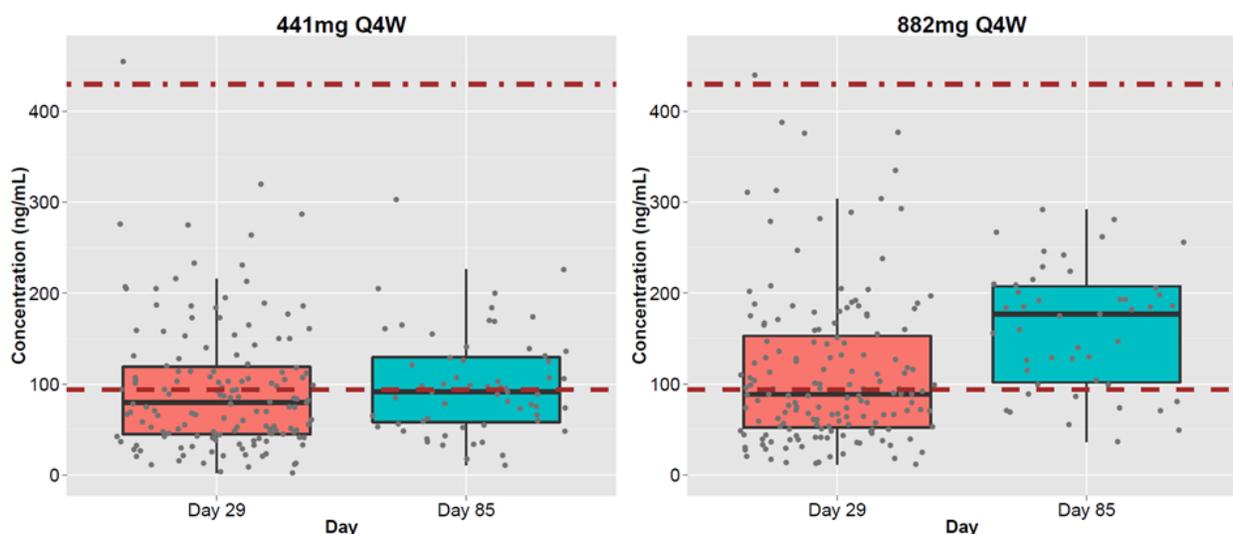
Though the results from Study ALK9072-003 demonstrated unequivocal efficacy for aripiprazole treatment (i.e. treatment with both oral and IM combined), the efficacy contribution only from the IM injection (i.e. aripiprazole lauroxil without any oral aripiprazole) was additionally confirmed using the following rationales:

First, by “correcting” the baseline PANSS score. This was done by using the PANSS score on day 29 after the oral aripiprazole regimen rather than day 1 score to account for the efficacy contribution from oral aripiprazole. Since the oral aripiprazole is given for the first 21 days and its terminal T<sub>1/2</sub> is 3 days, the exposure contribution due to only oral is likely to be insignificant by day 29 (i.e. 3x times the T<sub>1/2</sub>). Therefore, using the PANSS score of day 29 provides a “corrected” baseline score (which incorporates the efficacy due to oral) and comparing it to PANSS score on day 85 provides the efficacy contribution only from the IM injection. Statistical analysis demonstrated that PANSS score was significantly lower (P value < 0.05) on day 85 compared to day 29, supporting the efficacy contribution of IM injection. This analysis was performed by the statistics reviewer and the details are in the statistics review.

Second, by comparing the aripiprazole exposure (i.e. the active moiety) on day 85 vs. day 29. Since the efficacy is driven by the systemic exposure of aripiprazole, the significantly reduced PANSS score of day 29 clearly suggests that exposure levels are adequate on day 29. Moreover, if the exposure on day 85 (which is primarily only due to IM injection) is similar (or higher) than on day 29, then it would support the efficacy contribution of IM injection. Figure 2 clearly

demonstrates that exposures (for both dose levels) continue to increase from day 29 to day 85 providing direct evidence of exposure contribution of IM injection which in turn drives the efficacy.

**Figure 2: Observed Aripiprazole exposure on Day 85 vs. Day 29 for the 2 dose levels.**



In addition, from a PK perspective, the observed median aripiprazole concentrations on day 85 of subjects from the two treatment groups in Study ALK9072-003 are within the observed exposures levels for approved dose range (10 mg to 30 mg- QD) of oral aripiprazole (ABILIFY). Such observed exposure levels might be used to establish a range of steady state aripiprazole concentrations within which aripiprazole exposures are considered both tolerable and effective. The lower bound, 93.3 ng/mL, is defined as the mean steady state C<sub>min</sub> following 10 mg daily oral doses; the upper bound, 427 ng/mL, is defined as the mean steady state C<sub>max</sub> following 30 mg daily oral doses. Additionally, despite the different routes of administration (oral vs. intramuscular injection), the underlying shape of the PK profile is very similar for the 2 formulations. At steady state both formulations have a very flat profile with less than 25% drop in exposure within a dosing interval (i.e. C<sub>trough</sub> compared to C<sub>max</sub>).

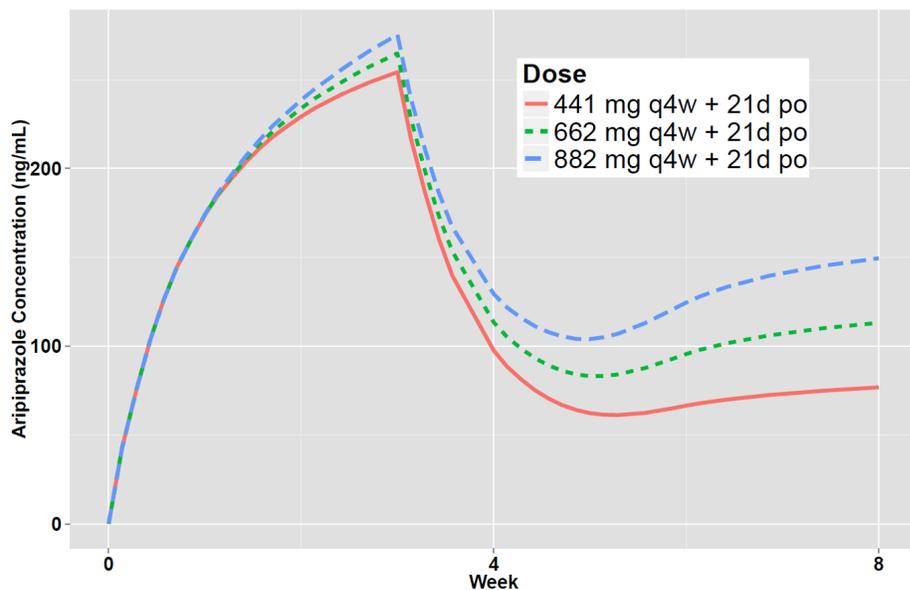
**2.1.2. Are the sponsor's proposed doses and dosing regimens appropriate for the general patient population?**

Yes.

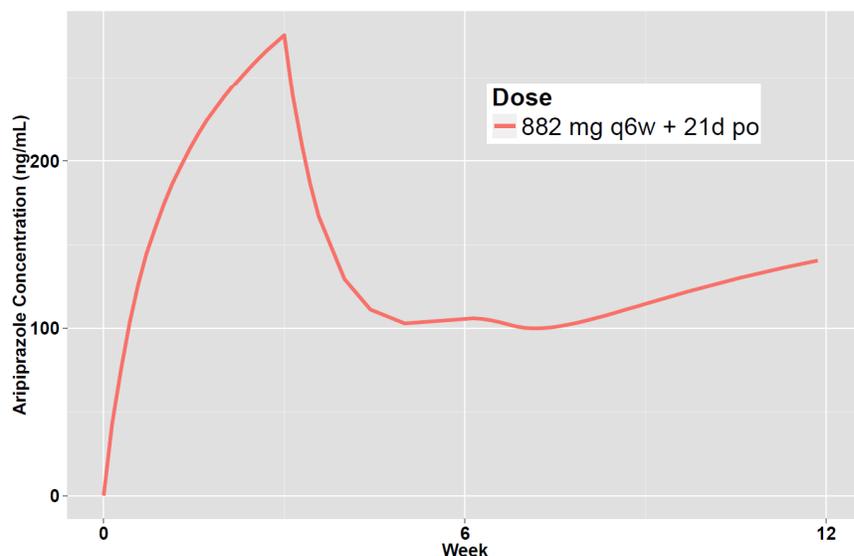
The sponsor suggested (a) doses of 441, 662 and 882 mg as an IM injection, (b) dosing regimens, monthly (q4w) for all dose levels and every 6 weeks (q6w) for 882 mg, and (c) a concomitant daily treatment with oral aripiprazole during the first 21 days following the 1<sup>st</sup> injection of aripiprazole lauroxil, are all considered appropriate.

The simulated mean aripiprazole concentration time profiles for the first and second IM injections along with 21 days of concurrent 15 mg oral aripiprazole administration at three monthly aripiprazole lauroxil doses (441 mg, 662 mg, and 882 mg monthly) and at 882 mg every six weeks are shown in Figure 3 and Figure 4, respectively. Aripiprazole concentrations are able to rise and reach therapeutic levels during the first dosing interval due to the concurrent oral aripiprazole doses. Although aripiprazole concentrations at the 441 mg dose level may drop below the therapeutic range for some time during the second dosing interval, efficacy is not likely to be compromised because the effectiveness of both 441 mg and 882 mg monthly doses with such dose initiation strategy has been demonstrated in the pivotal trial (Study ALK9072-003). Therefore, the proposed initiation doses and dosing regimens with 21 days of concurrent oral aripiprazole doses are considered to be acceptable.

**Figure 3: Simulated Mean aripiprazole Concentration Time Profiles for the 1st and 2nd monthly Aripiprazole Lauroxil Doses with 21 days of Concurrent Oral ABILIFY Administration**

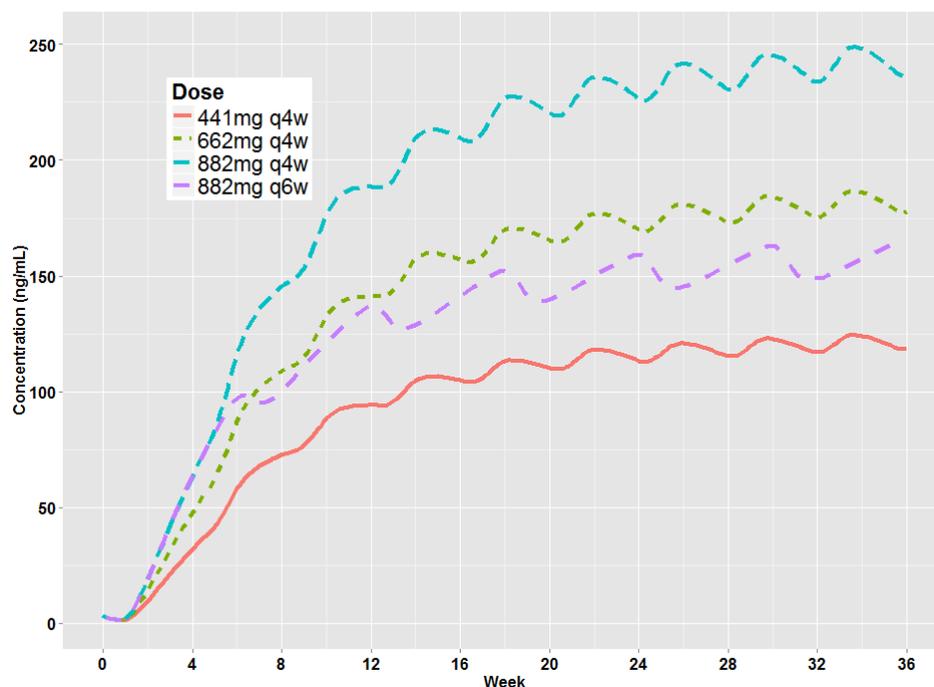


**Figure 4: Simulated Mean aripiprazole Concentration Time Profiles for the 1st and 2nd 882 mg every six weeks Aripiprazole Lauroxil Dose with 21 days of Concurrent Oral ABILIFY Administration**



For maintenance dosing regimens, 441 mg monthly and 882 mg monthly have been demonstrated to be efficacious and well tolerated in the pivotal efficacy trial (Study ALK9072-003). PK simulations were conducted to assess whether 662 mg monthly and 882 mg every six weeks, which have not been evaluated in clinical setting, can be accepted. Steady state mean aripiprazole exposures following 662 mg monthly and 882 mg every six weeks doses are within the steady state mean exposures of 441 mg monthly and 882 mg monthly doses (Figure 5). Therefore, the two unstudied doses, 662 mg monthly and 882 mg every six weeks, are also acceptable.

**Figure 5: Simulated Mean Aripiprazole Concentration Time Profiles following 441 mg, 662 mg and 882 mg Monthly as well as 882 mg every 6 weeks up to Steady State.**

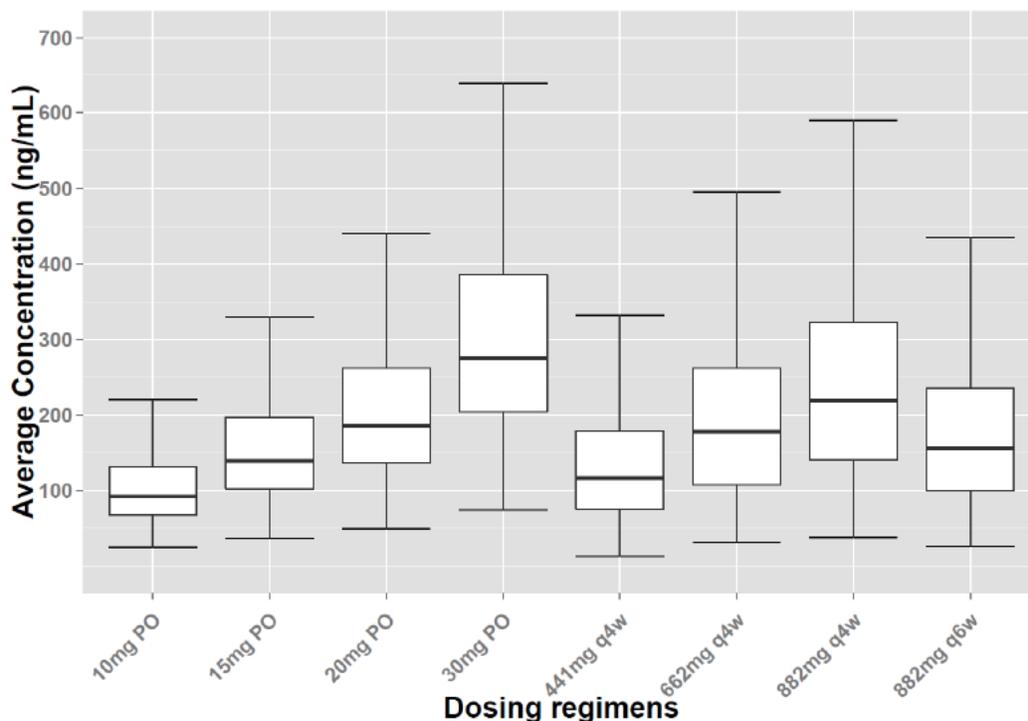


**2.1.3. What are the projected steady state exposure levels of aripiprazole at all dose levels and regimens of Aripiprazole Lauroxil compared to steady state levels for oral ABILIFY?**

The simulated median steady state average concentrations following 441 mg monthly, 662 mg monthly, 882 mg monthly and 882 mg every six weeks are 117 ng/mL, 178 ng/mL, 225 ng/mL, and 150 ng/mL, respectively. They are well within the range of observed exposures following approved oral ABILIFY doses (10mg, 15mg, 20mg and 30mg).

Simulated steady state average concentrations following all dose levels and regimens of Aripiprazole Lauroxil compared to those for oral ABILIFY are shown in **Figure 6**.

**Figure 6: Simulated Average Steady State Aripiprazole Concentrations for IM Depot 441 mg Monthly, 662 mg Monthly, 882 mg Monthly, 882 mg every Six Weeks and Oral 10, 15, 20, and 30 mg Daily Doses.**

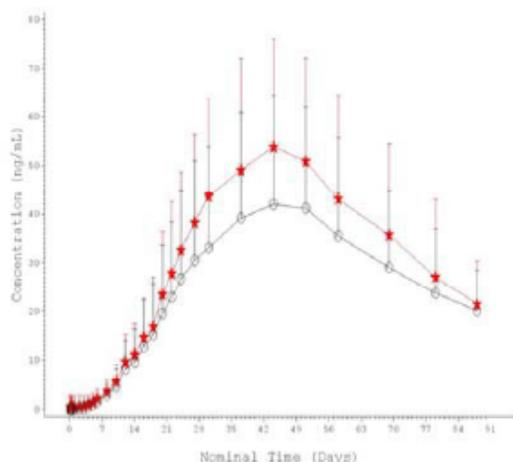


**2.1.4. Can Aripiprazole Lauroxil be administered at both sites- gluteal muscle and deltoid muscle?**

Yes. However, only the 441 mg dose can be injected at both sites. The higher doses (662 mg and 882 mg) are to be injected only at gluteal muscle.

The PK study (ALKS9072-101) performed at 441 mg of aripiprazole lauroxil demonstrates that both gluteal and deltoid sites results in similar exposure of all relevant drug-related moieties. Injection into the deltoid muscle resulted in higher mean exposure to aripiprazole (23%), dehydro-aripiprazole (24%) and *N*-hydroxymethyl-aripiprazole (40%), although the range of exposures observed between the two administration sites overlapped.

**Figure 7: Mean Concentrations of Aripiprazole Following Deltoid or Gluteal Administration of ALKS 9072 300 mg (Deltoid site = filled star, Gluteal site = empty circle)**



**Table 2: Summary of Aripiprazole, Dehydro-aripiprazole and N-hydroxymethyl-Aripiprazole Pharmacokinetic Parameters Following Deltoid or Gluteal Administration of ALKS 9072 300 mg**

Parameters	Aripiprazole		Dehydro-aripiprazole		N-hydroxymethyl-Aripiprazole	
	Deltoid site	Gluteal site	Deltoid site	Gluteal site	Deltoid site	Gluteal site
Cmax (ng/mL)	57.4 (21.6)	46.8 (23.6)	19.8 (7.03)	16.8 (10.8)	6.68 (2.63)	5.84 (3.72)
Tmax (days)	44.1	50	50.7	52.1	37	43
AUC0-last (days·ng /mL)	2744 (1150)	2275 (1077)	904 (365)	815 (539)	263 (145)	243 (190)
AUC0-∞ (days·ng /mL)	3351 (1558)	3598 (746)	1104 (432)	1600 (812)	388 (112)	484 (135)
t1/2 (days)	15.4 (4.64)	19.4 (3.82)	15.9 (2.08)	19.2 (4.56)	73.4 (19.4)	74.7 (21.4)

Data= mean (std. dev)

Additionally, injection site was found not to be a significant covariate in the PopPK model suggesting that deltoid and gluteal sites of administration are interchangeable.

However, the study to assess the effect of “site of injection- deltoid vs. gluteal” was performed at only the lowest dose of 441 mg. Therefore, only the lowest dose is suitable to be dosed into either muscle (deltoid or gluteal). The higher doses (662 and 882 mg) were only studied in gluteal muscle (not in deltoid) and are therefore recommended only for gluteal muscle administration.

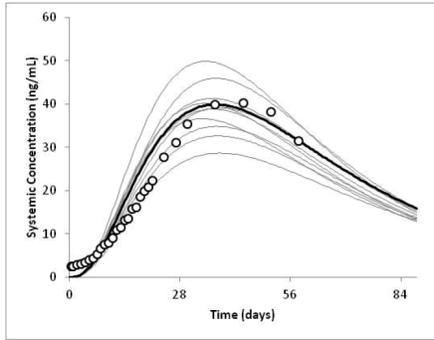
Additionally, there are other differences between the 441 mg dose and higher doses (injection volumes more for higher doses, length of needle more for higher doses). Similarly, the injection sites are also different with significantly higher muscle-mass in gluteal vs. deltoid. Therefore, only 441 mg dose is recommended to both sites (supported by clinical study -ALKS9072-101), whereas, the higher dose injections (662 mg and 882 mg) are recommended only for gluteal injection (since a comparative clinical study at the higher dose is unstudied and untested).

**2.1.5. Was an adequate PBPK model built to predict Aripiprazole PK after IM injection of Aripiprazole Lauroxil?**

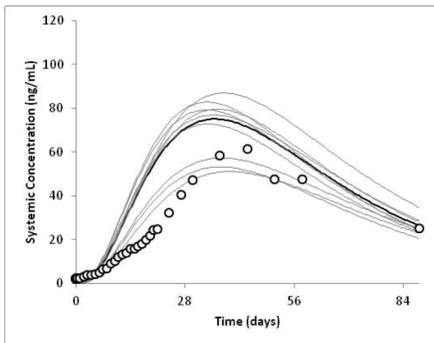
Yes.

A population based PBPK software Simcyp® (V13, release 1, Sheffield, UK) was used to develop the PBPK model for aripiprazole lauroxil. In order to mimic the slow appearance of aripiprazole (after intramuscular injection of aripiprazole lauroxil), sponsor modified the aripiprazole PBPK model by incorporating a skin absorption component to mimic the IM input. All the details about the PBPK model for aripiprazole lauroxil are in the methods section of PBPK report in Section 4. The ability of the PBPK model to predict systemic exposures of Aripiprazole is demonstrated by the figure below.

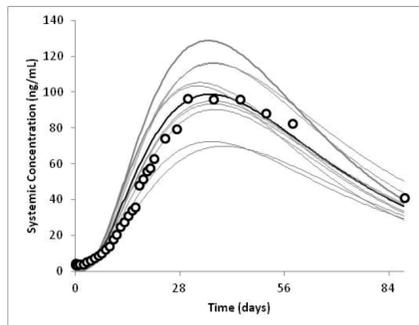
**Figure 8: Simulated (Lines) and Observed (Circles; Clinical Study ALK9072-001) Mean Plasma Concentration-Time Profiles of Aripiprazole following a Single Intramuscular Injection of 150 mg (Upper Panel), 300 mg (Middle Panel), or 400 mg (Lower Panel) Aripiprazole Lauroxil**



The grey lines represent the outcomes of simulated individual trials ( $10 \times 10$ ) and the solid black line is the mean data for the simulated population ( $n=100$ ).



The grey lines represent the outcomes of simulated individual trials ( $10 \times 8$ ) and the solid black line is the mean data for the simulated population ( $n=80$ ).



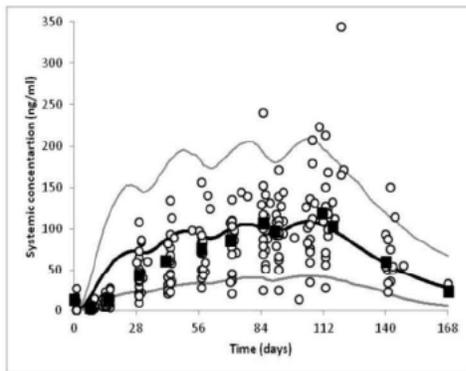
The grey lines represent the outcomes of simulated individual trials ( $10 \times 8$ ) and the solid black line is the mean data for the simulated population ( $n=80$ ).

**2.1.6. Was the PBPK model able to predict Aripiprazole exposures for various CYP2D6 polymorphic subjects (EM, IM and PM's) and what is the recommended dose for patients who are CYP2D6 PM's?**

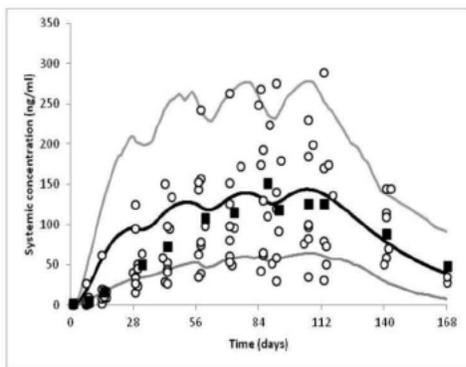
Yes.

As demonstrated in the figure below, the PBPK model was able to estimate the systemic exposures of aripiprazole for different polymorphic populations of CYP2D6.

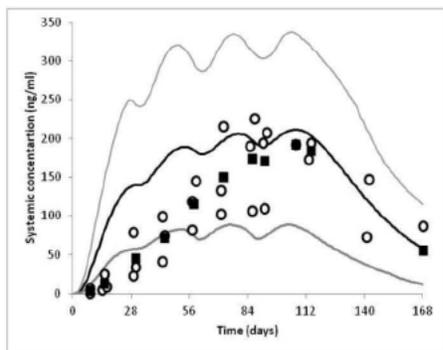
**Figure 9: Simulated (Lines) and Observed (Circles and Square; Clinical Study ALK9072-102) Mean Plasma Concentrations of Aripiprazole in CYP2D6 EMs (Upper Panel, n=25), IMs (Middle Panel, n=12) and PM Subjects (Lower Panel, n=3) following IM Injections of 300 mg Aripiprazole Lauroxil® Administered on Days 1, 29, 57 and 85.**



The solid black line is the mean data and the grey lines are the 5th and 95th percentiles for the simulated population data (n=250). The circles represent individual observed data and the squares are the mean of the observed data.



The solid black line is the mean data and the dashed lines are the 5th and 95th percentiles for the simulated population data (n=120). The circles represent individual observed data and the squares are the mean of the observed data.



The solid black line is the mean data and the dashed lines are the 5th and 95th percentiles for the simulated population data (n=30). The circles represent individual observed data and the squares are the mean of the observed data.

The Table below lists the PBPK predicted geometric Cmax and AUC of aripiprazole after intramuscular injection of Aripiprazole Lauroxil® in subjects with different CYP2D6 genotypes.

	441 mg		662 mg		882 mg		Fold-change from EM <sup>b</sup>	
	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax (ng/mL)	AUC <sup>a</sup> (ng h/mL)	Cmax	AUC
EMs	103	2721	154	4081	206	5442	1	1
IMs	132	3503	198	5254	264	7006	1.3	1.3
PMs	192	5126	287	7688	383	10251	1.9	1.9

<sup>a</sup>AUC calculated as steady state AUC divided by 24 (28 hr interval)

<sup>b</sup>Fold-changes were calculated using geometric mean value (Cmax or AUC) in EMs as denominator for IMs or PMs. Fold change values for IM/EM and PM/EM remain the same for all doses.

Based on the PBPK-model predicted steady state for subjects with different CYP2D6 genotypes, the following dose-adjustment strategy is recommended for PM's:

- To initiate ARISTADA (to aripiprazole naïve patients), start with the lowest dose (441 mg IM injection) and based on tolerability and efficacy, escalate to next higher dose after 2 monthly dosing at a certain level.
- Dose adjustments for patients with different CYP2D6 genotypes for drug-interactions are listed in Question 2.1.7.

**2.1.7. What is the recommended dose for patients taking Aripiprazole Lauroxil injection concomitantly with CYP3A4 modulators and/or CYP2D6 inhibitors on a short-term or long-term basis?**

PBPK-model was utilized to predict the effects of CYP3A4 modulators and CYP2D6 inhibitors on the PK of aripiprazole in subjects receiving intramuscular injection of aripiprazole lauroxil. The effect of concomitant dosing of these modulators was assessed for each dose in CYP2D6 EMs, IMs, or PMs, using the value in EMs without enzyme modulator(s) as reference (Table 3). The recommended dose-adjustments are:

- No dosage changes, if CYP modulators are added for less than 2 weeks
- Dose changes as following if CYP modulators added for greater than 2 weeks
  - o Strong CYP3A4 inhibitor: Reduce the dose of ARISTADA to the next lower strength. Patients on 441 mg ARISTADA can stay on, if tolerated.
  - o CYP2D6 inhibitor: Reduce the dose of ARISTADA to the next lower strength. Patients on 441 mg ARISTADA can stay on, if tolerated. No dose adjustment required for PM's of CYP2D6.
  - o Both CYP3A4 inhibitor and CYP2D6 inhibitor:

- Patient at 662 or 882 mg dose = Avoid use. However, if patients known to be PM's of CYP2D6, then reduce the dose of ARISTADA to the next lower strength.
- Patient at 441 mg dose= Stay on, if tolerated.
- CYP3A4 inducers: No dose adjustment for 662 and 882 mg dose. Increase the 441 mg dose to 662 mg.
- Additionally, dose adjustments as recommended in ABILIFY label should be used for the first 21 days of supplemental oral aripiprazole treatment.

**Table 3: Fold changes of PBPK Predicted Plasma Aripiprazole Exposure (Cmax and AUC, geometric means) from EMs Receiving the Same Dose of Aripiprazole Lauroxil® without CYP modulator(s).**

	Dosing of perpetrator(s)										Source data
	No inhibitor		1 week		2 weeks		3 weeks		4 weeks		
	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC	
EM 441 mg	1.0	1.0									Calculated from Table 1
EM 662 mg	1.5	1.5									
EM 882 mg	2.0	2.0									
Ketoconazole											
EM	1.0	1.0	1.3	1.1	1.4	1.2	1.5	1.4	1.6	1.5	Appendix Table 4
IM	1.3	1.3	1.8	1.5	2.0	1.7	2.3	2.0	2.3	2.1	
PM	1.9	1.9	3.0	2.3	3.8	2.9	4.5	3.5	4.8	3.9	
Quinidine											
EM	1.0	1.0	1.4	1.2	1.6	1.3	1.7	1.5	1.8	1.6	Appendix Table 5
IM	1.3	1.3	1.5	1.4	1.7	1.5	1.8	1.7	1.8	1.7	
PM	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	
Ketoconazole and Quinidine											
EM	1.0	1.0	2.4	1.5	3.3	2.1	4.1	2.9	4.5	3.3	Appendix Table 6
IM	1.3	1.3	2.5	1.8	3.5	2.4	4.2	3.1	4.6	3.5	
PM	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	NC <sup>b</sup>	
Carbamazepine											
EM	1.0	1.0	1.0	0.9	1.0	0.8	1.0	0.8	1.0	0.8	Appendix Table 7
IM	1.3	1.3	1.3	1.1	1.2	1.0	1.2	0.9	1.2	0.9	
PM	1.8	1.9	1.8	1.6	1.8	1.4	1.8	1.2	1.8	1.2	

<sup>a</sup>AUC was calculated as steady state AUC divided by 24 (28 hr interval)

<sup>b</sup>NC: not calculated

Ketoconazole is a strong CYP3A4 inhibitor, Quinidine is CYP2D6 inhibitor

**2.1.8. What is the recommendation for missed IM doses? When should full re-initiation with 21 days of supplemental oral doses be needed after missed IM doses?**

The recommendations for concomitant oral aripiprazole supplementation (7-day partial or 21-day full) for missed IM doses for the different dose levels are listed in Table 4. For the higher dose levels (662 mg and 882 mg monthly, or 882 mg every six weeks), the sponsor proposed recommendations are appropriate. No oral supplementation if the last injection was 8 weeks or less, 7-day partial oral supplementation if last injection was 8-to-12 weeks ago and 21-day full oral supplementation if last injection was greater than 12 weeks ago. However, at 441 mg monthly dose level, simulation results clearly demonstrate that (b) (4) IM injection with partial re-initiation (7 days of oral supplementation) would result in (b) (4) (Figure 10). In contrast, full re-initiation with 21 days of oral supplementation would be appropriate (b) (4) (Figure 11). Moreover, partial re-initiation with 7 days of oral supplementation is acceptable if time since last injection is >6 weeks but ≤7 weeks (Figure 12). Therefore, 7 weeks since last injection should be considered as the appropriate cutoff time point beyond which full re-initiation with 21 days of oral supplementation is needed at 441 mg monthly dose level. For further details, refer to the Pharmacometric Review.

**Table 4: Recommendation for Concomitant Oral Aripiprazole Supplementation Following Missed Doses. (Sponsor’s version with Agency’s recommendations for 441 mg dose)**

Dose of Patients Last ARISTADA Injection	Length of Time Since Last Injection		
	No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole
Monthly 441 mg	≤6 weeks	> 6 and ≤7 weeks	>7weeks
Monthly 662 mg	≤8 weeks	> 8 and ≤12 weeks	>12 weeks
Monthly 882	≤8 weeks	> 8 and ≤12 weeks	>12 weeks

mg			
882 mg every 6 weeks	≤8 weeks	> 8 and ≤12 weeks	>12 weeks

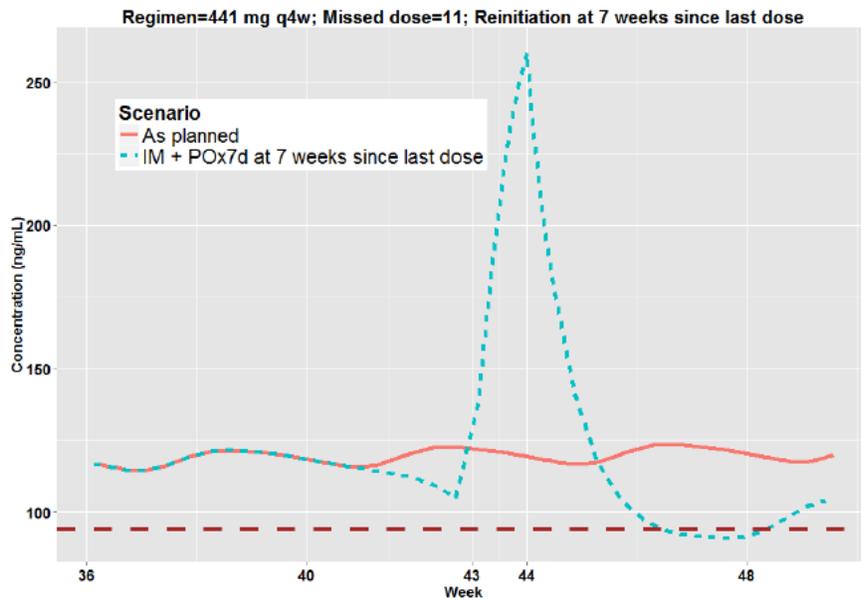
**Figure 10: Simulation for Re-initiation with IM Injection plus 7 days of Oral Doses (b) (4) Since Last Dose after Missing a Dose at Steady State at 441 mg Monthly Dose Level**



**Figure 11: Simulation for Re-initiation with IM Injection plus 21 days of Oral Doses** (b) (4)  
**Since Last Dose after Missing a Dose at Steady State at 441 mg Monthly Dose Level**



**Figure 12: Simulation for Re-initiation with IM Injection plus 7 days of Oral Doses at 7 Weeks Since Last Dose after Missing a Dose at Steady State at 441 mg Monthly Dose Level**



The recommendations for missed doses before steady state, i.e. 2nd and 3rd doses, should be the same as those for missed dose at steady state. (b) (4)

(b) (4)

**Figure 13: Simulation for Re-initiation with IM Injection only at (b) (4) Since the First Dose after Missing the Second Dose at 441 mg Monthly Dose Level**

(b) (4)

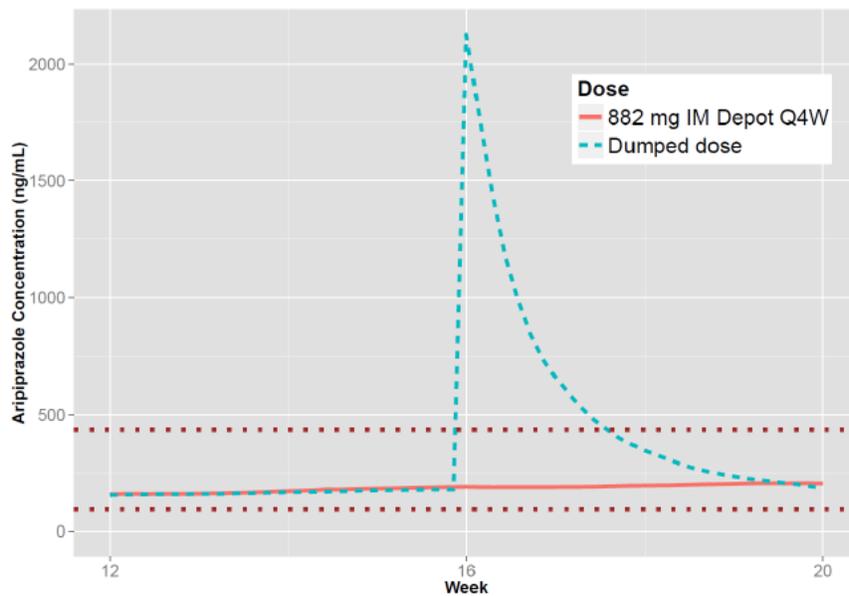
**2.1.9. What is the scenario if there is a dose-dumping after injection of Aripiprazole Lauroxil injection?**

The physiochemical properties of aripiprazole lauroxil (b) (4) make it very unlikely that dose dumping into the systemic circulation would occur. Moreover, no evidence of dose dumping was observed in the clinical trials (four Phase 1 trials) as well as the pivotal trial (study ALK9072-003). None of the subjects in four Phase 1 PK trials showed any rapid or unexplainable rise in exposure of aripiprazole after the IM injection. They all had an expected slow rise in systemic exposures with T<sub>max</sub> at least > 14 days. Similarly, in the pivotal Phase 3 efficacy study, none of the subjects had any unexpected spikes in exposure and aripiprazole levels were below 800 ng/mL from day 30 to day 85. The overall lack of any new or unexpected safety findings with this IM injection compared to the oral aripiprazole also suggests there were no dose-dumping.

Simulated aripiprazole concentrations following dose dumping at steady state (5<sup>th</sup> dose on week 16) of the highest dose level, 882 mg IM depot monthly, would lead to peak concentrations reaching ~2200 ng/mL. These levels would be significantly higher than the established upper

bound of the safe and tolerable margin using the 30 mg oral aripiprazole dose. Additionally, exposures will decline slowly and are likely to remain above acceptable limits for several weeks prior to returning to normal. For further details, refer to the Pharmacometrics Review. Therefore, it is possible that significant safety issues might arise in patients if there were to be dose-dumping.

**Figure 14: Simulated Mean Aripiprazole Concentrations vs. Time for Dose Dumping of 882 mg IM Depot. The upper horizontal dotted line represents observed mean steady-state C<sub>max</sub> at 30 mg QD oral dose and the lower horizontal dotted line represents observed mean steady C<sub>min</sub> at 10 mg QD oral dose.**



## **STANDARD QUESTIONS**

### ***2.1.10. What is the bioavailability of aripiprazole lauroxil IM injection product relative to the approved IR product?***

An adequate link has been established between aripiprazole lauroxil and oral aripiprazole, the reference list product. This PK link was established based on the pharmacokinetic data collected in a clinical trial when aripiprazole lauroxil was administered monthly and oral aripiprazole was given once daily as a supplement for the first 21 days.

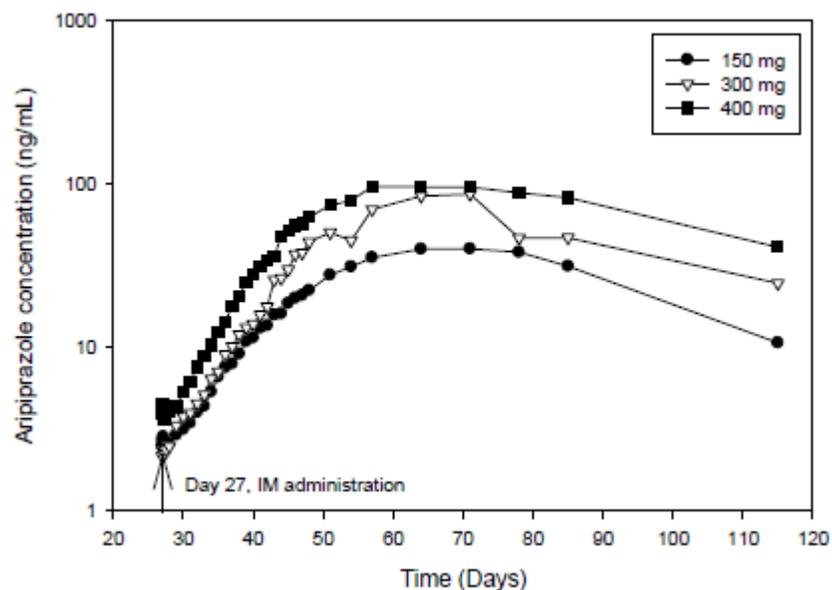
The relative bioavailability of aripiprazole following IM aripiprazole lauroxil was 58% compared to oral aripiprazole, which was derived from population PK modeling by simultaneously fitting oral aripiprazole and IM aripiprazole lauroxil data. Specifically, the bioavailability of aripiprazole following IM aripiprazole lauroxil relative to oral aripiprazole was estimated from the population PK model by fixing the bioavailability of oral aripiprazole to 1.

### ***2.1.11. What are the single-dose PK characteristics of Aripiprazole Lauroxil injection in adult patients?***

The pharmacokinetic profile following a single dose of aripiprazole lauroxil injection in adults meets the expectation for an extended-release formulation and is adequate to support a once monthly or once every 6 weeks dosing for higher doses.

The appearance of aripiprazole in plasma is gradual and prolonged following IM administration of aripiprazole lauroxil due to the slow dissolution of the drug from the injection site. Following a single IM dose, aripiprazole concentrations rose steadily, reaching maximal concentrations in 37-48 days. The mean terminal  $T_{1/2}$  of aripiprazole following aripiprazole lauroxil administration was independent of dose and ranged from 17 to 22 days. Aripiprazole lauroxil concentrations were BLQ in plasma across all clinical studies, including the pivotal efficacy study, ALK9072-003. The highest concentration of *N*-hydroxymethyl aripiprazole was less than 10% of aripiprazole. Dehydro-aripiprazole (active metabolite) exposure (AUC<sub>last</sub>) was approximately 29-35% of that for aripiprazole exposure across all dose levels. The mean terminal  $T_{1/2}$  of dehydro-aripiprazole was consistent with that observed for aripiprazole following aripiprazole lauroxil administration.

### **Figure 15: Mean Concentrations of Aripiprazole Following IM Administration of a single IM dose of Aripiprazole Lauroxil**



**Table 5: Summary of Pharmacokinetic Parameters for Aripiprazole Following a Single-dose Administration of Aripiprazole Lauroxil**

Dose level	Analyte	PK after 1 <sup>st</sup> dose			
		C <sub>max</sub> (ng/mL)	T <sub>max</sub> (day)	AUC <sub>inf</sub> (day*ng/mL)	T <sub>1/2</sub> (day)
221 mg AL	Aripiprazole	43 (22)	38.7 (9.5)	2715 (1275)	17 (3.3)
	Dehydroaripiprazole	14.9 (6.8)	45.6 (11.1)	1020 (435)	20 (5.2)
	N-hydroxymethyl aripiprazole	Not analyzed	Not analyzed	Not analyzed	Not analyzed
441	Aripiprazole	66.3 (32.2)	49 (9.6)	3817 (2382)	22.1 (4.3)

<b>mg AL</b>	Dehydroaripiprazole	21.4 (8.8)	49 (9.7)	NC	NC
	N-hydroxymethyl aripiprazole	Not analyzed	Not analyzed	Not analyzed	Not analyzed
<b>588 mg AL</b>	Aripiprazole	113.6 (32)	44 (11.7)	6229 (499)	18 (4.8)
	Dehydroaripiprazole	32.1 (9.9)	51.8 (15.3)	1819 (221)	17.7 (5.2)
	N-hydroxymethyl aripiprazole	Not analyzed	Not analyzed	Not analyzed	Not analyzed

Aripiprazole lauroxil concentrations were all BLLQ

**2.1.12. What are the multiple-dose PK characteristics of Aripiprazole Lauroxil injection in adult patients?**

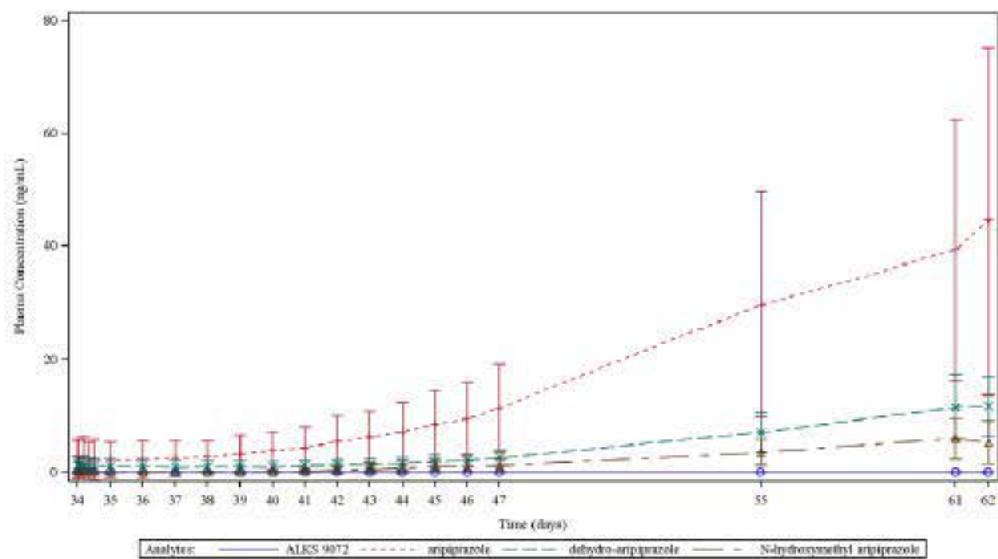
Following four doses of aripiprazole lauroxil, aripiprazole concentrations increased by 9-13-fold when compared to the first dose, and were approaching steady-state. Increases in total systemic exposure following repeated monthly administration of aripiprazole lauroxil were dose proportional over the studied dose range of 441 to 882 mg.

**Table 6: Pharmacokinetic Parameter Summary for IM Aripiprazole Lauroxil after 1st Dose and 4th Dose**

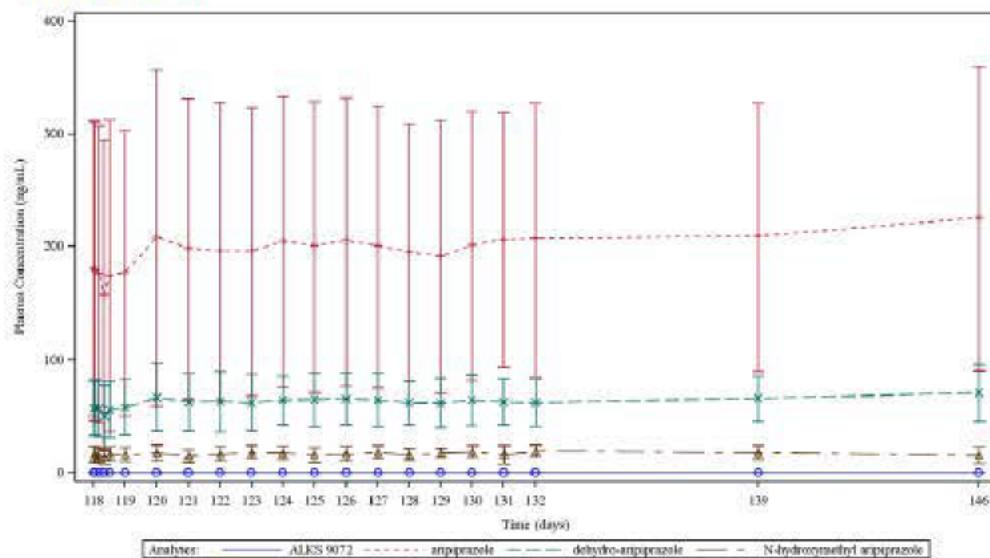
Dose level	Analyte	PK after 1 <sup>st</sup> dose				PK after 4 <sup>th</sup> dose			
		C <sub>max</sub> (ng/mL)	T <sub>max</sub> (day)	AUC <sub>tau</sub> (day*ng/mL)	T <sub>1/2</sub> (day)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (day)	AUC <sub>tau</sub> (day*ng/mL)	T <sub>1/2</sub> (day)
<b>441 mg AL</b>	Aripiprazole	-	-	439 (397)	-	133 (46)	21.1	2937 (954)	29 (6)
	Dehydroaripiprazole	-	-	122 (107)	-	51 (19)	28.1	1087 (406)	30 (6)

	N-hydroxymethyl aripiprazole	-	-	67(80)	-	18 (13)	13	323 (146)	30 (8)
<b>662mg AL</b>	Aripiprazole	-	-	356 (170)	-	207 (79)	28	4458 (1887)	29 (10)
	Dehydroaripiprazole	-	-	108 (67)	-	75 (38)	42	1605 (889)	27 (2)
	N-hydroxymethyl aripiprazole	-	-	43 (31)	-	22 (9)	13	454 (197)	30 (4)
<b>882 mg AL</b>	Aripiprazole	-	-	487 (340)	-	215 (136)	6	5559 (3452)	35 (6)
	Dehydroaripiprazole	-	-	119 (60)	-	73 (27)	12	1700 (624)	34 (6)
	N-hydroxymethyl aripiprazole	-	-	57 (35)	-	21 (6)	3	471 (158)	31 (4)

**Figure 16: Mean ( $\pm$  SD) Plasma Concentration-Time Profiles for All Analytes following the First Dose (top panel) and Fourth Dose (bottom panel) of 882 mg IM Aripiprazole Lauroxil (Days 36-42) (representative figure for all dose levels)**



Source: Figure 14.2.4.1



-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

PRAVEEN BALIMANE  
04/17/2015

XIAOFENG WANG  
04/17/2015

KEVIN M KRUDYS  
04/20/2015

I am also signing on behalf of Ping Zhao, the primary PBPK reviewer.

JEFFREY B KRAFT  
04/20/2015

CHRISTIAN GRIMSTEIN  
04/20/2015

HAO ZHU  
04/20/2015