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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product:	ARISTADA INITIO Aripiprazole lauroxil NanoCrystal® Dispersion (AL-NCD, aripiprazole lauroxil nano and ALKS 9072N)
Indication:	As a starting dose to initiate ARISTADA® (aripiprazole lauroxil) treatment for schizophrenia (b) (4)
Applicant:	Alkermes, Inc.
Review Division:	Psychiatry Products
Reviewer:	Amy M. Avila, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

This application is a 505(b)(2) NDA for aripiprazole lauroxil (ARISTADA INITIO) 675 mg to be administered as an intramuscular (IM) injection. This drug is not approved outside the U.S. The indication is as a starting dose to initiate ARISTADA (aripiprazole lauroxil) treatment for schizophrenia (b) (4) . Aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD), name used by the Applicant, is a new formulation of aripiprazole lauroxil (AL), which differs mainly in particle size with the former in the sub-micrometer range (proposed median particle size range of (b) (4) and the latter in the micrometer range. The two formulations also differ in their excipient profiles. Currently, initiation of treatment of ARISTADA requires the addition of 21-days of oral aripiprazole. The main purpose of ARISTADA INITIO will be to eliminate the need for the 21-days of oral aripiprazole when initiating ARISTADA dosing. The proposed dosing regimen is comprised of a single 675 mg dose of ARISTADA INITIO co-administered with a single oral dose of 30 mg aripiprazole; ARISTADA (up to 1064 mg) will be co-administered at a separate IM injection site.

Late in the review cycle, the Applicant changed the labeled strength of ARISTADA INITIO (b) (4) to 675 mg, which reflects the actual dose strength of the clinical and registration stability batches. This was in response to a recommendation by the Division emphasizing the potential for increased risk of prescribing and product selection errors due to the similarity in the nonproprietary name and dose strength of ARISTADA INITIO and ARISTADA. (b) (4)

(b) (4)

The application relies in part on the Agency's previous findings of safety and effectiveness for oral aripiprazole tablets (NDA 21-436 approved in 2002) and aripiprazole lauroxil (NDA 207533 approved in 2015). Both oral aripiprazole and aripiprazole lauroxil serve as the Listed Drugs (LD) for this NDA.

1.2 Brief Discussion of Nonclinical Findings

This review covers the review of all nonclinical studies with aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD) (drug name used by the Applicant), and a review of additional data and literature submitted to support the approval of ARISTADA INITIO 675 mg. Refer to the nonclinical review under NDA 207533 for a review of all studies with aripiprazole lauroxil (AL).

AL-NCD, like AL, is converted in vivo following intramuscular administration to aripiprazole, which is proposed to act as a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors and as an antagonist at serotonin 5-HT_{2A} receptors. AL-NCD has a faster dissolution profile compared to that of the marketed AL drug product due in part to the smaller drug substance particle size of aripiprazole lauroxil. Faster dissolution of AL-NCD after intramuscular injection results in a more rapid conversion of aripiprazole

lauroxil to aripiprazole. This was evident by increased absorption in rats and dogs, including earlier T_{max} values and higher C_{max} values for circulating aripiprazole in rats and dogs after intramuscular administration of similar doses of AL-NCD compared to AL.

Nonclinical studies conducted with AL-NCD include a 4-week (once weekly injections) intramuscular pharmacokinetic study in rats, and 4-week repeat-dose (once weekly injections) intramuscular toxicity studies in rats and dogs with 4-week recovery periods. CNS, cardiovascular, and respiratory function assessments were incorporated into the dog repeat-dose toxicity study. Dose-related local toxicity at the injection sites was observed at all dose levels in rats and dogs. Clinical signs of swelling at the injection site was observed in both species, and impaired limb function was seen in drug-treated dogs. Macroscopic findings of discoloration and swollen/thickened injection sites were observed in a dose-related manner in rats and dogs. Microscopic findings at the injection sites included granulomas and subacute/chronic inflammation at all dose levels in rats and dogs, and mineralization in mid and high dose dogs. The microscopic findings were not completely reversible 2 months following the last injection, but did show signs of partial reversibility of decreased severity. Similar injection site toxicity was observed in rat and dog repeat-dose toxicity studies with the approved larger particle size aripiprazole lauroxil (AL). A couple of the dogs administered AL-NCD had more severe local toxicity, however the design of the studies conducted with AL-NCD were different, once weekly injections for a month compared to monthly injections in studies conducted with AL. Therefore, an explanation for the increased severity of local injection site toxicity could be due to trauma associated with more frequent IM injections to the same muscle group. The clinically relevant finding of local toxicity at the injection site (injection site reactions) in rats and dogs will be detailed in the animal toxicology section of the label 13.2. Hypersensitivity reactions (reddened skin, excessive scratching, facial swelling, and injected sclera) were observed in a few high dose AL-NCD treated dogs and in all control-treated dogs. Hypersensitivity reactions were observed at a higher frequency in control dogs administered the vehicle compare to high dose AL-NCD treated dogs, therefore the reactions were attributed to excipients in the vehicle, most likely polysorbate-20, which is known in published literature to cause hypersensitivity reactions in dogs. The amount of polysorbate-20 in AL-NCD is higher than that of any FDA approved drug product for intramuscular administration. However, the Applicant provided nonclinical data and information from published literature to adequately qualify the levels of polysorbate-20 in ARISTADA INITIO 675 mg. Overall, nonclinical data submitted with the NDA support the approval of ARISTADA INITIO 675 mg for the indication as a starting dose to initiate ARISTADA treatment or to re-initiate ARISTADA treatment following a missed dose.

1.3 Recommendations

1.3.1 Approvability

The NDA is approvable from a nonclinical perspective.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

The Applicant submitted a separate label for ARISTADA INITIO. Nonclinical language on injection site toxicity with AL-NCD was included in section 13.2. All other nonclinical sections of the label were excerpted from the ARISTADA label. Below is the Applicant's proposed language for section 13.2. At the time this review was finalized, labeling negotiations were still underway with the Applicant.

Animal Data for ARISTADA INITIO (Aripiprazole Lauroxil)
Intramuscular administration of aripiprazole lauroxil to rats and dogs was associated with injection site tissue reactions at all doses in rats treated up to 4 weeks at doses of 15, 29, and 103 mg/animal (which are approximately 0.6 to 4 times and 0.9 to 6 times the MRHD of 675 mg on mg/m2 basis in males and females, respectively) and in dogs treated up to 4 weeks at doses of 147, 662, and 2058 mg/animal (which are approximately 0.7 to 10 times and 1 to 14 times the MRHD in males and females, respectively on mg/m2 basis). These injection site tissue reactions consisted of localized granulomatous inflammation, granuloma formation, and/or subacute/chronic inflammation. Swelling occurred in both species, and transiently impaired limb function was observed in dogs. The granulomas did not completely resolve 2 months following the last injection in the 4-week studies in rats or dogs.

2 Drug Information

2.1 Drug

CAS Registry Number: 1259305-29-7

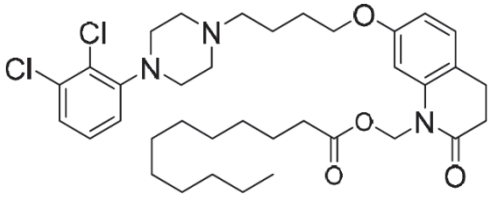
Generic Name: Aripiprazole lauroxil

Code Name: ALKS 9072N, AL-Nano, AL-NCD

Chemical Name: Dodecanoic acid, [7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2-oxo-1(2H)-quinolinyl]methyl ester

Molecular Formula/Molecular Weight: $C_{36}H_{51}Cl_2N_3O_4$ / 660.71 g/mol

Structure or Biochemical Description:



Pharmacologic Class: atypical antipsychotic

The following table summarizes the different names and code names used by the Applicant for each of the different chemical moieties in the drug product. For ease of

review, the same code name AL-NCD was predominantly used in this review. However, other code names (e.g., ALKS 9072N) are used in tables and figures excerpted from the Applicant's submission. It should be noted that the use of the word "nano" does not necessarily mean the drug is being defined scientifically as a nano-sized drug product. The proposed median particle size range for ARISTADA INITIO is [redacted] (b) (4).

Table 1: AL-NCD NDA Program Nomenclature

Common Name or Term	Alkermes Number or Alternative Names	Abbreviation	Comments
aripiprazole lauroxil NanoCrystal® Dispersion	ALKS 9072N aripiprazole lauroxil nano	AL-NCD AL-nano	Not applicable
aripiprazole lauroxil	ALKS 9072 RDC-3317	AL	Drug product formulation contains micrometer-sized particles[a]
aripiprazole	RDC-9864	ARP	Not applicable
dehydro-aripiprazole	RDC-3954	dARP	Not applicable
N-hydroxymethyl aripiprazole	RDC-5792	NHA	Not applicable

[a] "Aripiprazole lauroxil" is used in Module 2.6 to differentiate the chemical moiety from the drug product formulation with micrometer-sized particles (abbreviated as AL)

[Table excerpted from Nonclinical Introduction section of the NDA 209830.]

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 121179 for ALKS 9072N
NDA 207533 for ARISTADA (aripiprazole lauroxil) approved on 10/5/2015
NDA 021-436 for Abilify (oral aripiprazole) approved on 11/15/2002

Both oral aripiprazole and aripiprazole lauroxil serve as the listed drugs for this application.

2.3 Drug Formulation

A white to off-white aqueous extended-release suspension provided in a single-use syringe for intramuscular injection in the deltoid or gluteal muscle at the 675 mg dose strength.

Component	Amount Expressed as		
	amount	w/w%	mg/mL
Aripiprazole lauroxil	675.00 mg	(b) (4)	
Polysorbate 20	(b) (4)		
Sodium citrate dihydrate			
Sodium chloride			
Monobasic sodium phosphate dihydrate			
Dibasic sodium phosphate anhydrous			
Water for Injection			

[Excerpted from Drug Product section of NDA application, SDN 18.]

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product formulation. However, the amount of polysorbate 20 used in the AL-NCD drug product (b) (4) is higher than what is used in the aripiprazole lauroxil drug product (b) (4) (b) (4). In addition, because AL-NCD is intended to be used as initiation treatment for aripiprazole lauroxil and in combination, the total amount of polysorbate 20 delivered to humans is additive between the two products and results in amounts of polysorbate 20 higher than in any currently FDA approved drug product for intramuscular administration. When the two products are administered together, the total amount of polysorbate 20 is (b) (4) (b) (4). Therefore, a nonclinical safety review was conducted on polysorbate 20 as it relates to the amount used in the drug product (see section 10 of NDA review). Overall, the total amount of polysorbate 20 (b) (4) when the two drug products are co-administered is acceptable from a toxicological standpoint. However, because polysorbate 20 is known to cause hypersensitivity reactions in dogs, this reviewer recommends monitoring and possible labeling language for potential allergic reactions in humans.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants that are a concern from a toxicological standpoint. “All impurities are controlled in the drug substance, and no additional impurities or degradation products are observed in the aripiprazole lauroxil NCD (AL-NCD) drug product.” An extractables and leachables assessment was also performed on the AL-NCD vehicle (refer to chemistry review). A specification limit of < (b) (4) ppm was set (b) (4) in the drug product (b) (4) (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

ARISTADA INITIO is only to be used as a starting dose to initiate ARISTADA treatment or to re-initiate ARISTADA treatment following a missed dose of ARISTADA. ARISTADA INITIO is not intended for repeated dosing. The maximum clinical dosing regimen for ARISTADA INITIO and ARISTADA is the following: a single IM dose of 675 mg ARISTADA INITIO, a single 30 mg oral dose of aripiprazole, along with IM administration of ARISTADA up to 1064 mg dosage form. ARISTADA INITIO and ARISTADA can be administered intramuscularly either in the deltoid or gluteal muscle, but should not be administered at the same site.

2.7 Regulatory Background

On February 6, 2018, the Applicant sent the following comments to the Division
"Alkermes acknowledges the potential for increased risk of prescribing and product selection errors due to the similarity in the nonproprietary name and dose strength of AL-NCD and ARISTADA. To address this issue, Alkermes proposes to change the labeled dose of AL-NCD (b) (4) *to 675 mg, which reflects the actual dose strength of the clinical and registration stability batches."*
Preliminary meeting comments for a pre-NDA meeting were sent to the Applicant on May 2, 2107. The Applicant subsequently cancelled the face-to-face meeting.

IND 121179: SDN 14; 10/16/15
Applicant's response to Division's preliminary (written) comments from the End-of-phase 2 meeting received on 9/2/15.
Nonclinical comment to provide a justification for not conducting a combination toxicity study, because AL-NCD is intended to be co-administered with AL and oral aripiprazole. The Applicant provided the following justification in the NDA. AL-NCD and AL will be administered intramuscularly at different sites, therefore there will be no mixing of the two formulations and no concerns from a local tolerability standpoint. In addition, exposures to aripiprazole lauroxil and (b) (4) N-hydroxymethyl aripiprazole were higher in rats and dogs after IM administration of AL-NCD in the 4-week repeat-dose toxicity studies compared to the maximum clinical dosing regimen (i.e., a single IM dose of AL-NCD, a single 30 mg oral administration of aripiprazole, along with IM administration of AL up to 1064 mg) indicating adequate nonclinical coverage.

3 Studies Submitted

3.1 Studies Reviewed

Table 4: List of Studies Provided in Module 4

Alkermes Study No.	Vendor Study No.	Report Title
4.2.2 Pharmacokinetics		
4.2.2.1 Analytical Methods and Validation Reports		
AV-9072-07	(b) (4)13-247	Quantitative Determination of RDC-3317, RDC-9864, RDC-3954, and RDC-5792 in Extract from Treated Rat Plasma (EDTA) by LC/MS/MS
4.2.2.2 Absorption		
AT-3317-27	(b) (4)825-112	Once Weekly (Four Doses) Intramuscular Toxicokinetic Study of a Nanocrystal Coloidal Dispersion Formulation of Aripiprazole Lauroxil (ALKS 9072N) in Rats
4.2.3 Toxicology		
4.2.3.2 Repeat-dose Toxicity		
AT-3317-25	(b) (4)825-097	Once Weekly Once Weekly (Four Doses) Intramuscular Toxicity Study of a Nanocrystal Colloidal Dispersion Formulation of Aripiprazole Lauroxil (ALKS 9072N) in Rats with a 4-Week Recovery Period
AT-3317-26	(b) (4)825-098	Once Weekly (Four Doses) Intramuscular Toxicity Study of a Nanocrystal Colloidal Dispersion Formulation of Aripiprazole Lauroxil (ALKS 9072N) in Dogs with a 4-Week Recovery Period
4.2.3.7 Other Toxicity Studies		
4.2.3.7.7. Other		
LSC17-103	N/A	Polysorbate 20 White Paper: Nonclinical Safety Evaluation of Polysorbate 20

A series of in vitro and in vivo evaluations were completed to assess the biocompatibility of (b) (4) of aripiprazole lauroxil (results reported in Alkermes' Technical Report 702-06730). The Applicant concluded that the *"results from these studies established biocompatibility, with in vivo tests supporting compliance to USP* (b) (4)*."*
See review of the technical report under section 10 of this review.

3.2 Studies Not Reviewed

NA

3.3 Previous Reviews Referenced

Nonclinical review for NDA 207533

4 Pharmacology

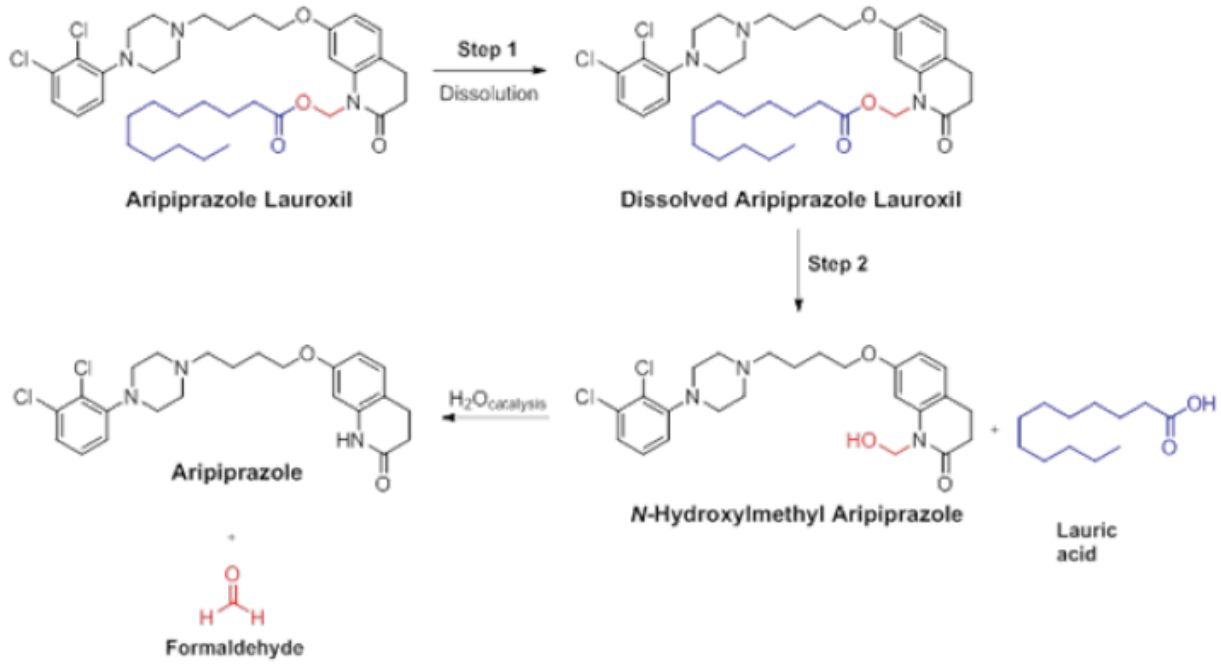
No pharmacology studies were conducted with AL-NCD because the only difference between it and aripiprazole lauroxil is the particle size, which should have no significant impact on the pharmacology of the drug. AL-NCD is converted in vivo following intramuscular administration to aripiprazole. Aripiprazole is believed to exert its pharmacological activity through a combination of partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors.

Safety pharmacology endpoints, neurofunctional, cardiovascular, and respiratory were incorporated into the dog repeat-dose toxicity study. Details of the procedures and results are included under review of that study in section 6.2.

5.1 PK/ADME

Conversion of AL-NCD to aripiprazole in vivo following intramuscular administration is governed by dissolution of the drug particles followed by hydrolysis. The conversion process is similar for both AL-NCD and the currently marketed micro-particle sized formulation of aripiprazole lauroxil (AL). The main difference between the two formulations is the aripiprazole lauroxil particle size, and the excipient profile. The drug particle size of AL-NCD is in the range of (b) (4), compared to a particle size in the range of (b) (4) in the currently marketed formulation (AL). The smaller particle size in the AL-NCD formulation results in faster dissolution than the micro-particle sized aripiprazole lauroxil, and therefore a faster appearance of circulating aripiprazole. The formulation of AL-NCD evaluated in the animal pharmacokinetic and toxicity studies is identical to the proposed commercial formulation, consisting of (b) (4) (average) particles of aripiprazole lauroxil (b) (4)% w/w) and containing (b) (4) polysorbate 20 at a concentration of (b) (4)% (w/w). The amount of (b) (4), polysorbate 20, and the aripiprazole lauroxil particle size are the main differences between the two formulations and factors that affect the dissolution rates and hence the amount of systemic exposure. This review discusses the PK/TK data with AL-NCD; for a review of PK studies with aripiprazole lauroxil refer to the nonclinical review for NDA 207533.

Figure 1: Conversion of Aripiprazole Lauroxil to Aripiprazole

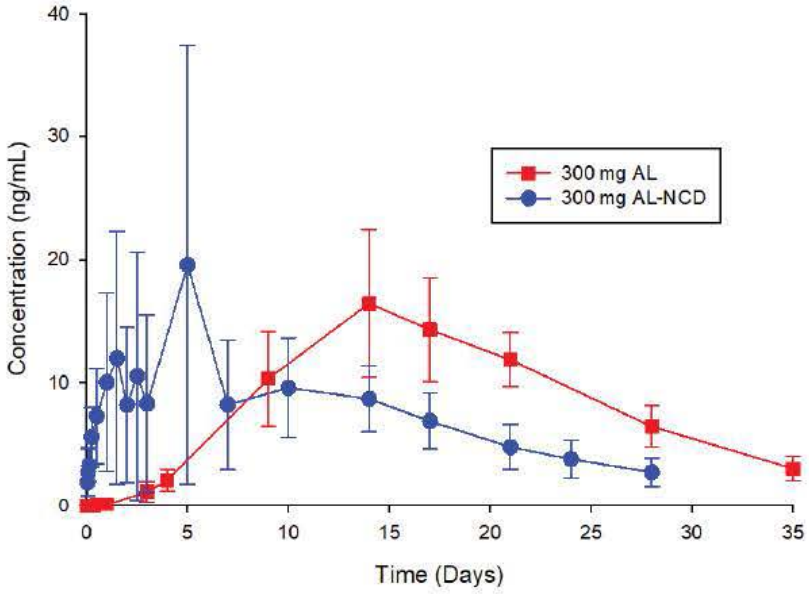


[Figure excerpted from Nonclinical Introduction section of NDA 209830.]

The faster dissolution rate results in increased absorption of the drug. Plasma or blood concentrations of aripiprazole and aripiprazole lauroxil following IM administration of AL-NCD and AL were compared in rats and dogs (although not in the same study). However, a direct comparison of AUC values could not be made due to differences in the dosing paradigm between studies with each formulation; the studies with AL-NCD used once weekly injections for 4-weeks and the studies with the larger particle sized formulation of AL used once monthly injections. Earlier T_{max} and higher C_{max} values for aripiprazole were observed in rats and dogs following single IM administrations of AL-NCD compared to AL.

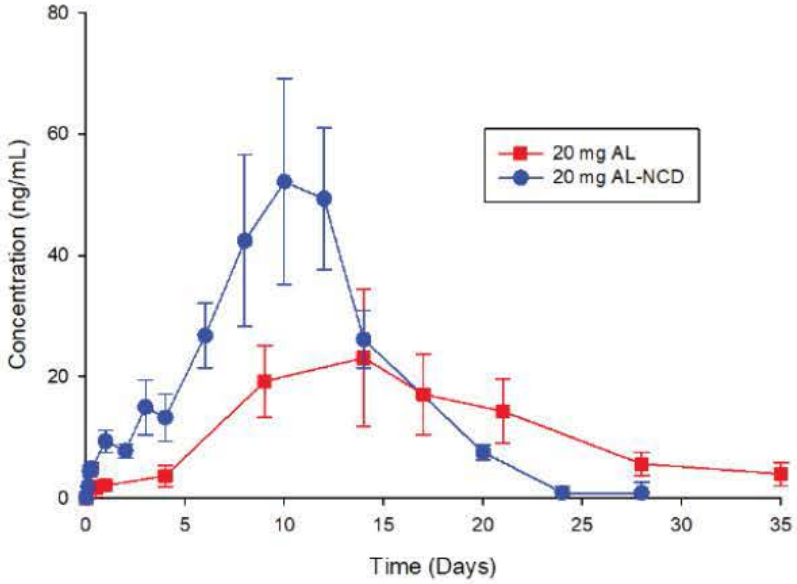
The mean aripiprazole T_{max} and C_{max} values were 5 days and 19.6 ng/ml, respectively following IM administration of 300 mg AL-NCD compared with 14 days and 16.4 ng/ml, respectively, following IM administration of 300 mg AL. Although T_{max} was reached at similar times in rats following a single IM administration of AL-NCD or AL of equal doses, C_{max} values were higher in rats given AL-NCD compared to those administered AL.

Figure 13: Mean (±SD) Concentration of Aripiprazole in Whole Blood Following a Single IM Administration of 300 mg AL-NCD or AL to Beagle Dogs



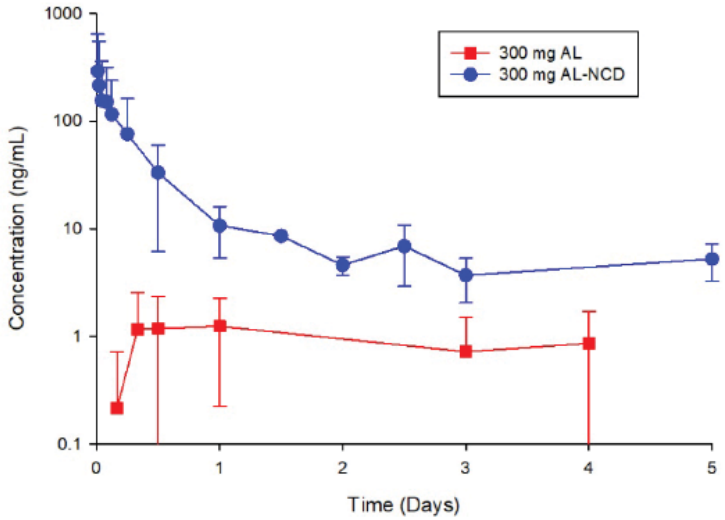
Source: AK-RDC-3317NCD-005, AT-3317-05

Figure 14: Mean (±SD) Concentration of Aripiprazole in Whole Blood Following a Single IM Administration of 20 mg AL-NCD or AL to Rats



Source: LSC15-121, AT-3317-04

Figure 15: Mean (±SD) Concentration of AL in Whole Blood Following a Single IM Administration of 300 mg AL-NCD or AL to Beagle Dogs



Source: AK-RDC-3317NCD-005, AT-3317-05

[Graphs excerpted from Pharmacokinetic written summary section of NDA 209830.]

5.2 Toxicokinetics

Study Title: Once Weekly (Four Doses) Intramuscular Toxicokinetic Study of a Nanocrystal Colloidal Dispersion Formulation of Aripiprazole Lauroxil (ALKS 9072N) in Rats

Study no.: AT-3317-27
Study report location: NDA 209830 SDN 1
Conducting laboratory and location (b) (4)

Date of study initiation: September 26, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: ALKS 9072N drug product, Lot Number: 467-0002AB, 99.6%

Purpose of the study: *"ALKS 9072N was evaluated in a previous toxicity study in rats (b) (4) Study Number 825-097), and as noted in Section 8.2.3.2, uncertainty in plasma exposure data for aripiprazole and N-hydroxymethyl aripiprazole in this study prompted the conduct of the current study. Aripiprazole lauroxil (also known as RDC-3317 and ALKS 9072) also has been evaluated in previous toxicity studies in rats (e.g., (b) (4) Study Numbers 825-022, 825-042, and 825-052). ALKS 9072N was evaluated in (b) (4) (b) (4) Study Number 825-097."*

Design:

Male and female Sprague-Dawley rats were administered ALKS 9072N or vehicle once weekly (Days 1, 8, 15, and 22) by intramuscular injection for four weeks.

Study Design

Group Number	Dose Level[a] (mg/animal)	Dose Volume (mL/site)	Dose Concentration[a] (mg/mL)	Number of Animals[e] Male	Number of Animals[e] Female
1	0[b]	0.2	0	4	4
2	10[c]	0.2	50	7	7
3	20[c]	0.2	100	7	7
4	70[b,d]	0.19	185	7	7

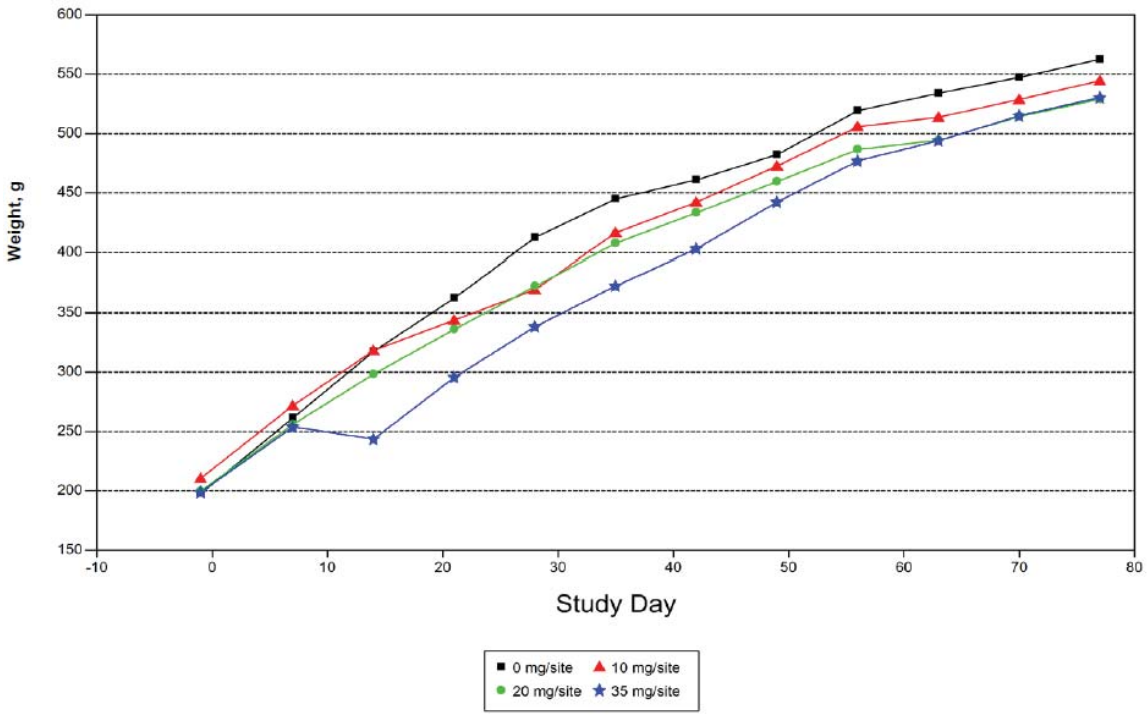
[a] Aripiprazole equivalents. Doses and concentrations of ALKS 9072N are 1.473 times greater based on molecular weights of 660.70 and 448.39 for ALKS 9072N and aripiprazole, respectively.
[b] Two injection sites, one in each hind limb.
[c] One injection site rotated weekly (i.e., first and third doses in the left hind limb; second and fourth doses in the right hind limb). Doses expressed as mg/site are equivalent to mg/animal for Groups 2 and 3.
[d] Total dose of 70 mg/animal. (35 mg/site)
[e] One extra animal /sex/group for possible replacement.

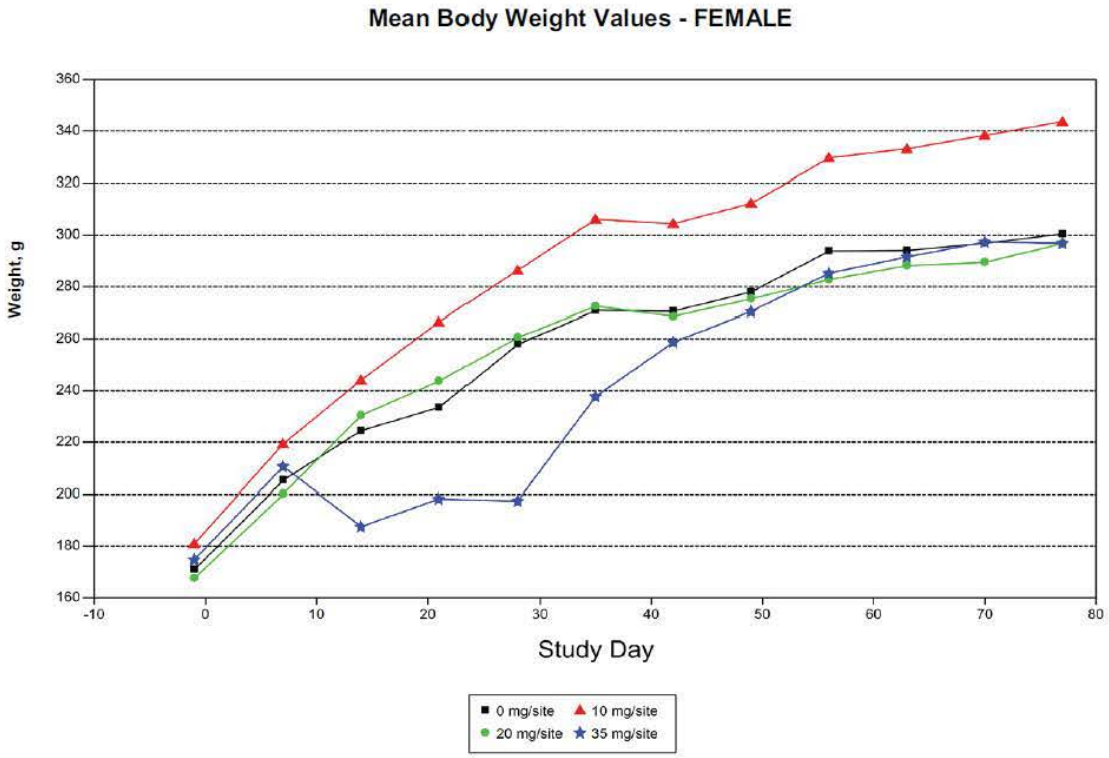
Parameters evaluated: mortality, clinical signs, body weight, and toxicokinetic assessment of ALKS 9072 (also known as RDC-3317 and aripiprazole lauroxil), RDC-9864 (aripiprazole), RDC-3954 (dehydro-aripiprazole) and RDC-5792 (N-hydroxymethyl aripiprazole) in whole blood. Whole blood samples were collected from the 0 mg/animal group at 24, 360, 840, 1848 hours postdose. Samples were collected from 10, 20, and 70 mg/animal groups at 12, 24, 96, 168, 192, 264, 336, 360, 432, 504, 516, 528, 600, 672, 840, 1008, 1176, 1344, 1512, 1680, and 1848 hours postdose.

Results:
All dose formulations were homogeneous and concentration values were within ± 10% of nominal. Two animals were euthanized prematurely due to poor condition. A male at 10 mg/animal was euthanized *in extremis* on day 23 and prior to euthanasia the animal was observed with clinical signs of audible/difficult breathing, decreased activity, both eyes completely closed, malocclusion, red material around muzzle/nose, red material in bedding/pan, rales, and sneezing. Macroscopic examination revealed swollen/thickened left limb at injection sites, malocclusion and the small intestine mildly distended with gas. No definitive cause of death was listed in the study report. A female at 70 mg/animal was also euthanized on day 23. The animal's health was declining and euthanasia was recommended due to a mechanical injury to its mouth and vocalization when handled; therefore, the premature death was not considered drug-related. Prior to euthanasia this animal showed clinical signs of hunched posture, decreased activity, both eyelids partially or completely closed, mechanical injury/mandible malaligned, porphyrin staining, and swelling and erythema at dose sites. Macroscopic examination revealed swollen/thickened injection sites, pale skin discoloration of both hind limbs at injection sites, and absent/ broken/ malocclusion/ overgrown teeth. Clinical signs

observed only in high dose animals included decreased activity, eyelids partially or fully closed, hair or skin discolored, hypersensitivity to touch, tremors, and vocalization. A few animals at 70 mg/animal were noted as thin and were given additional food by the veterinary staff. Swelling in the hind limbs at the injection sites was observed in all animals included controls, however it was much more frequent and pronounced in high dose animals. Swelling at the injection site(s) was first observed in the high dose animals on day 2 and then by days 9 or 16 at ≤ 20 mg/animal. Mean body weight values were 16-23% lower than controls for males and females at 70 mg/animal by week 2. However, body weight gain for this group was comparable to or greater than controls by week 3 for males or week 5 for females, suggesting complete reversibility.
The toxicokinetic analysis revealed no significant sex difference in exposure to ALKS 9072, RDC 9864, RDC 3954, and RDC 5792, therefore the exposure data were presented as males and females combined. Exposure to all analytes increased less than or roughly equal to dose-proportional on day 1 and greater than dose proportional on day 22. Except for ALKS 9072 at 10 and 20 mg/animal, exposure levels (both C_{max} and AUC) increased after repeated dosing from day 1 to day 22, with the greatest increase in exposure seen for RDC 9864 and RDC 3954 (>30-fold increase in AUC from day 1 to day 22). T_{max} values decreased after repeated dosing, from 168 hours on day 1, to 12 hours on day 22 for analytes RDC 9864, RDC 3954, and RDC 5792, and from 96 to 168 hours on day 1, to 24 hours on day 22 for ALKS 9072.

Mean Body Weight Values - MALE





Summary of Toxicokinetic Parameters - ALKS 9072				
Dose (mg/animal)[a]	Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-168} (hr•ng/mL)
10	1	5.82	168	389
	22	4.19	0	NA[b]
20	1	50.0	168	1980
	22	4.73	24	253
70	1	8.02	96	1140
	22	68.6	24	3940

[a]Aripiprazole equivalents
[b]Not reported due to a percent extrapolated greater than 25%.

Note: $AUC_{0-1176\ hr}$ exposure for ALKS 9072 (which reflected exposure up to the terminal necropsy in (b) (4) Study Number 825-097) was 996, 3090, and 20300 hr*ng/mL at 10, 20, and 70 mg/animal (35 mg/site), respectively.

Summary of Toxicokinetic Parameters - RDC 9864				
Dose (mg/animal) [a]	Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-168} (hr•ng/mL)
10	1	27.5	168	3300
	22	54.2	12	4910
20	1	35.1	168	3220
	22	125	24	12600
70	1	110	168	7880
	22	2310	12	303000

[a]Aripiprazole equivalents

Note: $AUC_{0-1176\ hr}$ exposure for RDC 9864 (which reflected exposure up to the terminal necropsy in [redacted] (b) (4) Study Number 825-097) was 19800, 42000, and 76700 hr*ng/mL at 10, 20, and 70 mg/animal (35 mg/site), respectively.

Summary of Toxicokinetic Parameters - RDC 3954				
Dose (mg/animal) [a]	Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-168} (hr•ng/mL)
10	1	2.16	168	243
	22	5.65	12	470
20	1	3.65	168	309
	22	16.1	24	1640
70	1	16.3	168	1010
	22	327	12	39400

[a]Aripiprazole equivalents

Note: $AUC_{0-1176\ hr}$ exposure for RDC3954 (which reflected exposure up to the terminal necropsy in [redacted] (b) (4) Study Number 825-097) was 1640, 5380, and 113000 hr*ng/mL at 10, 20, and 70 mg/animal (35 mg/site), respectively.

Summary of Toxicokinetic Parameters - RDC 5792				
Dose (mg/animal)[a]	Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-168} (hr•ng/mL)
10	1	49.9	168	5370
	22	67.5	12	6840
20	1	60.5	168	5430
	22	121	12	15800
70	1	185	168	13200
	22	485	12	66700

[a]Aripiprazole equivalents

Note: $AUC_{0-1176\ hr}$ exposure for RDC 5792 (which reflected exposure up to the terminal necropsy in (b) (4) Study Number 825-097) was 30100, 60900, and 252000 hr*ng/mL at 10, 20, and 70 mg/animal (35 mg/site), respectively.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were conducted.

6.2 Repeat-Dose Toxicity

Study title: Once weekly (four doses) intramuscular toxicity study of a nanocrystal colloidal dispersion formulation of aripiprazole lauroxil (ALKS 9072N) in dogs with a 4-week recovery period

Study no.:	AT-3317-26
Study report location:	NDA 209830 (from IND 121179) EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 14, 2014
GLP compliance:	Yes
QA statement:	Yes, date of amended final report: 2/28/17
Drug, lot #, and % purity:	ALKS 9072N drug product used in toxicology studies was supplied in 30 ml plastic bottles containing formulation B, lot no. DEX0068577-A for drug product, 99.95%

Key Study Findings

Dose-related local toxicity observed at all dose levels, which included granulomas, inflammation, and mineralization at the injection site. Impaired hind limb function and/or hind limb swelling was observed mainly at the high dose. Hypersensitivity reactions occurred in vehicle and high dose animals, attributed to excipients in the vehicle. Signs of local injection site toxicity were partially, but not completely, reversible at 2 months following the last injection.
NOAEL = 1400 mg/animal for systemic toxicity. No NOEL for local injection site toxicity.

Methods

Doses:	0, 100, 450, 700 mg aripiprazole equivalents/site Total for high dose = 1400 mg (divided into 700 mg/site) Equivalent to aripiprazole lauroxil doses of: 0, 147, 662, 2058 mg/animal
Frequency of dosing:	Once weekly (days 1, 8, 15, and 22)
Route of administration:	Intramuscular in hind limbs (both hind limbs for control and high dose groups), alternating hind limbs (1 site/week) for low and mid dose groups. The high dose was divided; 350 mg was injected to each hind limb. The vehicle group also received injections into each hind limb.
Dose volume:	3.7, 2, 2.4, 3.7 ml/site, respectively
Formulation/Vehicle/Control:	Nanocrystal colloidal dispersion formulation. ALKS 9072N Vehicle containing: (b) (4) polysorbate 20; sodium citrate dihydrate; sodium chloride, puriss; sodium phosphate monobasic (dihydrate); (b) (4) sodium phosphate dibasic (anhydrous); (b) (4) water for injection
Species/Strain:	Dog/Beagle (experimentally naïve) from (b) (4)
Number/Sex/Group:	5/sex/group
Age:	~6-7 months old at receipt
Weight:	Males: 8.40-10.69 kg, females: 6.50-8.40 kg: at randomization
Satellite groups:	3/sex/group were sacrificed on day 50, 28 days following last administration. 2/sex/group were allowed to recover for an additional 28 days and sacrificed on day 78.
Unique study design:	All animals were administered a 25 mg tablet of hydroxyzine 30 min. prior to sedation for dosing to treat hypersensitivity reactions. 4 mg/kg diphenhydramine was administered 15 min. prior to dosing. Animals were sedated with IV Dexdomitor (medetomidine) to effect (up to 0.5 mg/ml). Then animals were dosed with either vehicle or test article using a 21-gauge needle. Following dosing, each animal received antisedan (atipamezole) IM to wake up. 4 mg/kg diphenhydramine was administered IM within 5 min. of dosing if needed, based on evidence of

hypersensitivity reaction.

Deviation from study protocol: None that affected the overall outcome of the study.

Group Assignments

Group Number	Dose Level (mg/site)	Dose Volume (mL/site)	Dose Concentration[a] (mg/mL)	Number of Animals	
				Male	Female
1	0[b]	3.7	0	5[e]	5[e]
2	100[c]	2	50	5[e]	5[e]
3	450[c]	2.4	186.7	5[e]	5[e]
4	700[b,d]	3.7	186.7	5[e]	5[e]

[a] Aripiprazole equivalents. Doses and concentrations of ALKS 9072N are 1.473 times greater based on molecular weights of 660.70 and 448.39 for ALKS 9072N and aripiprazole, respectively.
[b] Two injection sites, one in each hind limb.
[c] One injection site rotated weekly (i.e., first and third doses in the left hind limb; second and fourth doses in the right hind limb)
[d] Total dose of 1400 mg/day
[e] Three animals/sex/group were submitted for terminal necropsy on Day 50, 28 days following the last administration. The last two animals/sex/group were allowed to recover for an additional 28 days.

Observations and Results

Mortality

None

Clinical Signs

All animals (males and females) in the control groups along with 1 high dose male and 3 high dose females showed signs of a hypersensitivity reaction including reddened skin following dosing on day 1. Additional signs in most of those animals included excessive scratching, facial swelling, and injected sclera. These animals were administered an additional dose of diphenhydramine and responded positively. There were no clinical signs of systemic toxicity. Drug-related signs of local toxicity were observed mainly in high dose animals and included impaired hind limb function and/or hind limb swelling. The findings were transient but sometimes required administration of an anti-inflammatory (rimadyl). A few drug-treated animals were observed to have decreased activity, but this finding could have been secondary to the impaired limb function and/or diphenhydramine treatment as well. One high dose female had an isolated incidence of tremors on day 8 only, but it was not considered drug-related. The same high dose female also developed an open, draining abscess on day 23. The animal was treated with meloxicam, baytril, and nolvasan and responded to treatment. The abscess was not considered drug-related because there was no dose or time response and the

contralateral hind limb was not affected. The abscess was considered most likely a bacterial infection secondary to the injection procedure. Reddened skin was still observed in 2 high dose females at the end of the 2-month recovery period. Vomiting was also observed in 2 high dose males at the end of the recovery period. Cageside observations were conducted twice daily, and detailed observations were conducted once weekly during the study.

Functional Observation Battery (FOB)

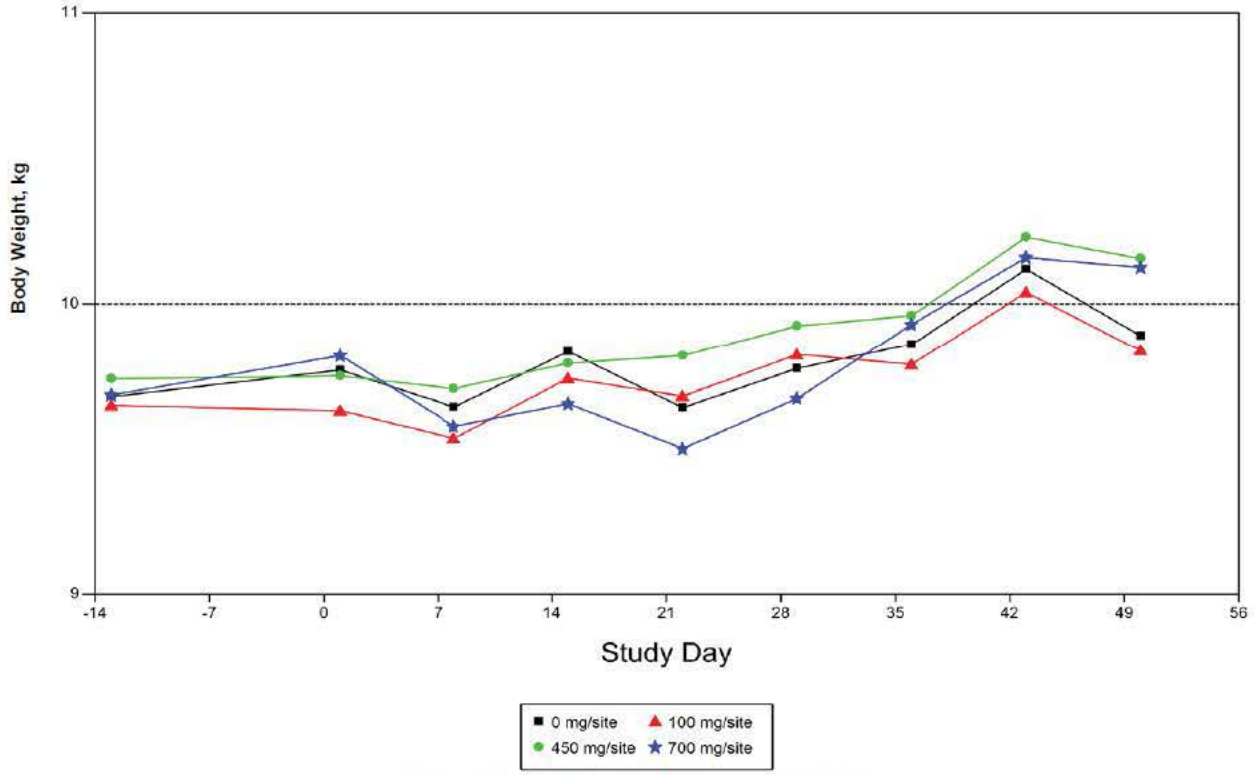
There was a decrease in activity/arousal and rearing for all groups, including controls, from pretest to day 2 values. The decrease was greatest in the high dose animals, which may be due to impaired hind limb function and swelling in those animals, therefore secondary to the local toxicity and not a direct effect. There were no changes in any of the other FOB assessments.

FOB assessments were conducted on all animals at pretest and again 24 hrs. following the first dose by testers that were blinded to the treatment groups. The parameters evaluated in the FOB were based on those outlined in Haggerty1. The observations included, but were not limited to, evaluation of activity and arousal, posture, rearing, locomotor activity, bizarre behavior, clonic and tonic movements, gait, mobility, limb position, limb and body tone, carriage, stereotypy, righting reflex, response to stimulus (approach, click, and touch), palpebral closure, pupil response, pupil size, piloerection, exophthalmus, lacrimation, salivation, and respiration. Qualitative and/or quantitative measures of defecation and urination were also recorded. Body weight and body temperature was also recorded.

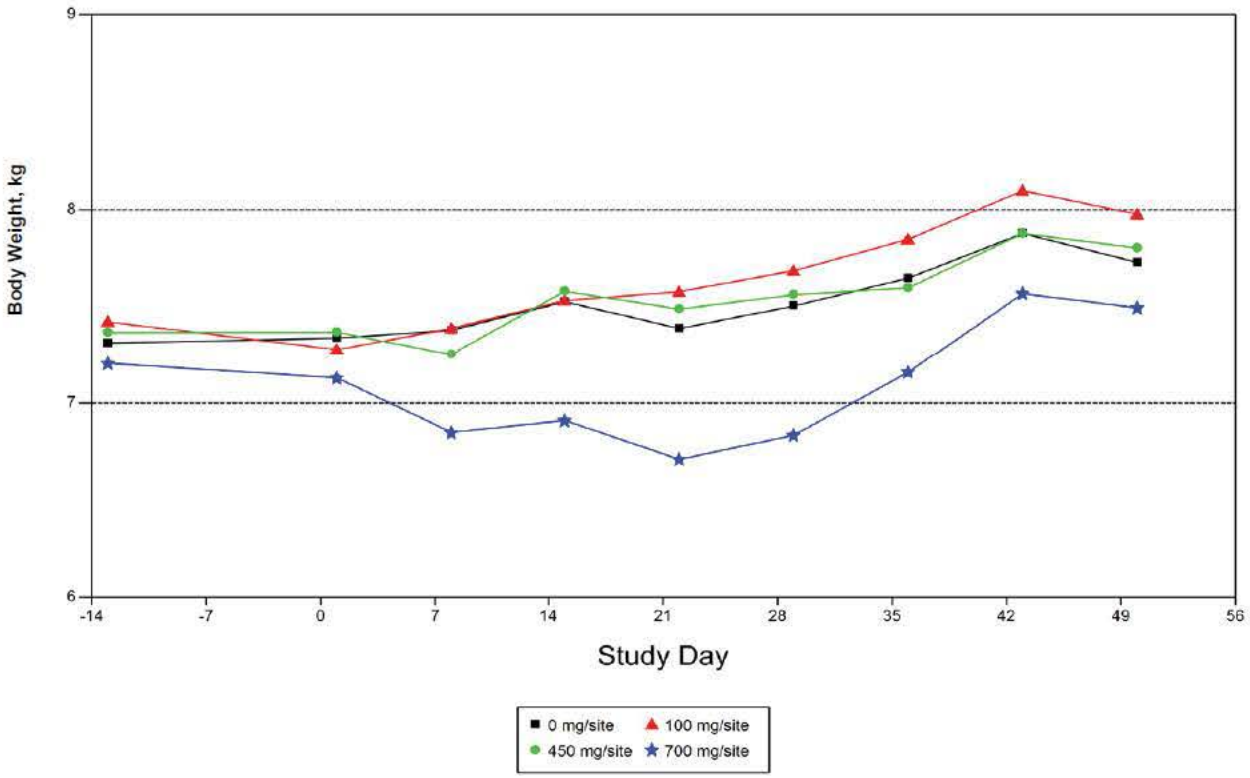
Body Weights

There was no statistically significant effect on body weight in any drug treated group either during the main study phase or recovery phase. However, high dose females lost body weight during the first 3 weeks of the study an overall body weight values for high dose females were decreased compared to controls throughout the entire study. Body weights for high dose females were comparable to all other dose groups during the recovery phase. The effects on body weight for high dose females correlated with effects on food consumption compared to controls. Body weights were recorded at the time of animal receipt, prior to randomization and weekly throughout the study.

Mean Body Weight Values - MALE

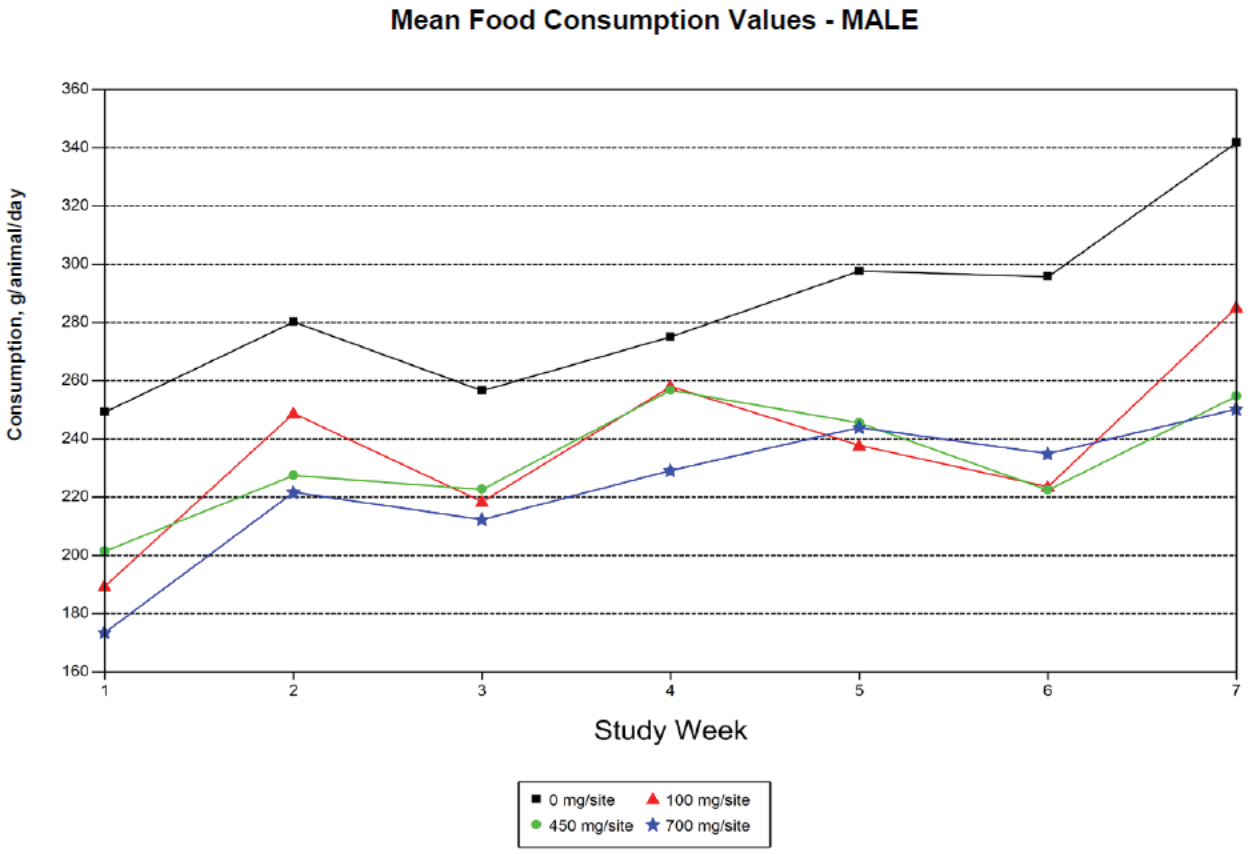


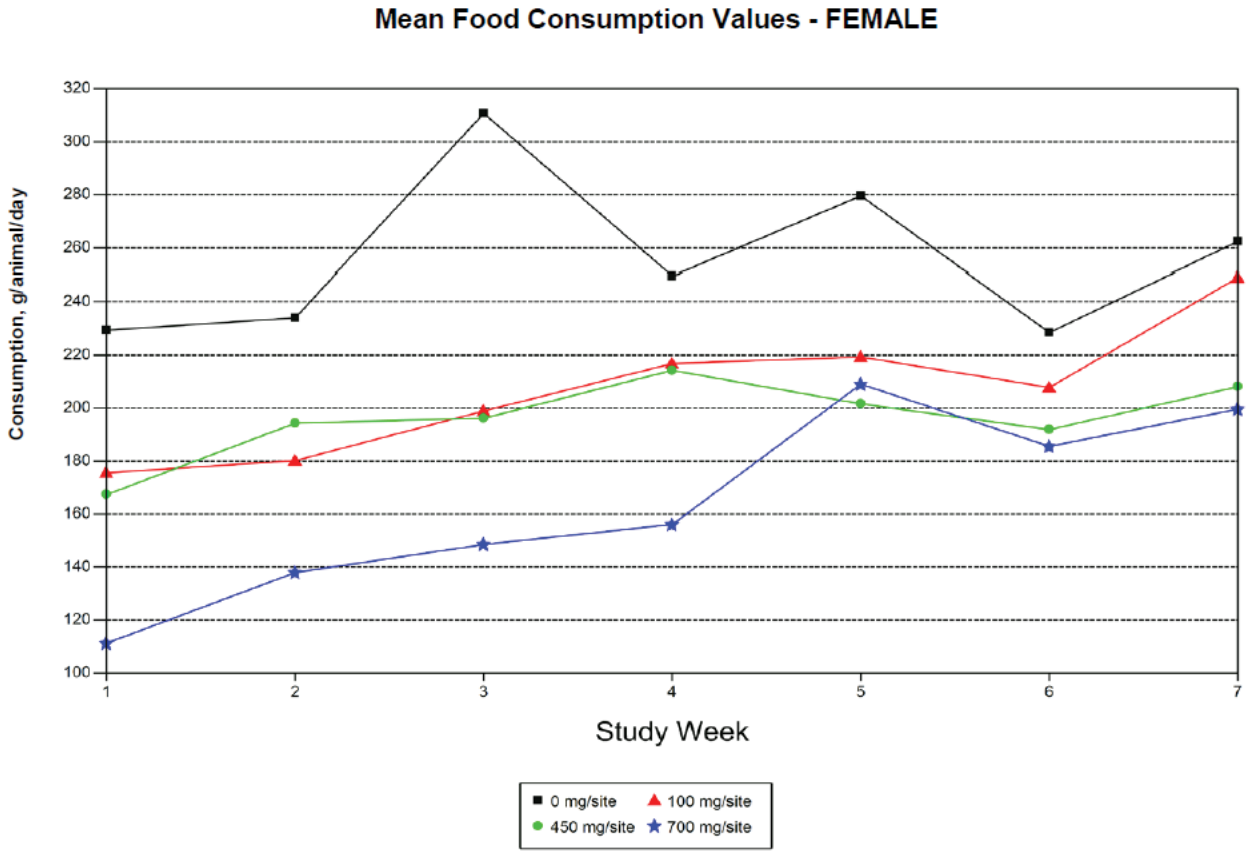
Mean Body Weight Values - FEMALE



Food Consumption

There were several instances of statistically significant decreases in food consumption for males and females at 450 and 1400 mg compared to controls. On average, drug-treated animals consumed less food than control animals during the dosing phase of the study. This was most evident for high dose females which corresponded to the effect on body weight.
Food consumption was measured and recorded weekly throughout the study.





Ophthalmoscopy

There were no findings in any group.
Eye exams were conducted on all animals at pretest and prior to terminal and recovery necropsies by a veterinary ophthalmologist.

ECG

There were no drug-related findings in any ECG parameters.
ECGs were recorded on all animals at pretest and 22-26 hrs. following the fourth dose. All tracings were evaluated and reported by a consulting veterinary cardiologist. QT_c values were calculated using Fridericia's formula.

Indirect blood pressure, heart rate

There were no drug-related findings.
The heart rate and blood pressure of each animal was measured and recorded pretest, 22 to 26 hours following the fourth dose, and prior to the terminal necropsy.

Pulmonary evaluations

There were no drug-related findings.
Pulmonary evaluations were conducted on all animals while animals were awake and confined in a sling. Pulmonary parameters evaluated include respiratory rate, tidal volume, and minute volume. Pulmonary parameters were monitored for at least 2 hours prior to the second dose and for at least 2 hours on either the first or second day postdose.

Hematology

There were no toxicologically significant drug-related findings. All effects were considered within the expected ranges for biological and/or procedure-related variation. Blood samples were collected from all animals via the jugular vein at pretest and prior to terminal and recovery necropsies. An adequate battery of hematology and coagulation parameters was evaluated.

Clinical Chemistry

There were no toxicologically significant drug-related findings. All effects were considered within the excepted ranges for biological and/or procedure-related variation. Blood samples were collected from all animals via the jugular vein at pretest and prior to terminal and recovery necropsies. An adequate battery of clinical chemistry parameters was evaluated.

Urinalysis

There were no toxicologically significant drug-related findings. All effects were considered within the excepted ranges for biological and/or procedure-related variation. Urine samples were collected using steel pans placed under the cages for at least 16 hours.

Gross Pathology

Macroscopic findings of discoloration and swollen/thickened injection sites were observed at all dose levels, with the incidence and severity being clearly dose-related. The findings were partially reversible after the 2-month recovery period, as only minimal to mild discoloration was observed in 1 or 2 animals at the mid and high dose but not fully recovered. The macroscopic findings correlated with microscopic findings at the injection site of granulomas and/or inflammation.

Test Article-related Macroscopic Observations – 1-Month Recovery									
Dose level: mg aripiprazole equivalents/animal		0		100		450		1400[a]	
Sex		M	F	M	F	M	F	M	F
Number Examined		3	3	3	3	3	3	3	3
Injection site, left, intramuscular									
Discoloration, tan		0	0	1	0	2	2	2	3
	-minimal	0	0	1	0	1	1	0	0
	-mild	0	0	0	0	1	1	1	3
	-severe	0	0	0	0	0	0	1	0
Swollen thickened,									
	-mild	0	0	0	0	0	0	1	0
Injection site, right, intramuscular									
Discoloration, tan		0	0	0	0	3	2	2	2
	-minimal	0	0	0	0	1	1	1	0
	-mild	0	0	0	0	2	1	0	1
	-severe	0	0	0	0	0	0	1	1
Swollen thickened,									
	-mild	0	0	0	0	0	0	1	0

M - Male
F - Female
[a] = one injection of 700 mg in each leg; total of 1400 mg aripiprazole equivalents/animal

Test Article-related Macroscopic Observations – 2-Month Recovery									
Dose level: mg aripiprazole equivalents/animal		0		100		450		1400[a]	
Sex		M	F	M	F	M	F	M	F
Number Examined		2	2	2	2	2	2	2	2
Injection site, left, intramuscular									
Discoloration, tan									
	-minimal	0	0	0	0	0	1	1	0
Injection site, right, intramuscular									
Discoloration, tan		0	0	0	0	1	1	2	0
	-minimal	0	0	0	0	1	1	1	0
	-mild	0	0	0	0	0	0	1	0

M - Male
F - Female
[a] = one injection of 700 mg in each leg; total of 1400 mg aripiprazole equivalents/animal

Organ Weights

Absolute and relative thymus weights were increased for males and females from all drug-treated groups. However, the increases were not dose-dependent or statistically significant and there were no corresponding microscopic findings therefore the findings were not considered toxicologically relevant. Similarly, absolute and relative thyroid weights were decreased in females at all dose levels, but the effects were not statistically significant and there were no corresponding microscopic findings and therefore were also not considered toxicologically relevant.

Histopathology

Adequate Battery: Yes
Peer Review: Yes
Histological Findings: Local toxicity at injection site only. No systemic toxicity findings were observed. At the 1-month post last dose necropsy, drug-related local toxicity was observed at the injection sites of animals at all dose levels and included granulomas, inflammation and/or mineralization. The incidence and severity was clearly dose-related. Only minimal inflammation was observed in one control female, which was attributed to trauma due to repeat IM injections at the same muscle group. A minimal granuloma was observed in only one animal at 100 mg. The granulomas were characterized by discrete organized areas of macrophages and/or giant cells forming a "wall" around a central core of necrotic and/or foreign material. Additional cell infiltrates sometimes included lymphocytes and fibroblasts primarily around the periphery of the lesion. Some granulomas contained focal mineralization. The following text is excerpted from the study report.

> Two animals had microscopic findings at the injection site that were different from other animals. One female (animal number 832) at 1400 mg aripiprazole equivalents/animal (700 mg/site) had inflammation characterized primarily by macrophages and lesser numbers of fibroblasts and lymphocytes (granulomatous inflammation) diffusely infiltrating muscle and connective tissue at the injection sites without evidence of overall organization of a typical granuloma but did have multiple small granulomas scattered throughout the inflammation. Associated with the granulomatous inflammation, there was mineral deposition and increased skeletal muscle degeneration compared to other animals given the test article. One male (animal number 816) at 100 mg aripiprazole equivalents/animal did not have macrophage dominated inflammation but had increased connective tissue between and within muscle bundles and associated muscle degeneration, increased numbers of new small blood vessels (neovascularization), and occasional infiltrates of mononuclear cells including macrophages containing pigment.

The applicant did not consider the microscopic findings to be adverse, because they did not affect the overall health of the animals and it is a normal reaction to multiple IM injections. However, this reviewer considers these findings to be adverse. At the end of the 2-month recovery period, there were still findings of granulomas and/or inflammation at all dose levels, including controls. There was some evidence of partial reversibility as the severity level was decreased but full recovery was not evident. The sponsor noted that the inflammatory response to the drug at the time of tissue collection varied depending on the length of time between injection and necropsy, and that the observed inflammation may also in part be due to trauma associated with multiple IM injections to the same muscle group. It should be noted that the general toxicity studies conducted with the larger particle size drug formulation (studies conducted for approval of ARISTADA under NDA 207533) were once monthly injections, not once weekly as was conducted for this study, therefore more severe signs of local injection site toxicity, especially inflammation, in the current studies may in part be due to more frequent IM injections. Of note, these findings were observed even when the animals were pre-treated with antihistamines and analgesics.

Test Article-related Microscopic Observations – 1-Month Recovery								
Dose level: mg aripiprazole equivalents/animal	0		100		450		1400[a]	
Sex	M	F	M	F	M	F	M	F
Number Examined	3	3	3	3	3	3	3	3
Injection site, left, intramuscular								
Granuloma	0	0	0	0	2	2	3	2
-mild	0	0	0	0	1	2	0	2
-moderate	0	0	0	0	1	0	2	0
-severe	0	0	0	0	0	0	1	0
Inflammation, granulomatous								
-mild	0	0	0	0	0	0	0	1
Inflammation, subacute/chronic	0	0	1	0	0	1	1	0
-minimal	0	0	0	0	0	1	1	0
-mild	0	0	1	0	0	0	0	0
Mineralization	0	0	0	0	2	1	2	2
-minimal	0	0	0	0	2	1	0	1
-mild	0	0	0	0	0	0	2	1
Injection site, right, intramuscular								
Granuloma	0	0	0	1	3	2	3	2
-minimal	0	0	0	1	0	0	0	0
-mild	0	0	0	0	2	1	0	0
-moderate	0	0	0	0	1	1	1	2
-severe	0	0	0	0	0	0	2	0
Inflammation, granulomatous								
-moderate	0	0	0	0	0	0	0	1
Inflammation, subacute/chronic								
-minimal	0	1	0	0	0	0	0	0
Mineralization	0	0	0	0	1	1	3	2
-minimal	0	0	0	0	1	1	1	1
-mild	0	0	0	0	0	0	2	1
Injection site, right, lumbar (epaxial), intramuscular								
Inflammation, granulomatous								
-severe	0	0	0	0	0	0	0	1

M - Male
F - Female
[a] = one injection of 700 mg in each leg; total of 1400 mg aripiprazole equivalents/animal

Test Article-related Microscopic Observations – 2-Month Recovery								
Dose level: mg aripiprazole equivalents/animal	0		100		450		1400[a]	
Sex	M	F	M	F	M	F	M	F
Number Examined	2	2	2	2	2	2	2	2
Injection site, left, intramuscular								
Granuloma	0	0	0	0	0	1	2	1
-minimal	0	0	0	0	0	0	1	0
-mild	0	0	0	0	0	1	1	1
-moderate	0	0	0	0	0	0	0	0
Inflammation, granulomatous								
-mild	0	0	0	0	1	0	0	0
Inflammation, subacute/chronic								
-minimal	1	1	0	0	0	0	1	1
Injection site, right, intramuscular								
Granuloma	0	0	0	0	0	1	2	0
-mild	0	0	0	0	0	1	1	0
-moderate	0	0	0	0	0	0	1	0
Inflammation, granulomatous								
-mild	0	0	0	0	2	0	0	0
Inflammation, subacute/chronic	1	0	1	0	2	1	1	0
-minimal	1	0	1	0	0	1	0	0
-mild	0	0	0	0	2	0	1	0

M - Male
F - Female
[a] = one injection of 700 mg in each leg; total of 1400 mg aripiprazole equivalents/animal

Toxicokinetics

Blood samples were collected from treated animals at 12, 24, 96, 168, 192, 264, 336, 360, 432, 504, 516, 528, 600, 672, 840, 1008, 1176, 1344, 1512, 1680 and 1848 hours following the first dose and from control animals at 24, 360, 840, and 1848 hours following the first dose. Samples on dosing days were collected predose.
ALKS 9072 = aripiprazole lauroxil, ALKS 9864 = aripiprazole, ALKS 3954 = dehydro-aripiprazole, ALKS 5792 = N-hydroxy (b) (4)

There were no gender differences in exposure levels for any of the moieties, therefore all male and female values were combined. The T_{max} for aripiprazole lauroxil was 12 hrs., and T_{max} values for the other analytes average about 24 hrs., but ranged from 24-168 hrs. There was no increase in exposure levels over time from day 1 to day 22 for aripiprazole lauroxil, but there was large amount of accumulation over time for each of the other analytes (over 10-fold increase in AUC and C_{max} values at the 1400 mg dose). Exposure levels of aripiprazole, the dehydro- metabolite and the N-hydroxy (b) (4) were roughly equivalent, compared to exposure levels of aripiprazole lauroxil on day 22 which were much lower. It should be noted that C_{max} levels of all 4 analytes after administration of AL-NCD are higher than after administration of the micron formulation (AL).

Summary of Toxicokinetic Parameters - ALKS 9072					
Dose (mg/site) [a]	Day	$AUC_{0\text{-}168}$ (hr•ng/mL)	$AUC_{0\text{-}tlast}$ (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
100	1	1560	1540	36.5	NA
	22	1390	1380	26.9	NA
450	1	3780	3780	81.8	12
	22	5660	5660	155	12
700	1	12500	12500	196	12
	22	15500	15500	304	12
[a] Aripiprazole equivalents					

Summary of Toxicokinetic Parameters - RDC-9864					
Dose (mg/site) [a]	Day	$AUC_{0\text{-}168}$ (hr•ng/mL)	$AUC_{0\text{-}tlast}$ (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
100	1	1590	1590	15.6	24
	22	2860	2860	31.8	24
450	1	3400	3400	29.9	24
	22	15600	15600	174	24
700	1	11500	11500	107	96
	22	160000	160000	2180	24
[a] Aripiprazole equivalents					

Summary of Toxicokinetic Parameters - RDC 3954					
Dose (mg/site) [a]	Day	$AUC_{0\text{-}168}$ (hr•ng/mL)	$AUC_{0\text{-}tlast}$ (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
100	1	1210	1210	13.9	24
	22	2290	2290	27.8	24
450	1	3180	3180	33.8	24
	22	16200	16200	186	24
700	1	13900	13900	127	24
	22	122000	122000	1310	24
[a] Aripiprazole equivalents					

Summary of Toxicokinetic Parameters - RDC 5792					
Dose (mg/site) [a]	Day	AUC_{0-168} (hr•ng/mL)	$AUC_{0-tlast}$ (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
100	1	3920	3920	36.4	24
	22	6130	6130	61.3	24
450	1	7620	7620	64.5	96
	22	29100	29100	253	24
700	1	25500	25500	200	168
	22	120000	120000	1340	24
[a] Aripiprazole equivalents					

Dosing Solution Analysis

The results of the homogeneity and concentration analyses were within the acceptable ranges.

Study title: Once weekly (four doses) intramuscular toxicity study of a nanocrystal colloidal dispersion formulation of aripiprazole lauroxil (ALKS 9072N) in rats with a 4-week recovery period

Study no.:	AT-3317-25
Study report location:	NDA 209830(from IND 121179) EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 28, 2014
GLP compliance:	Yes
QA statement:	Yes, final amended study report dated 2/27/17
Drug, lot #, and % purity:	ALKS 9072N drug product used in toxicology studies was supplied in 30 ml plastic bottles containing formulation B, lot no. DEX0068577-A for drug product, 99.95%.

Key Study Findings

One high dose female was sacrificed moribund; death was considered drug-related. Decrease in body weight for high dose males and females that correlated with a decrease in food consumption and was completely reversible. Local injection site toxicity of granulomas and subacute/chronic inflammation observed at all dose levels, frequency and severity was dose-related, partial reversibility. Drug-related swelling at the injection site at all doses, fully reversible.

NOAEL = 20 mg/animal for males and females due to decreased body weight at higher doses in males and females and death in a high dose female. No NOEL for local injection site toxicity.

Methods

Doses:	0, 10, 20, 35 mg/site (total dose = 0, 10, 20, 70 mg aripiprazole equivalents) Equivalent to aripiprazole lauroxil doses of: 0, 15, 29, 103 mg/animal
Frequency of dosing:	Once weekly for 4 weeks (on days 1, 8, 15, and 22)
Route of administration:	Intramuscular to hind limbs. The low and mid dose groups received one injection to alternating hind limbs. The control and high dose groups received 2 injections to both hind limbs.
Dose volume:	0.2, 0.2, 0.2, 0.19 ml/site for the control, 10, 20, and 35 mg/site groups
Formulation/Vehicle:	Nanocrystal colloidal dispersion formulation. ALKS 9072N Vehicle containing: (b) (4) polysorbate 20; sodium citrate dihydrate; sodium chloride, puriss; sodium phosphate monobasic (dihydrate); (b) (4) sodium phosphate dibasic (anhydrous); (b) (4) water for injection
Species/Strain:	Rat/Sprague-Dawley (CD) from (b) (4)
Number/Sex/Group:	16/sex/group
Age:	6 weeks at receipt
Weight:	At randomization: males: 234-275 g, females: 172-215 g
Satellite groups:	Toxicokinetics group: 6/sex/drug-treated groups and 3/sex/control groups
Unique study design:	10 animals/sex/group were necropsied on day 50 (28 days following the last dose). The remaining 6 animals/sex/group were allowed to recover for an additional 28 days and necropsied 2-months following the last dose.
Deviation from study protocol:	None that affected the outcome of the study.

Group Assignments			
Group Number	Dose Level[a] (mg/site)	Number of Animals	
		Male	Female
	Main Study		
1	0[b]	16[e]	16[e]
2	10[c]	16[e]	16[e]
3	20[c]	16[e]	16[e]
4	35[b,d]	16[e]	16[e]
	Toxicokinetic		
5	0[b]	3	3
6	10[c]	6	6
7	20[c]	6	6
8	35[b,d]	6	6

[a] Aripiprazole equivalents. Doses and concentrations of ALKS 9072N are 1.473 times greater based on molecular weights of 660.70 and 448.39 for ALKS 9072N and aripiprazole, respectively.
[b] Two injection sites, one in each hind limb.
[c] One injection site rotated weekly (i.e., first and third doses in the left hind limb; second and fourth doses in the right hind limb).
[d] Total dose of 70 mg/day.
[e] 10 animals/sex/group were submitted for terminal necropsy on Day 50, 28 days following the last administration. The last 6 animals/sex/group were allowed to recover for an additional 28 days.

Observations and Results

Mortality

One high dose female was sacrificed moribund on day 22. The following details regarding the condition of the animal are excerpted from the study report. "*Prior to euthanasia, this animal lost a significant amount of body weight (pretest weight, 187 g; Day 21 weight, 141 g). The animal exhibited the following: thinness; hunched posture; red stained muzzle/nose; and decreased activity. On Day 22 the animal was noted by the veterinary staff as declining in health status. Euthanasia was recommended. Macroscopic observations in this animal included depletion of body fat and bilateral swollen/thickened injection sites with tan foci/focus. Microscopic findings included severe granulomas and mild myofiber degeneration/necrosis in both injection sites. Likely associated with the inflammation at the injection sites, an increased proportion of immature myeloid cells (left shift) was present in the bone marrow. Minimal individual hepatocyte necrosis was present in the liver and the thymus had moderate decrease of lymphocytes. The cause of clinical signs and need for euthanasia could not be determined by macroscopic or microscopic examination of tissues. This death was potentially test article-related.*"

This reviewer agrees that this death could be drug related.

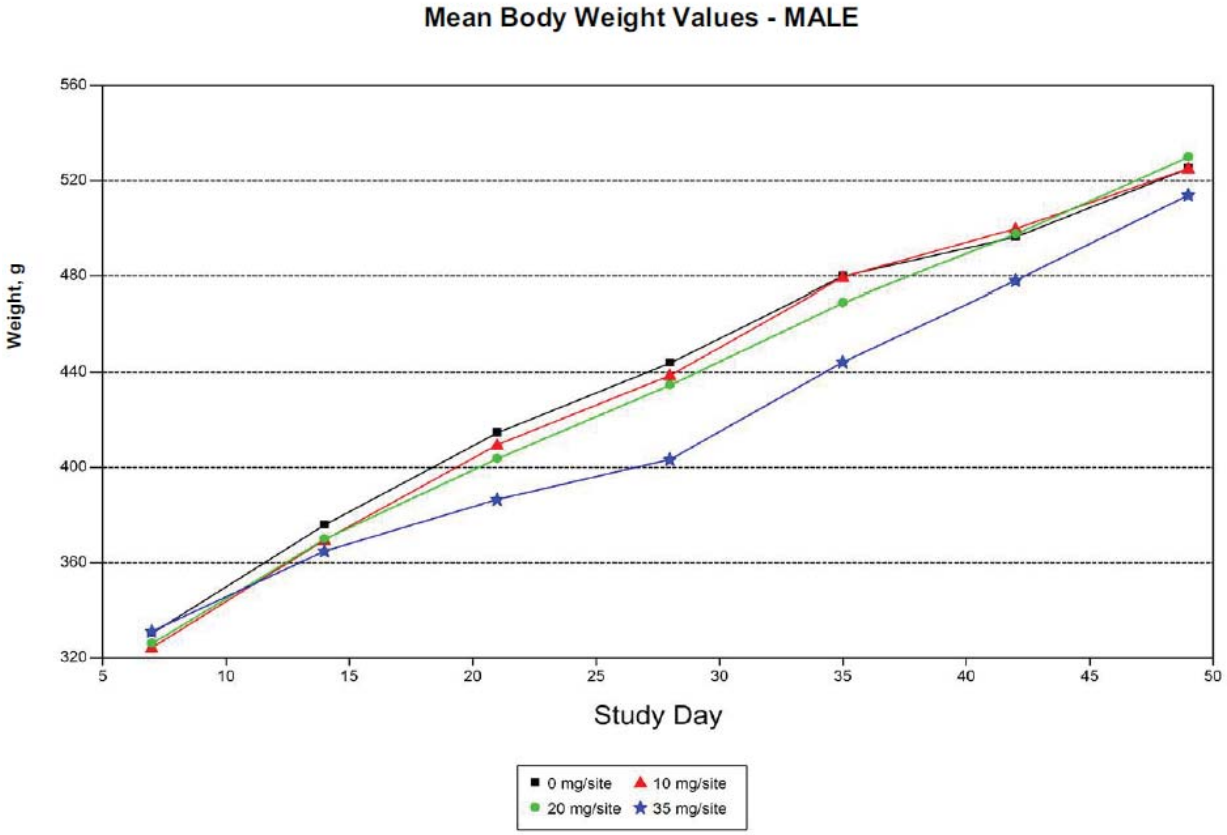
Clinical Signs

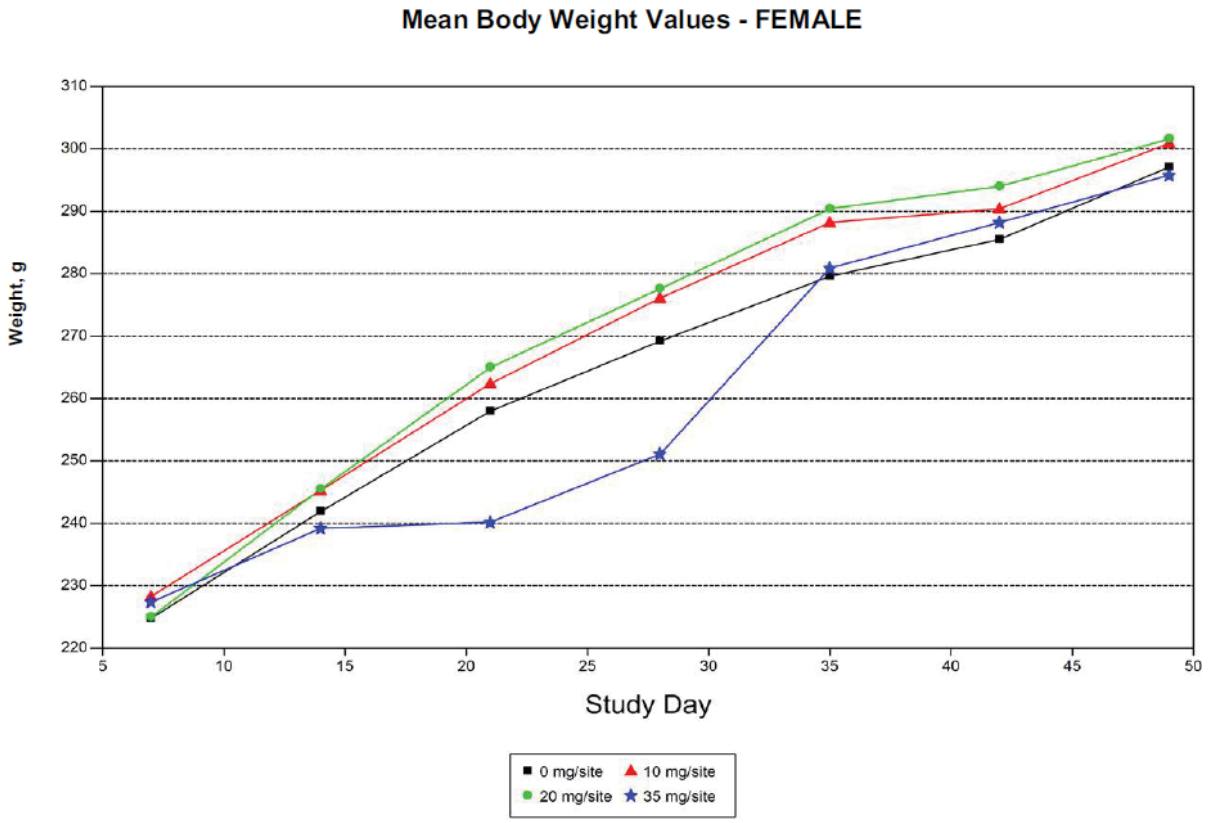
Swelling at the injection site was observed at all doses; 2 males and 4 females at 10 mg, and in all males at 20 and 70 mg and in 15 females each at 20 and 70 mg. The

frequency increased from 20 to 70 mg. There were no signs of swelling in any control animals, indicating that the effect was drug-related and not due to the vehicle or the injection procedures. One male and 4 females at 70 mg were noted as being thin in appearance during the dosing phase and into week 1 of the recovery phase. The injection site swelling was almost completely reversible, as only 1/6 males and 2/6 females at 70 mg had swelling. Cageside observations were conducted twice daily and detailed clinical observations were conducted pretest and weekly during the dosing and recovery periods.

Body Weights

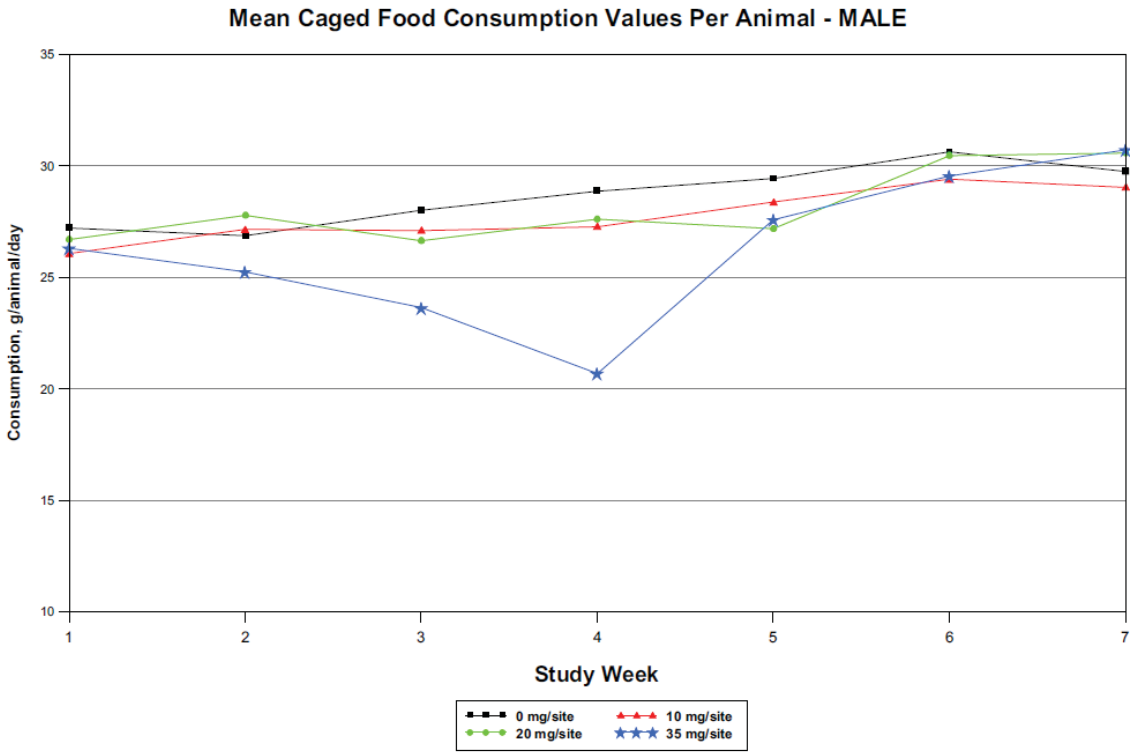
There was a decrease in absolute body weight during weeks 3 through 5 for males and females at 70 mg, 9% and 7% compared to controls, respectively, and reached statistical significance for males only. The effects on body weight were reversible during the recovery period. The decrease in body weight for males and females correlated with a decrease in food consumption. Body weights were recorded two days following receipt, prior to randomization, prior to the first dose (Day -1 or 1), and weekly during the study and the recovery period.

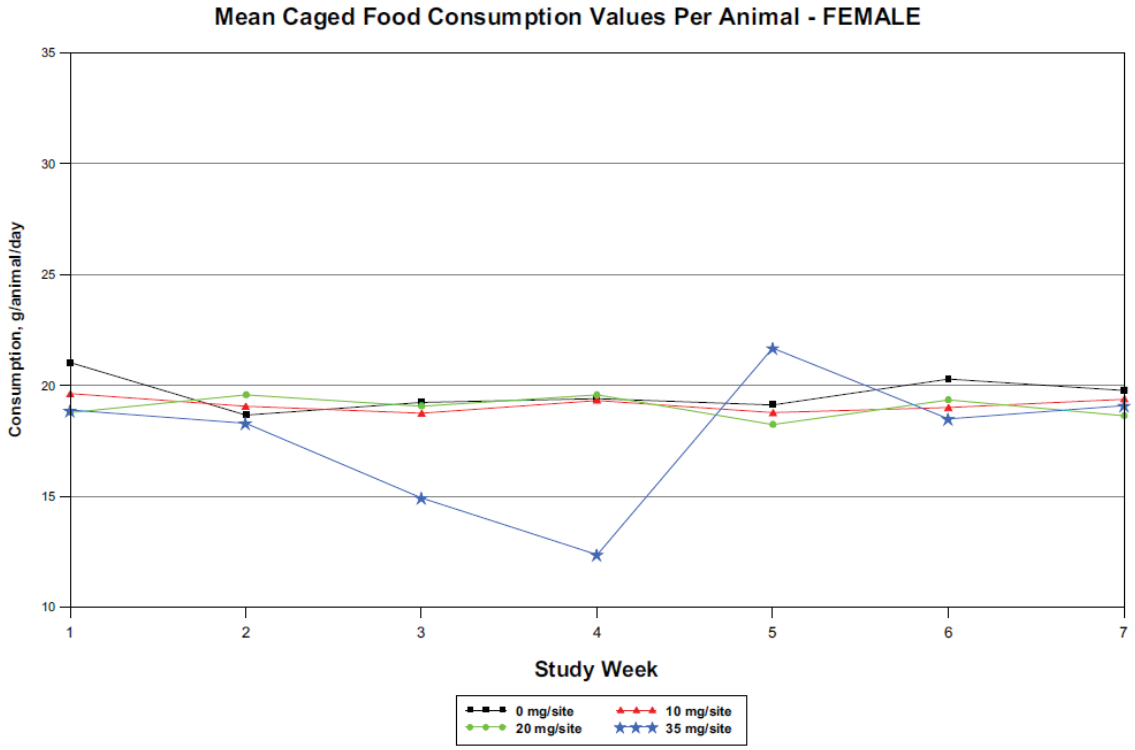




Food Consumption

There was a significant decrease in food consumption for males and females at 70 mg, with a maximum decrease of 28% and 36% compared to controls for males and females respectively at week 4. This decrease correlated with the effect on body weights. The decrease in food consumption was completely reversible by the end of the recovery period. Food consumption was measured and recorded weekly throughout the dosing and recovery periods.





Ophthalmoscopy

There were no drug-related findings. Eye exams were conducted on all animals pretest and on main study animals before terminal and recovery necropsies.

Hematology

There were no drug-related findings. Blood samples were collected prior to terminal and recovery necropsies. An adequate battery of hematology and coagulation parameters was evaluated.

Clinical Chemistry

There were no drug-related findings. Blood samples were collected prior to terminal and recovery necropsies. An adequate battery of clinical chemistry parameters was evaluated.

Urinalysis

There were no drug-related findings. Animals were individually housed in stainless steel metabolism cages, and urine was collected for at least 12 hours, prior to terminal and recovery necropsies.

Gross Pathology

Macroscopic findings of swollen/thickened injection site (at injection sites 1 and/or 2) were observed in 1 male and 2 females at 70 mg following the terminal necropsy. There were no macroscopic findings in animals at the 2-month recovery necropsy, indicating reversibility.

Organ Weights

There were a few instances of significant and/or dose-related changes in organ weights in drug-treated animals compared to controls. There was a statistically significant decrease in absolute and relative prostate weights in high dose males, 18% compared to controls, however relative prostate weights were comparable to the control group in the 2-month recovery group animals indicating reversibility. Absolute and relative ovary weights were significantly increased in high dose females 26% compared to controls, and were still increased 29% compared to controls in the 2-month recovery group, but did not reach statistical significance. In addition, uterus+cervix weights were statistically significantly decreased in mid and high dose females, 26% compared to controls, and were still decreased 29% compared to controls in the 2-month recovery group, but did not reach statistical significance. There were no correlating microscopic findings for any of the organ weight changes, therefore the findings are not considered toxicologically relevant.

Histopathology

Adequate Battery: Yes
Peer Review: Yes

Histological Findings: Local injection site toxicity.
Granulomas and inflammation at the injection site(s) were observed at all dose levels in both males and females. The incidence and severity of both the granulomas and inflammation was dose-related. Two males and two females had minimal inflammation at the injection site, which is probably due to repeated injections into the same muscle group. There was evidence of partial reversibility of the local toxicity after a 2-month recovery period. Only 1 mid dose female had a granuloma, but a control female also

had a granuloma, therefore the finding is most likely due to trauma of repeated IM injections and not drug-related. The severity of the granulomas and inflammation in the high dose animals was lessoned in the recovery group animals, indicating partial reversibility, but not complete. The local injection site toxicity was similar to what was observed with the larger particle size aripiprazole lauroxil drug formulation (rat toxicity studies conducted for approval of ARISTADA under NDA 207533).

Test Article-related Microscopic Observations – 1-Month Recovery

Dose level: mg aripiprazole equivalents/animal	0		10		20		70[a]	
Sex	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	9
Injection site 1, intramuscular								
Granuloma	0	0	0	0	1	2	8	7
-minimal	0	0	0	0	1	1	4	3
-mild	0	0	0	0	0	1	4	4
Inflammation, subacute/chronic	2	0	2	2	7	2	10	8
-minimal	2	0	2	2	6	2	3	6
-mild	0	0	0	0	1	0	7	2
Injection site 2, intramuscular								
Granuloma	0	0	1	1	2	0	6	9
-minimal	0	0	1	1	2	0	4	6
-mild	0	0	0	0	0	0	2	3
Inflammation, subacute/chronic	1	2	3	2	6	6	10	9
-minimal	1	2	3	2	4	6	3	3
-mild	0	0	0	0	2	0	6	6
-moderate	0	0	0	0	0	0	1	0

M - Male
F – Female
[a] = 35 mg/site in both hindlimbs; 70 mg aripiprazole equivalents/animal

Test Article-related Microscopic Observations – 2-Month Recovery								
Dose level: mg aripiprazole equivalents/animal	0		10		20		70[a]	
Sex	M	F	M	F	M	F	M	F
Number Examined	6	6	6	6	6	6	6	6
Injection site 1, intramuscular								
Granuloma	0	1	0	0	0	1	2	3
-minimal	0	1	0	0	0	1	1	3
-mild	0	0	0	0	0	0	1	0
Inflammation, subacute/chronic	0	1	4	0	1	3	4	3
-minimal	0	1	4	0	1	3	2	3
-mild	0	0	0	0	0	0	2	0
Injection site 2, intramuscular								
Granuloma	0	0	0	0	0	0	5	3
-minimal	0	0	0	0	0	0	5	2
-mild	0	0	0	0	0	0	0	1
Inflammation, subacute/chronic	0	3	1	1	2	2	5	6
-minimal	0	3	1	1	2	2	5	5
-mild	0	0	0	0	0	0	0	1

M - Male
F – Female
[a] = 35 mg/site in both hindlimbs; 70 mg aripiprazole equivalents/animal

Toxicokinetics

Blood samples for TK analysis were collected from 0 mg/site animals at 24, 360, 840, and 1848 hours postdose. Samples were collected from 10, 20, and 35 mg/site animals at 12, 24, 96, 168, 192, 264, 336, 360, 432, 504, 516, 528, 600, 672, 840, 1008, 1344, 1512, 1680, and 1848 hours postdose. Samples collected on dosing days were collected predose.
ALKS 9072 = aripiprazole lauroxil, ALKS 9864 = aripiprazole, ALKS 3954 = dehydro-aripiprazole, ALKS 5792 = N-hydroxy (b) (4)

Summary of Toxicokinetic Parameters - ALKS 9072					
Dose (mg/day)[a]	Day	$AUC_{0\text{-}168}$ (hr•ng/mL)	$AUC_{0\text{-}tlast}$ (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
10	1	NA	NA	4.47	12
	22	NA	NA	2.91	24
20	1	256	243	5.66	12
	22	296	268	4.50	24
70	1	647	538	12.8	12
	22	641	613	11.6	12

[a] Aripiprazole equivalents

Summary of Toxicokinetic Parameters - RDC-9864				
Dose (mg/site)[a]	Day	AUC_{0-168} (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
10	1	4960	37.7	168
	22	6770	50.4	24
20	1	8620	96.0	168
	22	17200	125	24
70	1	22200	211	168
	22	137000	1160	24
[a] Aripiprazole equivalents				

Summary of Toxicokinetic Parameters - RDC 3954				
Dose (mg/site)[a]	Day	AUC_{0-168} (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
10	1	229	2.12	96
	22	366	2.95	12
20	1	375	4.70	168
	22	1320	12.3	24
70	1	1680	17.5	168
	22	21100	172	12
[a] Aripiprazole equivalents				

Summary of Toxicokinetic Parameters - RDC 5792				
Dose (mg/site)[a]	Day	AUC_{0-168} (hr•ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
10	1	2880	23.5	96
	22	3090	23.7	24
20	1	1240	9.07	96
	22	3460	30.6	0
70	1	7140	59.3	168
	22	39500	363	24
[a] Aripiprazole equivalents				

Dosing Solution Analysis

The dose formulations were homogenous and the dose concentrations were within the acceptable range.

7 Genetic Toxicology

No genetic toxicology studies were conducted with AL-NCD. Refer to the approved labels for the listed drugs, aripiprazole lauroxil and oral aripiprazole, for nonclinical data.

8 Carcinogenicity

No carcinogenicity studies were conducted with AL-NCD. Refer to the approved labels for the listed drugs, aripiprazole lauroxil and oral aripiprazole, for nonclinical data.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted with AL-NCD. Refer to the approved labels for the listed drugs, aripiprazole lauroxil and oral aripiprazole, for nonclinical data.

10 Special Toxicology Studies

Safety evaluation of excipient polysorbate 20 in the AL-NCD drug product:
The Applicant submitted a safety evaluation report (report LSC17-103) for the excipient polysorbate 20, because the amount of polysorbate 20 in the AL-NCD drug product is higher than that in any currently FDA approved drug product for intramuscular administration (see table below). The report included a regulatory summary of polysorbate 20, clinical and nonclinical safety data for polysorbate 20 and related polysorbates from published literature, and an overview of findings from nonclinical toxicology studies in rats and dogs conducted by the Applicant that included vehicle control groups containing polysorbate 20. Those toxicity studies were not designed specifically to address the safety of polysorbate 20, as the studies lacked a control group that did not contain polysorbate 20, therefore, a direct comparison of any toxic effects of polysorbate 20 could not be made. Instead, the Applicant provided historical control data at the laboratory conducting the study and made pre-study to post-dose comparisons for the vehicle control groups containing polysorbate 20.

(b) (4)

(b) (4) It should be noted that the amount of polysorbate 20 in 675 mg of AL-NCD is (b) (4) The overall impact of this small change is minimal and therefore this reviewer did not ask the Applicant to re-submit all tables.

Table 2: Mass of Polysorbate 20 Administered Intramuscularly Initially in Aripiprazole Lauroxil Clinical Dosing Regimens Relative to Other Long Acting Injectable Antipsychotic Agents

Treatment	PS 20 Administered IM (mg)[a]		PS 20 Mass Relative to Invega Trinza (×)	
	Source	Total	Local[b]	Systemic[c]
(b) (4) mg AL-NCD[d] 882 mg ARISTADA	(b) (4)		(b) (4)	
(b) (4) mg AL-NCD[d] 1064 mg ARISTADA				
Invega Sustenna[e]			NA	NA
Invega Trinza[f]			NA	NA

Note: two aripiprazole lauroxil clinical dosing regimens are shown to provide data for the maximum amount of PS 20 in approved doses of ARISTADA, including 882 mg (given monthly or every 6 weeks) and 1064 mg (given every 2 months).

Abbreviations: IM = intramuscular; mg = milligram; NA = not applicable; PS 20 = polysorbate 20

[a] Values taken from Technical Report 700-02704 for ARISTADA and Technical Report 700-06979 for AL-NCD.

[b] Calculated by dividing the largest mass of PS 20 administered per injection site (ie, from AL-NCD) in the aripiprazole lauroxil treatment initiation regimen by the mass of PS 20 administered with Invega Trinza.

[c] Calculated by dividing the total mass of PS 20 administered in the aripiprazole lauroxil clinical dosing regimen by the mass of PS 20 administered with Invega Trinza.

[d] A 30 mg oral dose of aripiprazole also is administered with AL-NCD to initiate treatment prior to administration of ARISTADA.

[e] Based on administration of 1.5 mL of drug product (maximum dose of 234 mg) containing 12 mg/mL of PS 20 (Janssen Pharmaceuticals Inc. 2017a).

[f] Based on administration of 2.625 mL of drug product (maximum dose of 819 mg) containing 10 mg/mL of PS 20 (Janssen Pharmaceuticals Inc. 2017b).

[Table excerpted from Study report LSC17-103 “Nonclinical safety evaluation of polysorbate 20” in the NDA 209830 submission.]

Polysorbate 20 (commonly referred to as Tween 20®) is used (b) (4) in the AL-NCD drug product. (b) (4)

The Applicant provided information from the literature on the acceptable group daily intake (ADI) for polysorbate 20 and related polysorbates (i.e., PS 40, PS 60, PS 65, and PS 80) in humans to be 25 mg/kg/day, which was determined by a joint FAO/WHO Expert Committee on Food Additives (JECFA) and FDA (Food and Drug Administration 1999; Joint Expert Committee on Food Additives 1974). There is also extensive nonclinical published literature on the nonclinical and clinical safety of polysorbates. However, the published nonclinical general toxicity data on polysorbate 20 is >50 years old, therefore the studies were not conducted up to current standards, and most of the data is from orally administered studies, except for one short duration

intramuscular/subcutaneous study in monkeys. Data from these studies provide little support for the safety assessment of polysorbate 20 in AL-NCD to be administered intramuscularly. The most relevant data to support the safety of polysorbate 20 in AL-NCD comes from the nonclinical toxicity studies in rats and dogs conducted by the Applicant. The vehicle used in the 4-week rat and dog toxicity studies (studies AT-3317-25 and AT-3317-26, respectively) contained (b) (4) polysorbate 20. There were no signs of systemic toxicity to the vehicle in either rats or dogs except for hypersensitivity reactions in dogs. There were no signs of local toxicity to the vehicle in rats. However, in dogs there were signs of a hypersensitivity reaction to the vehicle, or a component(s) of the vehicle. Clinical signs including reddened skin, excessive scratching, facial swelling, and injected sclera were present predominantly in control dogs, and to a lesser extent in dogs from the high dose group. Although all drug-treated groups were administered the test article in the same vehicle, high dose groups were administered the largest volume, 3.7 ml/site, the same as the control groups. The low dose and mid dose groups were administered a smaller volume, 2.0 and 2.4 ml/site, of test article in vehicle, respectively. This may explain why the hypersensitivity reactions were only observed in control and high dose groups. A possible explanation proposed by the Applicant as to why hypersensitivity reactions were observed less frequently in the high dose groups is that polysorbate 20 is used as a (b) (4) in AL-NCD and is adsorbed to the surface of the particles and, consequently, may not be immediately bioavailable systemically upon IM administration, as opposed to a faster absorption of polysorbate 20 in the vehicle not containing any drug product (the control animals). Although the observance of hypersensitivity reactions in dogs caused by the vehicle is a safety concern, hypersensitivity reactions in dogs have been associated with administration of surfactants (including polysorbate 20) (Cirstea and Suhaciu 1964), and therefore were not an unexpected finding in the study. The reactions were also managed via treatment with antihistamines.

The Applicant did not conduct any genetox, carcinogenicity, or reproduction and development toxicity studies with polysorbate 20, but instead relied on findings in published literature for all related polysorbates, not just polysorbate 20. One published study showed that polysorbate 20 caused cytotoxicity, apoptosis, and DNA damage, using the COMET assay, in A549 cells (human lung cancer cells) and human umbilical vein endothelial cells (Eskandani et al, 2013). However, a major limitation of the COMET assay in that study was that only one concentration of polysorbate 20 was used, which was a highly cytotoxic concentration, and the cells were directly treated using only one timepoint. Findings in published literature on related polysorbates, suggest that polysorbates as a group are not genotoxic when evaluated using both *in vitro* and *in vivo* genotoxicity assays (Efsa Panel on Food Additives and Nutrient Sources Added to Food (Ans) 2015; Kawachi et al, 1980). There is no evidence of any developmental effects of polysorbate 20, or other polysorbates, in rats after repeated oral administration (Efsa Panel on Food Additives and Nutrient Sources Added to Food (Ans) 2015). However, the reproductive and developmental studies in the published literature were not conducted up to current standards.

Extensive toxicity data for polysorbate 20 was found on the ToxNet web-site (U.S. National Library of Medicine Toxicology Data Network). Based on the data provided, there is no evidence of carcinogenicity of polysorbate 20 in rats, mice, or hamsters administered polysorbate 20 orally in the diet or to mice administered topically to the skin. However, these studies were not conducted up to current standards and the duration of drug treatment was less than life-time exposures. Carcinogenicity studies were conducted with polysorbate 80 in feed, which were conducted more up to current standards, and showed a lack of carcinogenicity in female F344/N rats and in B6C3F1 mice; in male F344/N rats, there was an increase in benign pheochromocytomas of the adrenal medulla that is most likely not relevant to humans (National Toxicology 1992).

Table 3: Summary of Human and Repeat-Dose General Toxicology Studies with Polysorbate 20

Species	Route of Admin	Study Duration	Dose/ Concentration	Findings	Reference
Rat	Dietary	8 Weeks	3 or 5% in diet	Mild diarrhea and weight gain suppression	(Krantz and Et Al. 1943)
Hamster	Dietary	28 Weeks	5% in diet	Marked diarrhea and weight gain suppression	(Eagle and Poling 1956)
Mouse	Dietary	22 Months	5 or 10% in diet	Mild diarrhea was observed at 10% dietary level	(Ewing and Tauber 1965)
Monkey (rhesus)	Oral	17 Months	1 g/day	No significant histologic visceral changes	(Krantz et al, 1948)
Monkey (rhesus)	IM/SC	20 Days	275 mg/day	Local injection site reactions; well tolerated systemically	(Krantz et al, 1948)
Species	**Route of Admin**	**Study Duration**	**Dose/ Concentration**	**Findings**	**Reference**
Humans (Adults)	Oral	7 Days	6 g/day total dose (~100 mg/kg/day assuming 60 kg human)	No adverse effects reported	(King et al, 1979)
Humans (Infants to Toddlers)	Oral	13-53 Days	96-800 mg/day total dose (~48-400 mg/kg/day assuming 2 kg infant)	No adverse effects reported	(Johnson et al, 1950)

Abbreviations: Admin = administration; conc = concentration; IM = intramuscular; IV = intravenous; SC = subcutaneous

Note: findings summarized from (Food Safety Commission 2007)

[Table excerpted from Study report LSC17-103 “Nonclinical safety evaluation of polysorbate 20” in the NDA 209830 submission.]

Table 6: Nonclinical to Clinical Dose Multiples of Polysorbate 20 from Alkermes' Nonclinical Studies Relative to the Clinical Dosing Regimens Yielding the Greatest Amounts of PS 20

Nonclinical Study/Clinical Dosing Regimen	PS 20 in Veh. or Form Dosed (% w/w)[a]	Dose Vol. (mL)	PS 20 per Dosing Day (mg)	Body Weight (kg)	PS 20 Dose (mg/kg)	Dose Multiple (mg/kg)[b]	PS 20 Dose (mg/kg HED[c])	Dose Multiple (mg/kg HED)[b]	Dose Multiple (mg/site)[d]
4-week IM AL-NCD rat	1.6	0.4[e] (0.2/site)	6.4[e] (3.2/site)	0.29[f]	22	30/29	3.5	4.8/4.7	0.08/0.08
4-week IM AL-NCD dog	1.6	7.4[e] (3.7/site)	118[e] (59/site)	8.6[f]	14	19/19	7.6	10/10	1.5/1.5
AL-NCD initiation regimen + 882 mg ARISTADA	--	--	43.9 total (38.96 from AL-NCD and 4.97 from ARISTADA)[g]	60[h]	0.73	--	--	--	--
AL-NCD initiation regimen + 1064 mg ARISTADA	--	--	45.0 total (38.96 from AL-NCD and 6.00 from ARISTADA)[g]	60[h]	0.75	--	--	--	--

Abbreviations: ARP = aripiprazole; form = formulation; HED = human equivalent dose; IM = intramuscular; PS 20 = PS 20; veh = vehicle

[a] Information for vehicles administered in the 4-week rat and dog studies and the highest dose of AL-NCD drug product to be administered in Study ALK9072-B101. Density of the nonclinical vehicle is 1 g/mL.

[b] Polysorbate 20 dose multiples are expressed relative to the two clinical treatment regimens yielding the greatest amounts of PS 20 ((b) (4) AL-NCD + 882 mg ARISTADA/(b) (4) AL-NCD + 1064 mg ARISTADA).

[c] mg/kg doses in rat and dog were converted to human equivalent doses by multiplying mg/kg values by 0.16 and 0.54, respectively (Center for Drug Evaluation and Research 2005).

[d] Polysorbate 20 mass from the AL-NCD injection in humans used for the calculation.

[e] Doses administered at two sites.

[f] Mean body weight (combined genders) on vehicle administration days.

[g] From Alkermes Technical Reports 700-02704 and 700-06979.

[h] Assumed body weight for calculation purposes.

[Table excerpted from Study report LSC17-103 "Nonclinical safety evaluation of polysorbate 20" in the NDA 209830 submission.]

Recommendation:

Overall, the Applicant provided adequate data to qualify the amount of polysorbate 20 in the AL-NCD drug product for intramuscular administration, including data from published literature and sponsor-conducted nonclinical studies. There is an adequate safety margin of approximately 5- and 10-fold (based on mg/m^2 comparisons) in rats and dogs, respectively compared to the maximum amount of polysorbate 20 (45.7 mg) in the clinical treatment regimen (675 mg AL-NCD + 1064 mg Aristada). The overall assessment is that the amount of polysorbate 20 in the AL-NCD drug product (b) (4) (b) (4) does not pose a substantial risk to humans.

(b) (4)

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11 Integrated Summary and Safety Evaluation

ARISTADA INITIO (aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD)) is a new formulation of aripiprazole lauroxil (AL) with a smaller (sub-micron) aripiprazole lauroxil particle size and different excipient profile. The Applicant submitted a 505(b)(2) NDA with aripiprazole lauroxil and oral aripiprazole as the listed drugs. The main purpose of ARISTADA INITIO will be to eliminate the need for the 21 days of oral aripiprazole when initiating ARISTADA dosing. The proposed dosing regimen is comprised of a single 675 mg dose of ARISTADA INITIO co-administered with a single oral dose of 30 mg aripiprazole; ARISTADA (up to 1064 mg) will be co-administered at a separate IM injection site.

Aripiprazole lauroxil is converted in vivo to aripiprazole. The smaller particle size of AL-NCD results in faster dissolution and conversion to aripiprazole and increased absorption, which was evident by earlier T_{max} values of aripiprazole in dogs and higher

C_{max} values of aripiprazole in rats and dogs after IM administration of AL-NCD compared to AL.

The high doses used in the rat and dog repeat-dose toxicity studies with AL-NCD were the maximal feasible doses based on physico-chemical limitations of the formulation and maximum acceptable IM dose volumes/sites of administration in rats and dogs. The clinical and commercial formulation of AL-NCD (formulation B) was used in the nonclinical studies.

In a 4-week repeat dose toxicity study with AL-NCD in rats, rats were administered once weekly intramuscular injections of AL-NCD at doses of 0, 15, 29, 103 mg/animal (0, 10, 20, 70 mg aripiprazole equivalents/animal). Control animals were administered the vehicle containing the same excipients used in the clinical formulation. One high dose female was sacrificed moribund and the death was considered drug-related. A decrease in body weight was observed for high dose males and females that correlated with a decrease in food consumption and was completely reversible. Drug-related swelling at the injection site was observed at all doses, but was fully reversible. Local injection site toxicity of granulomas and subacute/chronic inflammation was observed at all dose levels, with the frequency and severity being dose-related, and evidence of partial, but not complete reversibility of the microscopic findings. The NOAEL for systemic toxicity was 29 mg AL-NCD/animal. There was no NOEL for local injection site toxicity.

In a 4-week repeat dose toxicity study with AL-NCD in dogs, dogs were administered once weekly intramuscular injections of AL-NCD at doses of 0, 147, 662, 2058 mg/animal (0, 100, 450, 1400 mg aripiprazole equivalents/animal). Control animals were administered the vehicle containing the same excipients used in the clinical formulation. Impaired hind limb function and/or hind limb swelling was observed mainly at the high dose. Hypersensitivity reactions occurred in vehicle and high dose animals, which was attributed to excipients in the vehicle, most likely polysorbate-20. Dose-related local toxicity was observed at the injection site at all dose levels, which included granulomas, subacute/chronic inflammation, and mineralization. Signs of local injection site toxicity were partially, but not completely, reversible at 2 months following the last injection. The NOAEL for systemic toxicity was 2058 mg AL-NCD/animal. There was no NOEL for local injection site toxicity.

Note, the dosing regimen in the repeat-dose toxicity studies with AL-NCD in rats and dogs of once a week for four weeks is more frequent than that of the intended clinical dosing administration of only once to initiate dosing of ARISTADA or after a missed dose of ARISTADA.

Dose levels were described in terms of aripiprazole equivalent doses in the toxicity studies; doses of AL-NCD are approximately 1.47× greater given the molecular weights of aripiprazole lauroxil (660.70 g/mole) and aripiprazole (448.39 g/mole). In rats, the dose range of 10 to 70 mg aripiprazole equivalents/animal is equal to an AL-NCD dose range of 15 to 103 mg aripiprazole lauroxil/animal; these doses are 0.6 to 4 times and 0.9 to 6 times the 675 mg clinical dose of AL-NCD on a mg/m^2 basis in male and female

rats, respectively. In dogs, the dose range of 100 and 1400 mg aripiprazole equivalents/animal is equal to a dose range of 147 to 2058 mg aripiprazole lauroxil/animal; these doses are 0.7 to 10 times and 1 to 14 times of the 675 mg clinical dose of AL-NCD on a mg/m^2 basis in male and female dogs, respectively. To convert the AL-NCD doses in mg/animal to mg/m^2 equivalents, the average body weight for rats and dogs at the end of the 4-week studies were first used to convert the doses to mg/kg. Dosing margins compared to the clinical dose for local toxicity in rats and dogs were expressed using body surface area comparisons for AL-NCD, because aripiprazole lauroxil was not measurable in plasma of humans. Although no NOEL was identified for the local injection site toxicity in rats and dogs, dose ranges that were used in the study and findings were detailed in section 13.2 of the label and expressed as aripiprazole lauroxil dose multiples compared to the human dose of 675 mg.

Given that AL-NCD and AL will be co-administered (although at different muscle sites) total systemic exposure of aripiprazole lauroxil and all analytes (aripiprazole, the N-hydroxymethyl aripiprazole (b) (4), and the major metabolite of aripiprazole dehydro-aripiprazole) were evaluated in humans. Systemic exposure of analytes at the maximum aripiprazole lauroxil dosing regimen (i.e., a single IM dose of AL-NCD, a single 30 mg oral administration of aripiprazole, along with IM administration of AL up to 1064 mg) showed that aripiprazole lauroxil and N-hydroxymethyl aripiprazole were <10% of total drug related exposure (Applicant's table 7 below). In addition, exposure to aripiprazole lauroxil and N-hydroxymethyl aripiprazole were higher in rats and dogs after IM administration of AL-NCD in the 4-week repeat-dose toxicity studies compared to the maximum clinical dosing regimen (see Applicant's table 8 below) indicating adequate nonclinical coverage.

Table 7: Comparison of Systemic Exposure to Aripiprazole Lauroxil and its Metabolites in Aripiprazole Lauroxil Dosing Regimens in Humans

	Aripiprazole Lauroxil		Aripiprazole		Dehydro-aripiprazole		*N*-hydroxymethyl Aripiprazole	
Clinical Dosing Regimen	AUC (ng*day/mL)	% Total Exposure[a]	AUC (ng*day/mL)	% Total Exposure[a]	AUC (ng*day/mL)	% Total Exposure[a]	AUC (ng*day/mL)	% Total Exposure[a]
AL-NCD initiation regimen + 882 mg AL IM[b]	NC	0%	3571	69.9%	1127	22.1%	407.2	8.0%
AL-NCD initiation regimen + 1064 mg AL IM[c]	NC	0%	3550	69.3%	1115	21.8%	459.1	9.0%[d]
882 mg AL IM[e]	NC	0%	5559	71.9%	1700	22.0%	471.8	6.1%
1064 mg AL IM[f]	NC	0%	3665	62.9%	1596	27.4%	564.9	9.7%

Abbreviations: AL = aripiprazole lauroxil formulation with micron-sized drug particles; AL-NCD = aripiprazole lauroxil NanoCrystal Dispersion; ARP = aripiprazole; IM = intramuscular; NC = not calculable

[a] % total exposure was estimated by dividing exposure to the analyte by the sum of aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethyl aripiprazole exposures. Because exposure was not calculable for aripiprazole lauroxil, a value of "0" was used for calculations.

[b] Exposure data reflect AUC_{0-28} from Study ALK9072-B102 in humans receiving 662 mg AL-NCD + 882 mg AL + 30 mg oral aripiprazole.

[c] Exposure (AUC_{0-28}) was estimated by adding analyte exposure following a 662 mg dose of AL-NCD (Study ALK9072-B101) to that following a 1064 mg dose of AL (NDA 207,533, Study ALK9072-A105) for the same 28-day period post dose administration. Aripiprazole and dehydro-aripiprazole exposure from the 30 mg oral dose were not accounted for.

[d] Value for *N*-hydroxymethyl aripiprazole is an overestimate as the contribution of aripiprazole and dehydro-aripiprazole exposure to total drug-related exposure was not considered for the 30 mg oral aripiprazole dose.

[e] Exposure data reflect AUC for the 28-day period following the 4th dose of 882 mg AL in NDA 207,533, Study ALK9072-002. Values for aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethyl aripiprazole were NC, 1700, 5559, and 471.8 ng*day/mL, respectively.

[f] Exposure data reflect AUC for the 28-day period following the 4th dose of 1064 mg AL in Study ALK9072-A105. Values for aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethyl aripiprazole were NC, 1596, 3665, and 564.9 ng*day/mL, respectively.

Table 8: Nonclinical to Clinical Exposure Coverage for Aripiprazole Lauroxil and *N*-hydroxymethyl Aripiprazole

Species	Nonclinical Study/ Number	NOAEL (mg/animal)[a]	Nonclinical $AUC_{(0\text{-}672hr)}$ in ng*hr/mL[b]	AL-NCD initiation regimen + 882 mg AL IM		AL-NCD initiation regimen + 1064 mg AL IM	
				$AUC_{(0\text{-}672\ hr)}$ in ng*hr/mL[c,e]	Exposure Multiple (×)	$AUC_{(0\text{-}672\ hr)}$ in ng*hr/mL[d,e]	Exposure Multiple (×)
Rat	AL-NCD 4-Week Rat (AT-3317-25)	20	ALa: 921 NHA: 52500	ALa: NR NHA: 9770	ALa: >1 NHA: 5.4	ALa: NR NHA: 11000	ALa: >1 NHA: 4.8
	AL 6-Month Rat (AT-3317-14)	70	ALa: 27.8[e] NHA: 26400[e]	ALa: NR NHA: 9770	ALa: >1 NHA: 2.7	ALa: NR NHA: 11000	ALa: >1 NHA: 2.4
Dog	AL-NCD 4-Week Dog (AT-3317-26)	1400	ALa: 51800 NHA: 305000	ALa: NR NHA: 9770	ALa: >1 NHA: 31	ALa: NR NHA: 11000	ALa: >1 NHA: 28
	AL 9-Month Dog (AT-3317-13)	1400	ALa: 1040[e] NHA: 21500[e]	ALa: NR NHA: 9770	ALa: >1[f] NHA: 5.1[f]	ALa: NR NHA: 11000	ALa: >1[f] NHA: 4.5[f]

Abbreviations: AL = aripiprazole lauroxil formulation with micron-sized drug particles; AL-NCD = aripiprazole lauroxil NanoCrystal Dispersion; ALa = aripiprazole lauroxil analyte; IM = intramuscular; NOAEL = no-observed adverse effect level; NR = not reported (due to minimal/non-quantifiable exposure to analyte); NHA = *N*-hydroxymethyl aripiprazole (RDC-5792)

[a] Doses are in mg aripiprazole equivalents; doses of AL-NCD are approximately 1.47× greater given the molecular weights of AL-NCD (660.70 g/mole) and aripiprazole (448.39 g/mole).

[b] Combined gender exposure data were obtained with validated bioanalytical assays for all analytes. For the AL-NCD studies (AT-3317-25 and AT-3317-26), AL and NHA were measured in plasma and reported; the exception was NHA in rats, which was measured subsequently in whole blood in Study AT-3317-27 due to incurred sample reanalysis failure for NHA in the plasma assay. For the AL studies conducted with micron-sized particles (AT-3317-13 and AT-3317-14), AL and NHA were measured in whole blood.

[c] Exposure data from Study ALK9072-B102 in humans receiving 662 mg AL-NCD + 882 mg AL + 30 mg oral aripiprazole.

[d] Human $AUC_{(0\text{-}672\ hr)}$ was estimated by adding analyte exposure following a 662 mg dose of AL-NCD (Study ALK9072-B101) to that following a 1064 mg dose of AL (NDA 207,533, Study ALK9072-A105) for the same 28-day period post dose administration.

[e] AUC values over the first 28 days post-dosing that were reported in ng*day/mL were converted to ng*hr/mL by multiplying by 24. Values were rounded to 3 significant figures.

[f] Values were normalized to the clinical matrix to account for differences in whole blood to plasma analyte exposures in dogs as determined in NDA 207,533, Study AT-3317-22; this was done by dividing values by whole blood to plasma $AUC_{0\text{-}tlast}$ ratios for AL and NHA (ie, 0.554 and 0.435, respectively). Given human $AUC_{(0\text{-}672\ hr)}$ for AL was not calculated due to limited/non-quantifiable exposure to this analyte, exposure multiples were reported as ">1" when nonclinical AUC values were reported; these reported values for AL were not corrected for matrix-related differences in exposure.

[Table excerpted from Toxicology Written Summary section of the NDA.]

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/s/

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