CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207533Orig1s000

PHARMACOLOGY REVIEW(S)

This is an addendum to the Nonclinical NDA Review and Evaluation for aripiprazole lauroxil dated April 30, 2015 (the Review). Further consideration was given to certain nonclinical information proposed for inclusion in section 8.1 Pregnancy of the labeling. It was determined that it was not necessary (b) (4)

For clarification we also note the following:

- The Review (e.g., Section 1.2) refers to aripiprazole as the active moiety. However, the active moiety is N-hydroxymethyl aripiprazole, not aripiprazole. Although the Review included some background information on aripiprazole lauroxil and some chemistry, the active moiety determination for aripiprazole lauroxil and related chemistry will be documented in a memorandum by Dr. Norman Schmuff.

- The sponsor is relying on the listed drug Abilify tablets (NDA 21436). Section 2.2 excerpts from the Alkermes NDA 207533 "Table 2: Nonclinical references for approved findings for the reference listed drug Aripiprazole (Abilify)" which identifies the Abilify Package insert and the Summary Basis of Approval for Abilify Oral tablets. Of these two references, we relied for approval only on the Agency's findings of safety and effectiveness for Abilify tablets as reflected in the approved labeling.

- The Review (p. 87) states, in determining the relevance of the aripiprazole tablet animal data to aripiprazole lauroxil, that "[i]t is emphasized that the API (aripiprazole) is the same, and therefore, the findings should be the same; the difference being the formulation and delivery of the API." However, the active ingredient is aripiprazole lauroxil, not aripiprazole. Alkermes has adequately bridged to the findings of safety and effectiveness for Abilify Tablets as documented in other discipline reviews.

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

/s/

AMY M AVILA
09/28/2015

AISAR H ATRAKCHI
09/28/2015

Tertiary Pharmacology/Toxicology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 207533
Submission date: August 22, 2014
Drug: aripiprazole lauroxil
Applicant: Alkermes, Inc.
Indication: Treatment of schizophrenia
Reviewing Division: Division of Psychiatry Products

Discussion:
The pharmacology/toxicology reviewer and supervisor recommended that aripiprazole lauroxil could be approved from the pharmacology/toxicology perspective for the indication listed above.

The exact mechanism of aripiprazole in the treatment of schizophrenia is unknown. Therefore, the established pharmacologic class is “atypical antipsychotic” as with other members of this class.

This NDA relied, in part, on the Agency’s finding of safety for aripiprazole, which is reasonable because the active moiety is the same. Additional nonclinical studies of aripiprazole lauroxil were also submitted.

Aripiprazole lauroxil is a long-term injectable formulation. Granulomas at the site of injection were observed in some long-term animal studies with aripiprazole lauroxil. The duration and size of the clinical trial might not have been sufficient to show these effects. These effects in animals are described in the proposed labeling, which is reasonable.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that this NDA may be approved for the above indication. Additional comments on labeling have been provided separately.

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

/s/

PAUL C BROWN
08/13/2015

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	207533
Supporting document/s:	SDN 1, 3, 7, 18
Applicant's letter date:	August 22, 2014
CDER stamp date:	August 22, 2014
Product:	Aripiprazole lauroxil extended release suspension for injection
Indication:	Schizophrenia
Applicant:	Alkermes Inc.
Review Division:	Psychiatry Products
Reviewer:	Amy M. Avila, Ph.D.
Supervisor/Team Leader:	Aisar Atrakchi, Ph.D.
Division Director:	Mitchell Mathis, M.D.
Project Manager:	Sharon Sagoo

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207533 are owned by Alkermes or are data for which Alkermes has obtained a written right of reference.
Any information or data necessary for approval of NDA 207533 that Alkermes does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207533.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

This application is a 505(b)(2) NDA for aripiprazole lauroxil (Aristada). The indication is the treatment of schizophrenia. Aripiprazole lauroxil is a new molecular entity and is being developed as a long-term injectable intramuscular formulation. This drug is not approved outside the U.S.

Aripiprazole lauroxil is a covalently bonded modification of aripiprazole. The application relies in part on the Agency's previous findings of safety and effectiveness for oral aripiprazole (NDA 21-436) for the treatment of schizophrenia.

1.2 Brief Discussion of Nonclinical Findings

Aripiprazole lauroxil was adequately assessed in nonclinical studies and there are no findings that would prevent the approval of this drug.

Following intramuscular injection, aripiprazole lauroxil is converted to the active moiety, aripiprazole. During the biotransformation, a novel intermediate is formed, N-hydroxymethyl aripiprazole, and formaldehyde and lauric acid are generated as by-products. Aripiprazole concentrations in rats and dogs following maximum feasible doses of aripiprazole lauroxil are at or below those achieved following the maximum recommended human intramuscular dose of 882 mg aripiprazole lauroxil. For this reason, the sponsor is relying on the FDA's previous findings of safety and effectiveness for oral aripiprazole and its metabolites.

Aripiprazole lauroxil binds to similar receptors as aripiprazole (D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2c}) although at much lower affinity and has no functional activity. There were no adverse aripiprazole lauroxil-related effects on any of safety pharmacology endpoints (cardiovascular, respiratory, and neurofunctional assessments), with the exception of decreased locomotor activity in female dogs.

Toxicity studies in two species (rats and dogs) were conducted with intramuscularly administered aripiprazole lauroxil to support chronic use. These studies did not reveal any systemic toxicity to aripiprazole lauroxil. The NOAEL for systemic toxicity was the highest dose tested in each of the rat and dog studies. The systemic NOAEL dose in rats is approximately 2 and 4-times the maximum recommended human dose (MRHD) of 882 mg aripiprazole lauroxil and approximately 8 and 10-times the MRHD in males and females respectively, based on mg/m^2. However, local toxicity of dose-related injection site tissue reactions was observed at all dose levels in all rat and dog toxicity studies. Granulomas, which were dose-related with respect to frequency and severity, developed in both species and were not fully reversible 2 months after the last injection in rats and 4 months after the last injection in dogs, indicating a very slow recovery process. The sponsor considered that these effects (b) (4) ; however this reviewer disagrees with that conclusion and emphasizes the lack of full reversibility in section 13.2 of the label.

Aripiprazole lauroxil was non-genotoxic in an in vitro Ames gene mutation assay and chromosomal aberration assay, which is in contrast to reported findings with aripiprazole. A possible explanation is that the concentrations of aripiprazole that were formed in vitro in the aripiprazole lauroxil studies were not high enough to induce a positive response. Aripiprazole lauroxil was not teratogenic in rats and rabbits when administered intramuscularly at doses up to 6 an 18 times the MRHD based on mg/m^2. This is also in contrast to findings with oral aripiprazole where aripiprazole produced possible teratogenic effects in rats and rabbits. Intramuscular administration of aripiprazole lauroxil to rats caused adverse effects on male and female fertility parameters, which is in contrast to findings observed with aripiprazole in which no impairment of fertility was seen. The highest dose resulted in lower mating, fertility, and fecundity indices in females and lower mating and fertility indices in males and an overall impairment in fertility. The dose is approximately 11 and 6 times the MRHD based on mg/m^2 in males and females, respectively. Nonclinical data describing the adverse genotoxic, reproductive and fertility effects of aripiprazole are incorporated into the label for aripiprazole lauroxil.

The aripiprazole lauroxil drug product contains the excipient sorbitan monolaurate (SML) (b) (4) % w/v). SML is a novel excipient for intramuscular administration; although it is used in approved drug products for other routes of administration (oral, ophthalmic, and topical) up to 4.74% in a topical formulation. The sponsor provided adequate data to qualify SML for intramuscular administration, including data from published literature and sponsor-conducted nonclinical studies. The overall assessment is that the amount of SML in the aripiprazole lauroxil drug product (b) (4) % w/v) does not pose a substantial risk to humans.

Formaldehyde and lauric acid are released during the conversion of aripiprazole lauroxil to aripiprazole. The maximum amount of formaldehyde predicted to be released in an 882 mg dose of aripiprazole lauroxil is (b) (4) mg, and the maximum amount of lauric acid predicted to be released is (b) (4) mg with an additional (b) (4) mg derived from sorbitan monolaurate. These maximum levels of formaldehyde and lauric acid generated over the course of monthly dosing, do not pose a substantial risk to humans since they are below the amounts ingested (from the environment), and/or generated endogenously.

1.3 Recommendations

1.3.1 Approvability

This application is recommended for approval from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None at this time

1.3.3 Labeling

Reviewer proposed labeling (draft) for sections: 8.1, 12.1, 13.1, and 13.2. Only the nonclinical portions of section 8.1 are included in this review (risk summary and animal data). All data for aripiprazole came from the most recently approved Abilify® label (December, 2014). The language for the aripiprazole animal data was changed slightly to be consistent with that of aripiprazole lauroxil; however no changes in content were made. At the time this review was finalized, labeling negotiations were still in progress.

8.1 Pregnancy

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no available data on ARISTADA use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at doses up to 6 and 18 times, respectively, the maximum recommended human dose (MRHD) of 882 mg on body surface area (mg/m^2 basis). However, these doses of aripiprazole lauroxil did not result in exposures to aripiprazole as high as those achieved following oral and intravenous administration of aripiprazole which caused developmental toxicity and possible teratogenic effects in rats and rabbits. [see Data]. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data for Aripiprazole lauroxil:

Aripiprazole lauroxil did not cause adverse developmental or maternal effects in rats or rabbits when administered intramuscularly during the period of organogenesis at doses of 17.6, 48.5, or 144.1 mg/animal in pregnant rats which are approximately 1 to 6 times the maximum recommended human dose (MRHD) of 882 mg on mg/m^2 basis, and at doses of 241, 723, and 2893 mg/animal in pregnant rabbits which are approximately 1 to 18 times the MRHD on mg/m^2 basis.

Animal Data for Aripiprazole:

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day which are approximately 1 to 10 times the maximum recommended human oral dose [MRHD] of 30 mg/day on mg/m^2 basis of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight, and undescended testes. Delayed skeletal ossification was observed at 3 and 10 times the oral MRHD on mg/m^2 basis.

At 3 and 10 times the oral MRHD on mg/m^2 basis, delivered offspring had decreased body weights. Increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia were observed in offspring from the highest dose group (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to the highest dose. Postnatally, delayed vaginal opening was seen at 3 and 10 times the oral MRHD on mg/m^2 basis and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

(b) (4)

In pregnant rabbits treated with oral doses of 10, 30, and 100 mg/kg/day which are 2 to 11 times human exposure at the oral MRHD based on AUC and 6 to 65 times the oral MRHD on mg/m^2 basis of aripiprazole during the period of organogenesis decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternebrae were observed at 3 and 11 times the MRHD based on AUC.

(b) (4)

In rats treated with oral doses of 3, 10, and 30 mg/kg/day which are 1 to 10 times the oral MRHD on mg/m^2 basis of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at the highest dose. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

(b) (4)

12.1 Mechanism of Action

Following intramuscular injection, ARISTADA (b) (4)
The mechanism of action of aripiprazole is unknown. However, the efficacy of aripiprazole (b) (4) *be mediated through a combination of partial agonist activity D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the adverse reactions of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha$_1$ receptors).*

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies have not been conducted with aripiprazole lauroxil.

Lifetime carcinogenicity studies with oral aripiprazole have been conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human oral dose [MRHD] of 30 mg/day based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the oral MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses which are 0.1 to 0.9 times human exposure at the oral MRHD based on AUC and 0.5 to 5 times the oral MRHD on mg/m^2 basis. In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose which is 0.1 times human exposure at the oral MRHD based on AUC and 3 times the oral MRHD on mg/m^2 basis; and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose which is 14 times human exposure at oral MRHD based on AUC and 19 times the oral MRHD on mg/m^2 basis.

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

Aripiprazole lauroxil was not mutagenic in the in vitro bacterial reverse mutation assay or clastogenic in the in vitro chromosome aberration assay in human peripheral blood lymphocytes.

Aripiprazole and its metabolite (2,3-DCPP) were clastogenic in the in vitro chromosome aberration assay in Chinese hamster lung (CHL) cells both in the presence and

absence of metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the in vitro assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the oral in vivo micronucleus assay in mice; however, the response was due to a mechanism not considered relevant to humans.

Impairment of Fertility

Animal Data for Aripiprazole lauroxil:

In a rat fertility study, aripiprazole lauroxil was administered intramuscularly. Males were treated with doses of 17.6, 48.5, or 144.1 mg /animal, which are approximately X (requested that the sponsor add the multiples compared to the low doses as well) to 11 times the MRHD of 882 mg on mg/m^2 basis, on Days 1, 21, and 42 prior to and through mating; females were treated at these doses, which are approximately X to 6 times the MRHD on mg/m^2 basis, once 14 days prior to mating.

In females, persistent diestrus was observed at all doses and the mean number of cycles was significantly decreased at the highest dose together with an increase in the copulatory interval (delay in mating). Additional changes at the high dose included slight increases in corpora lutea and preimplantation loss, decline in mating, fertility, and fecundity indices in females and lower mating and fertility indices in males.

Animal Data for Aripiprazole:

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day, which are 0.6 to 6 times the oral MRHD of 30 mg/day on mg/m^2 basis, aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrous cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 2 and 6 times the oral MRHD on mg/m^2 basis and decreased fetal weight was seen at the highest dose which is 6 times the oral MRHD on mg/m^2 basis.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day, which are 6 to 19 times the oral MRHD on mg/m^2 basis, aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at the highest dose and prostate atrophy was seen at the mid and high dose which is 13 and 19 times the oral MRHD on mg/m^2 basis, but no impairment of fertility was seen.

13.2 Animal Toxicology and/or Pharmacology

Intramuscular administration of aripiprazole lauroxil to rats and dogs was associated with injection site tissue reactions at all doses in rats treated up to 6 months at doses of 14.7, 29,4, and 102.9 mg/animal (which are approximately X [requested that the sponsor add the multiples compared to the low doses as well] to 2 times and X to 4 times the MRHD of 882 mg on mg/m^2 basis in males and females, respectively) and in dogs treated up to 9 months at doses of 147, 662, and 2058 mg/animal (which are

approximately X to 8 times and X to 10 times the MRHD in males and females, respectively on mg/m^2 basis). These injection site tissue reactions consisted of localized granulomatous inflammation and granuloma formation. Transiently impaired limb function and swelling occurred in dogs. The granulomas did not completely resolve 2 months following the last injection in the 6 month rat study and 4 months following the last injection in the 9 month dog study (the low dose groups were not examined for reversibility in these studies).

Orally administered aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg, which is 19 times the oral MRHD of 30 mg/day on mg/m^2 basis, and in a 2-year carcinogenicity study at doses of 40 mg/kg and 60 mg/kg, which are 13 and 19 times the oral MRHD on mg/m^2 basis and 7 to 14 times human exposure at the oral MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

2 Drug Information

2.1 Drug

CAS Registry Number: 1259305-29-7

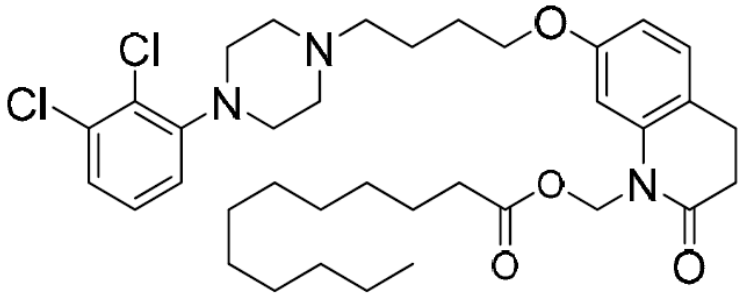
Generic Name: aripiprazole lauroxil

Code Name: ALKS 9072, RDC-3317

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

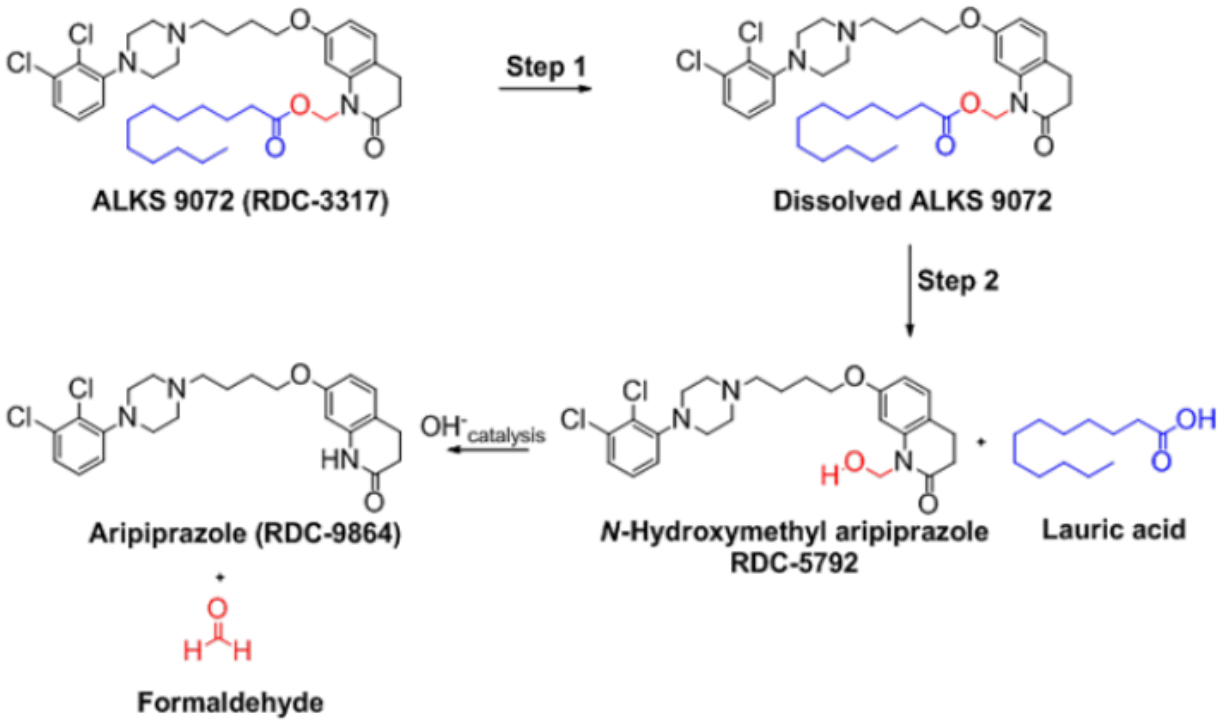
Structure or Biochemical Description:



Pharmacologic Class: antipsychotic

The following is the Sponsor's schematic of the conversion of aripiprazole lauroxil to aripiprazole.

Figure 1: Metabolic Pathway of Aripiprazole Lauroxil: Conversion to Aripiprazole



[Figure excerpted from NDA 207533 submission; pharmacokinetics written summary section]

Table 1: Aripiprazole lauroxil nomenclature

Common Name	Alkermes Number	Abbreviation
Aripiprazole lauroxil	RDC-3317; ALKS 9072	AL
N-hydroxymethyl aripiprazole	RDC-5792	NHA
Aripiprazole	RDC-9864	ARP
Dehydro-aripiprazole	RDC-3954	dARP

[Table excerpted from NDA 207533 submission; nonclinical overview section]

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 107,249
NDA for oral aripiprazole # 21-436, DMF (b) (4)
The sponsor is relying in part on the Agency's previous findings of safety and efficacy for oral aripiprazole (NDA 21-436) for the treatment of schizophrenia.

Table 2: Nonclinical references for approved findings for the reference listed drug Aripiprazole (Abilify®)

Study Type	Reference
Species Selection for Nonclinical Safety Assessment (Module 2.4, Section 1.2.1)	Summary Basis of Approval (SBA) for Abilify® Oral Tablet NDA, [NDA 21-436; 2002]
Safety Pharmacology (Module 2.4, Section 2.3)	
Distribution (Module 2.4, Section 3.2.3)	
Systemic Toxicity in Acute & Repeat-Dose Toxicity Studies (Module 2.4, Sections 4.1.2 and 5.3)	
Immunotoxic and Phototoxic Effects & Abuse Liability (Module 2.4, Section 4.1.7)	
Pharmacokinetics (Module 2.4, Section 5.1)	
DART Studies (Module 2.4, Sections 4.1.5.1 and 5.5)	
Mechanism of Action (Module 2.4, Section 2.1)	Abilify® Package Insert [Otsuka Pharmaceutical Company 2013]
Secondary Pharmacodynamics (Module 2.4, Section 2.2)	
Distribution (Module 2.4, Section 3.2.3)	
Genotoxicity Potential (Module 2.4, Sections 4.1.3 and 5.4)	
Carcinogenicity (Module 2.4, Sections 4.1.4 and 4.1.7)	
Development & Reproductive Toxicology (Module 2.4, Sections 4.1.5 and 5.5)	

[Tables excerpted from NDA 207533; nonclinical overview section]

2.3 Drug Formulation

Extended-release injectable suspension for intramuscular injection provided in a single use pre-filled syringe. Proposed doses: 441, 662, and 882 mg.

Table 3: Composition of proposed aripiprazole lauroxil commercial drug formulation

Component	Amount (% w/w)	Function	Rationale
(b) (4) drug substance	(b) (4)	Active	(b) (4)
Sorbitan Monolaurate (SML)		(b) (4)	
Polysorbate 20			
Sodium Chloride			
Sodium Phosphate Dibasic Anhydrous			
Sodium Phosphate Monobasic			
WFI			

[Table excerpted from NDA 207533 submission; drug product section]

2.4 Comments on Novel Excipients

The aripiprazole lauroxil drug product suspension consists of aripiprazole lauroxil drug substance (b) (4) %), with a particle size centered in the range of about (b) (4) µm suspended in an aqueous injection vehicle. The to-be-marketed vehicle formulation, which was used in the multiple dose clinical study and in most nonclinical toxicity studies, contains sorbitan monolaurate (SML). SML is a (b) (4) in the vehicle with a final concentration of (b) (4) % in the suspension. SML has been used in approved drug products for other routes of administration (oral, ophthalmic, and topical), but is not found in currently approved human parenteral (e.g., IM, intravenous, subcutaneous) products. Therefore it is considered novel for this route of administration. The Sponsor conducted nonclinical safety studies to assess the overall safety of SML. This reviewer considers SML to be adequately qualified with respect to the amounts to be used in to-be marketed-marketed aripiprazole lauroxil drug product when administered via the intramuscular route. For the complete review all submitted information and data, see section 10 (Special Toxicology Studies). The following is the results from a search of FDA's inactive ingredient search for approved drug products:

Table 4: FDA Inactive Ingredient Database search of sorbitan monolaurate

Search Results for: "sorbitan monolaurate"

INACTIVEINGREDIENT[6]	ROUTE;DOSAGE FORM[7]	CAS NUMBER[8]	UNII[9]	MAXIMUM POTENCY[10]
(b) (4)				

Update Frequency: Quarterly
Data Through: September 16, 2013
Database Last Updated: October 24, 2013

2.5 Comments on Impurities/Degradants of Concern

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is patients with schizophrenia. The proposed dosing regimen is deltoid or gluteal administration, once monthly injections (441, 662, or 882 mg) or every 6 weeks (882 mg).

2.7 Regulatory Background

The following meetings had nonclinical questions/comments.
Pre-IND meeting: April 6, 2010
End of phase 2 meeting: September 15, 2011
Pre-NDA meeting: May 19, 2014

3 Studies Submitted

3.1 Studies Reviewed

Table 5: Nonclinical studies submitted with aripiprazole lauroxil

Study	Study No.	Concentration or Dose[a]	Tabulated Summary
Single-Dose Toxicity Incorporating Safety Pharmacology Endpoints (Dog Studies)			
Single-Dose IM Study in Rats	AT-3317-04	10, 20, 60 (30×2 sites) mg/rat	2.6.7.7
Single-Dose IM Study in Dogs	AT-3317-05	100, 300, 1000 (500×2 sites) mg/dog	2.6.7.7
Repeat-Dose Toxicity Incorporating Safety Pharmacology Endpoints (Dog Studies)			
4-Month IM Study in Rats	AT-3317-10	10, 20, 60 (30×2 sites) mg/rat; (4 monthly doses)	2.6.7.8
6-Month IM Study in Rats	AT-3317-14	10, 20, 70 (35×2 sites) mg/rat; (6 monthly doses)	2.6.7.8
4-Month IM Study in Dogs	AT-3317-09	100, 300, 1200 (600×2 sites) mg/dog; (4 monthly doses)	2.6.7.8
9-Month IM Study in Dogs	AT-3317-13	100, 450, 1400 (700×2 sites) mg/dog; (9 monthly doses)	2.6.7.8
Safety Pharmacology[b]			
hERG Patch Clamp Assay	AT-3317-08	0.03, 0.1, 0.3 µM	2.6.3.4

Study	Study No.	Concentration or Dose[a]	Tabulated Summary
Pharmacokinetic			
Single-Dose IM Study Comparing Whole Blood and Plasma Exposure of Analytes	AT-3317-22	1400 (700×2 sites)	2.6.5.3
Genotoxicity			
Bacterial Mutagenicity	AT-3317-06	50-5000 µg/plate	2.6.7.9
Mammalian Chromosomal Aberration	AT-3317-07	62.5-500 µg/mL	2.6.7.9
Developmental and Reproductive Toxicology			
IM Fertility and Early Embryonic Development to Implantation Study in Rats (males and females treated)	AT-3317-19	Males – 12, 33, 98 (49×2 sites) mg/rat; 3 doses on Days 1, 21, and 42 Females – 12, 33, 98 (49×2 sites) mg/rat 2 weeks prior to mating	2.6.7.12
IM Embryofetal Development Study in Rats	AT-3317-20	12, 33, 98 (49×2 sites) mg/rat; single dose on GD 3	2.6.7.13
IM Preliminary Embryofetal Development Study in Rabbits	AT-3317-18	164 (1 dose on GD 3), 656 (328×2 sites×1 dose on GD 3), 1968 (328×2 sites×3 doses on GD 3, 10, and 17) mg/rabbit	2.6.7.13
IM Definitive Embryofetal Development Study in Rabbits	AT-3317-21	164 (1 dose on GD 3), 492 (246×2 sites×1 dose on GD 3), 1968 (492×2 sites×2 doses on GD 3 and 10) mg/rabbit	2.6.7.13

Notes: All studies were conducted in accordance with US FDA GLP Regulations, 21 CFR Part 58.
Abbreviations: GD = gestation day; IM = intramuscular

[a] Doses of aripiprazole lauroxil for in vivo studies are reported in mg aripiprazole equivalents/animal; doses of aripiprazole lauroxil are ~1.47× greater based on differences in molecular weights of aripiprazole lauroxil (660.70 g/mole) and aripiprazole (448.39 g/mole). Aripiprazole lauroxil concentrations in genetic toxicity assays are reported in µg aripiprazole lauroxil/plate or µg aripiprazole lauroxil/mL.

[b] Neurofunctional, respiratory, and cardiovascular safety pharmacology endpoints were include in single-dose, 4-month, and/or 9-month repeat-dose general toxicology studies as noted in Table 4.

[Tables excerpted from NDA 207533; nonclinical overview section]

3.2 Studies Not Reviewed

A detailed written review of all methods of analysis studies is not included in this review.

3.3 Previous Reviews Referenced

Prior to June 30, 2014, the nonclinical reviewer for IND 107,249 was Dr. Elzbieta Chalecka-Franaszek. Many of the nonclinical studies which were submitted under IND 107,249 were reviewed by Dr. Chalecka-Franaszek and are summarized in this NDA review (see original IND review for detail).

4 Pharmacology

4.1 Primary Pharmacology

Following intramuscular injection, aripiprazole lauroxil is converted to aripiprazole. In vitro, aripiprazole lauroxil (AL) inhibited binding of agonists or antagonists to similar dopamine and serotonin receptor subtypes as aripiprazole (ARP) (D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2c}) (study no. LSC09-129). However, the percent inhibition of specific binding was much less for aripiprazole lauroxil compared to aripiprazole for the majority of receptor subtypes. Aripiprazole lauroxil had no measurable functional activity (agonistic or antagonistic) at these receptors up to the highest usable concentration (limited by solubility) compared to aripiprazole, with the exception of weak agonist activity at the 5-HT_{1A} receptor (EC_{50} > 3 µM) (study no. LSC09-193). Therefore, the efficacy of aripiprazole lauroxil is most likely due to aripiprazole and aripiprazole-related active metabolites. The sponsor did not investigate the binding potential of the intermediate, N-hydroxymethyl aripiprazole.

Table 6: Inhibition of agonist binding by 1x10^{-7} M aripiprazole lauroxil or aripiprazole at select dopamine and serotonin receptors

Receptor	Agonist Radioligand	Assay	Compound	% Inhibition of Control Specific Binding[a]
D_{2S}	1 nM [^{3}H] 7-OH-DPAT	human recombinant (HEK-293 cells)	AL ARP	61 100
D_3	0.15 nM [^{3}H] 7-OH-DPAT	human recombinant (CHO cells)	AL ARP	48 97
5-HT_{1A}	0.3 nM [^{3}H] 8-OH-DPAT	human recombinant (HEK-293 cells)	AL ARP	78 99
5-HT_{2A}	0.2 nM [^{125}I] (±)DOI	human recombinant (HEK-293 cells)	AL ARP	75 100
5-HT_{2B}	0.2 nM [^{125}I] (±)DOI	human recombinant (CHO cells)	AL ARP	74 99
5-HT_{2C}	0.2 nM [^{125}I] (±)DOI	human recombinant (CHO cells)	AL ARP	73 75

AL = aripiprazole lauroxil (RDC-3317); ARP = aripiprazole

[a] Percent inhibition of control specific binding = (100 - (measured specific binding/control specific binding) × 100)) obtained in the presence of AL or ARP

Table 7: Inhibition of antagonist binding by $1x10^{-7}$ M aripiprazole lauroxil or aripiprazole at select dopamine and serotonin receptors

Receptor	Antagonist Radioligand	Assay	Compound	% Inhibition of Control Specific Binding[a]
D_{2S}	0.3 nM [^{3}H] spiperone	human recombinant (HEK-293 cells)	AL ARP	31 99
D_{2L}	0.3 nM [^{3}H] spiperone	human recombinant (HEK-293 cells)	AL ARP	35 101
D_3	0.3 nM [^{3}H] spiperone	human recombinant (CHO cells)	AL ARP	75 100
5-HT_{2A}	0.5 nM [^{3}H] ketanserin	human recombinant (HEK-293 cells)	AL ARP	32 97
5-HT_{2B}	2 nM [^{3}H] mesulergine	human recombinant (CHO cells)	AL ARP	80 101
5-HT_2c	1 nM [^{3}H] mesulergine	human recombinant (CHO cells)	AL ARP	48 75

AL = aripiprazole lauroxil (RDC-3317); ARP = aripiprazole

[a] Percent inhibition of control specific binding = (100 - ((measured specific binding/control specific binding) × 100)) obtained in the presence of AL or ARP

Table 8: Aripiprazole lauroxil agonist activity in select dopamine and serotonin functional assay

Receptor Activity	Stimulus	Assay	Compound[a]	EC_{50}[b](agonist) (M)
D_{2S}	none (3 µM dopamine for control)	human recombinant (HEK-293 cells)	AL ARP	NC[c] 4.5×10^{-8}
D_3	none (300 nM dopamine for control)	human recombinant (CHO cells)	AL ARP	NC 4.9×10^{-8}
5-HT_{1A}	none (100 nM 8-OH-DPAT for control)	human recombinant (CHO cells)	AL ARP	$>3.0 \times 10^{-6}$ 1.1×10^{-7}
5-HT_{2A}	none (100 nM serotonin for control)	human recombinant (HEK-293 cells)	AL ARP	NC 9.4×10^{-8} (est[d])
5-HT_{2B}	none (100 nM serotonin for control)	human recombinant (CHO cells)	AL ARP	NC 2.2×10^{-9}
5-HT_2c	none (300 nM serotonin for control)	human recombinant (HEK-293 cells)	AL ARP	NC NC

AL = aripiprazole lauroxil (RDC-3317); ARP = aripiprazole

[a] Concentration ranges tested for AL and ARP ranged from 3×10^{-10} to 1×10^{-5} M and 1×10^{-10} to 1×10^{-5} M, respectively

[b] Concentration producing a half-maximal specific response

[c] Not calculable. Concentration-response curve showed <25% effect at highest usable concentration

[d] Estimated; maximum effect below 35% (partial agonist)

Table 9: Aripiprazole lauroxil antagonist activity in select dopamine and serotonin functional assay

Receptor Activity	Stimulus	Assay	Compound[a]	IC_{50}[b] (antagonist) (M)
D_{2S}	dopamine (30 nM)	human recombinant (HEK-293 cells)	AL ARP	NC[c] ND[d]
D_3	dopamine (10 nM)	human recombinant (CHO cells)	AL ARP	NC 1.9×10^{-6}
5-HT_{1A}	8-OH-DPAT (10 nM)	human recombinant (CHO cells)	AL ARP	NC NC
5-HT_{2A}	serotonin (3 nM)	human recombinant (HEK-293 cells)	AL ARP	NC 2.8×10^{-7}
5-HT_{2B}	serotonin (0.1 nM)	human recombinant (CHO cells)	AL ARP	NC ND
5-HT_{2C}	serotonin (10 nM)	human recombinant (HEK-293 cells)	AL ARP	NC 7.6×10^{-7}

AL = aripiprazole lauroxil (RDC-3317); ARP = aripiprazole

[a] Concentration ranges tested for AL and aripiprazole ranged from 3×10^{-10} to 1×10^{-5} M and 1×10^{-10} to 1×10^{-5} M, respectively

[b] Concentration causing half-maximal inhibition of the control-specific agonist response

[c] Not calculable. Concentration-response curve showed <25% effect at highest usable concentration

[d] Not determined. Test compound induced an agonist effect

[The above pharmacology tables were excerpted from NDA 207533 submission; pharmacology written summary section]

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted with aripiprazole lauroxil. Aripiprazole has actions at receptors other than those (i.e., D_2, 5-HT_{1A}, and $5HT_{2A}$) linked to efficacy, and these effects may have clinical relevance. For example, antagonist activity at α1 adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole (Abilify® Package Insert).

4.3 Safety Pharmacology

Cardiovascular, neurofunctional (functional observational battery) and pulmonary assessments were incorporated into the single-dose, 4-month repeat-dose, and 9-month repeat-dose (cardiovascular endpoints only) toxicology studies in dogs.

Cardiovascular:

The potential for aripiprazole lauroxil to inhibit the hERG (human ether-á-go-go-related gene) and have an effect on the cardiovascular system was evaluated in the hERG patch clamp assay using human embryonic kidney cells. The final concentrations of aripiprazole lauroxil used in the assay were 0.03, 0.1, and 0.3 µM. (b) (4)

Aripiprazole lauroxil inhibited hERG current by 5.7 ±1.3%, 27.7 ±0.6%, and 60.3 ± 2.7%

at 0.03, 0.1, and 0.3 μM, respectively, with an IC_{50} of 0.22 μM. The IC_{50} value for aripiprazole lauroxil was similar to those reported for aripiprazole and dehydro-aripiprazole, which inhibited hERG current *in vitro*, with IC_{50} values of 0.263 μM (118 ng/ml) and 0.289 μM (129 ng/ml), respectively.

In vivo cardiovascular assessments, including heart rate and quantitative and qualitative assessments of electrocardiograms (ECGs) were evaluated in the single-dose study in dogs. Measurements were recorded pretest and 2 weeks post dose, which was the anticipated T_{max} for aripiprazole, and prior to the 1-month and 2-month necropsies. There were no drug-related effects. Similar cardiovascular assessments were included in the 4-month repeat-dose dog study and measurements were taken pretest, 3 days after the first dose, which is the approximate T_{max} for aripiprazole lauroxil, and prior to the necropsy 1 month after the fourth dose. There were no drug-related effects for any parameter including QT interval prolongation. Heart rate, quantitative and qualitative assessments of ECGs, and indirect blood pressure parameters (systolic, diastolic, and mean arterial blood pressure) were evaluated in the 9-month repeat-dose dog study and measurements were taken pretest and prior to the necropsy 1 month after the ninth dose (this time frame is beyond the T_{max} for aripiprazole lauroxil and all metabolites, however these assessments were also conducted to evaluate any adverse effects of the excipient, sorbitan monolaurate). There were no drug-related effects.

Neurofunctional:
A functional observational battery (FOB) was included in the single-dose study in dogs. Evaluations were conducted pretest and 2 weeks post dose, which is the approximate T_{max} of aripiprazole, N-hydroxymethyl aripiprazole and dehydro-aripiprazole. Decreases in locomotor activity (46%-59% compared to controls) were observed at all dose levels for females and in some males, although due to differences between baseline responses in males from the control and drug-treated groups, it was difficult to conclude if the effects seen in males were drug-related. The decreased locomotor activity may be attributed, in part, to impaired limb function which was noted clinically in some animals. A similar FOB was included in the 4-month repeat-dose dog toxicity study and evaluations were conducted pretest and during week 2. There were no drug-related effects.

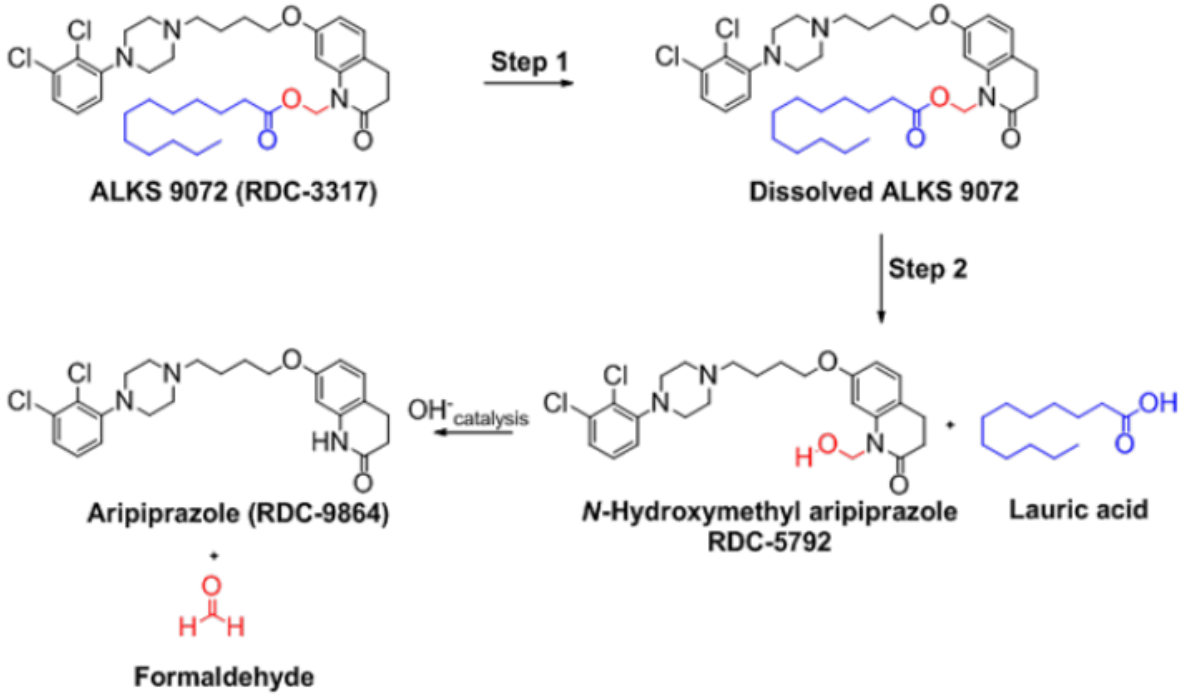
Respiratory:
Pulmonary assessments (respiratory rate, tidal volume, and minute volume) were included in the single-dose study in dogs. Evaluations were conducted pretest, 2 weeks post dose (which is the approximate T_{max} and aripiprazole, N-hydroxymethyl aripiprazole and dehydro-aripiprazole) and prior to the 1-month and 2-month necropsies. There were no drug-related findings. Similar pulmonary assessments were included in the 4-month study in dogs and assessments were taken pretest and on days 1 or 2 after the second monthly dose (which is near the T_{max} for aripiprazole lauroxil). There were no drug-related effects.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The biotransformation of aripiprazole lauroxil to the active moiety, aripiprazole, involves dissolution of [redacted] (b) (4) aripiprazole lauroxil at the injection site, uptake by the vascular system, followed by enzymatic cleavage by esterases in the blood to release lauric acid and the intermediate, N-hydroxymethyl aripiprazole. Dissociation of the N-hydroxymethyl group by water-mediated hydrolysis releases aripiprazole and formaldehyde.

Figure 2: Illustration of Biotransformation of Aripiprazole Lauroxil to Aripiprazole



[Figure excerpted from NDA 207533 submission; pharmacokinetics written summary section]

Pharmacokinetic (PK) parameters were measured in the single and repeat dose toxicity studies in rats and dogs. The only dedicated PK studies with aripiprazole lauroxil included a single-dose intramuscular study comparing whole blood and plasma exposure of all analytes in dogs, and an in vitro metabolism study investigating the stability of aripiprazole lauroxil and N-hydroxymethyl aripiprazole in rat, dog and human plasma.

Common Name	Alkermes Number	Abbreviation
Aripiprazole lauroxil	RDC-3317; ALKS 9072	AL
N-hydroxymethyl aripiprazole	RDC-5792	NHA
Aripiprazole	RDC-9864	ARP
Dehydro-aripiprazole	RDC-3954	dARP

[Table excerpted from NDA 207533 submission; nonclinical overview section]

Method of analysis:
GLP bioanalytical methods were developed and validated to determine concentrations of aripiprazole lauroxil, N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole in rat whole blood, dog whole blood and plasma, rabbit whole blood, and human plasma.

Absorption:
Concentrations of aripiprazole lauroxil were low and many times not measureable in rats due to the recognized high level of esterase activity in rat blood. However in dog, aripiprazole lauroxil concentrations were measurable at all dose levels to a varying degree. Aripiprazole lauroxil exposure levels were higher in dogs after a single intramuscular (i.m.) administration compared to multiple dosing and were measurable for <2 weeks following administration. Systemic exposure to aripiprazole and its metabolite, dehydro-aripiprazole, was limited in rats and dogs. It was not possible to increase exposures of aripiprazole in animal studies due the physiochemical properties of the formulation and limitations in dose volume/administration sites. As a result, exposure margins for aripiprazole and dehydro-aripiprazole in both rats and dogs compared to humans were <1.0. Therefore, nonclinical studies conducted in support of oral aripiprazole tablet (NDA 021-436; 2002) are referenced to provide an adequate safety assessment for aripiprazole and its metabolites (mainly dehydro-aripiprazole). Exposure to the intermediate N-hydroxymethyl aripiprazole was higher in both rats and dogs than in humans providing for an adequate safety assessment and determination of exposure margins > 1.

Following single or repeat intramuscular administration of aripiprazole lauroxil to rats, the highest amount of systemic exposure in whole blood was for N-hydroxymethyl aripiprazole > aripiprazole > dehydro-aripiprazole > aripiprazole lauroxil. Female rats had higher exposure levels of aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole compared to male rats irrespective of dose. There were no consistent differences between exposure levels of aripiprazole lauroxil in male and female rats (when measurable). There was very little drug accumulation (generally < 2-fold) for aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole in rats after repeat intramuscular dosing of aripiprazole lauroxil.

A similar exposure level profile was observed in dogs following single and repeat intramuscular administration of aripiprazole lauroxil, with the highest amount of systemic exposure to N-hydroxymethyl aripiprazole > aripiprazole > dehydro-aripiprazole >

aripiprazole lauroxil. Female dogs had about a 2-fold higher exposure to dehydro-aripiprazole compared to male dogs at most dose levels, while there was no evidence of any gender differences in exposure for any of the other analytes. There was very little drug accumulation (<2-fold) for all analytes in dogs after repeat intramuscular dosing of aripiprazole lauroxil.

Only sporadic and low levels of aripiprazole lauroxil were measurable in plasma from clinical studies (<lower limit of quantification (LLOQ) of 1 ng/ml). In contrast to rats and dogs, the highest systemic exposure in humans following an 882 mg intramuscular dose of aripiprazole lauroxil is for aripiprazole lauroxil, followed by aripiprazole > dehydro-aripiprazole and > N-hydroxymethyl aripiprazole, with no quantifiable measurement of aripiprazole lauroxil (refer to tables 12 and 13 below for human PK exposure data).

The time to maximal exposure (T_{max}) of aripiprazole lauroxil in rat whole blood ranged from 1-14 days. While T_{max} for aripiprazole, N-hydroxymethyl aripiprazole and dehydro-aripiprazole ranged from 9-18 days (average ~14 days for each analyte) after i.m. administration of aripiprazole lauroxil to rats. T_{max} values for all analytes were similar across dose levels and dosing interval.
T_{max} values for aripiprazole lauroxil and all analytes in dogs was similar to those observed in rats. T_{max} values for aripiprazole lauroxil in dogs varied and were not always able to be calculated (0.5-28 days) following i.m. administration. T_{max} values for aripiprazole, N-hydroxymethyl aripiprazole and dehydro-aripiprazole ranged from 7-15.5 days (average ~14 days for each analyte) after i.m. administration of aripiprazole lauroxil.

Whole blood was used as the sample matrix for nonclinical studies in order to better stabilize aripiprazole lauroxil and N-hydroxymethyl aripiprazole post-collection, while plasma was used as the sample matrix for all clinical trials. Therefore, a single-dose dog PK study (AT-3317-22) was conducted to compare exposure levels of aripiprazole lauroxil and all metabolites in plasma versus whole blood following a single intramuscular administration of aripiprazole lauroxil (1400 mg aripiprazole equivalents/animal) to male and female beagle dogs. There were no consistent gender differences in exposure levels or PK parameters for any analyte in whole blood or plasma. The combined mean T_{max} for aripiprazole lauroxil in both plasma and whole blood was 3.0 days and T_{max} values for all metabolites ranged from 13.0-16.0 days in both plasma and whole blood. The combined mean $t_{1/2}$ values for aripiprazole lauroxil and all metabolites ranged from 10.9-19.4 days in whole blood and 10.0-14.7 days in plasma. With the exception of aripiprazole, for which AUC and C_{max} values were comparable in plasma and whole blood, the AUC and C_{max} values for aripiprazole lauroxil, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole were higher in dog plasma than in whole blood. Since the nonclinical safety margins for aripiprazole lauroxil and all metabolites were based on calculations in whole blood compared to human exposures in plasma, the nonclinical safety margins would actually be equivalent or higher when comparing exposure levels in plasma (at least for dogs).

Table 10: Plasma PK parameters for aripiprazole lauroxil (RDC-3317), aripiprazole (RDC-9864), dehydro-aripiprazole (RDC-3954) and N-hydroxymethyl aripiprazole

(RDC-5792) in male and female dogs administered single intramuscular injection of aripiprazole lauroxil (1400 mg aripiprazole equivalents/animal)

Mean (±SD) Plasma PK Parameters for RDC-3317, RDC-9864, RDC-3954 and RDC-5792

Analyte	Sex	$AUC_{0-\infty}$ (day•ng/mL)	AUC_{0-55} (day•ng/mL)	$AUC_{0-tlast}$ (day•ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (day)	T_{max}* (day)
RDC-3317	Male	NC	31.6±7.35	28.5±7.79	4.06±1.63	NC	1.00
	Female	58.2	50.4±11.3	45.2±8.74	6.66±2.60	10.0	3.00
	Combined	58.2	41.0±13.4	36.8±11.8	5.36±2.46	10.0	3.00
RDC-9864	Male	1290±212	1140±246	1140±246	43.8±13.0	14.6±4.25	16.0
	Female	1460±197	1310±240	1310±240	58.2±21.8	14.5±7.15	16.0
	Combined	1370±214	1220±245	1220±245	51.0±18.5	14.5±5.54	16.0
RDC-3954	Male	734±353	677±315	677±315	28.1±13.2	11.0±2.26	16.0
	Female	1040±423	980±441	980±441	49.1±32.5	11.5±2.28	16.0
	Combined	887±401	829±395	829±395	38.6±25.9	11.2±2.16	16.0
RDC-5792	Male	3560±674	3090±715	3090±715	113±41.4	15.2±4.76	16.0
	Female	4180±318	3690±334	3690±334	148±44.8	14.2±3.11	13.0
	Combined	3870±593	3390±614	3390±614	131±44.7	14.7±3.83	16.0

*Median T_{max} is shown.
NC = not calculated; insufficient data.

Table 11: Whole blood PK parameters for aripiprazole lauroxil (RDC-3317), aripiprazole (RDC-9864), dehydro-aripiprazole (RDC-3954) and N-hydroxymethyl aripiprazole (RDC-5792) in male and female dogs administered single intramuscular injection of aripiprazole lauroxil (1400 mg aripiprazole equivalents/animal)

Mean (±SD) Whole Blood PK Parameters for RDC-3317, RDC-9864, RDC-3954 and RDC-5792

Analyte	Sex	$AUC_{0-\infty}$ (day•ng/mL)	AUC_{0-55} (day•ng/mL)	$AUC_{0-tlast}$ (day•ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (day)	T_{max}* (day)
RDC-3317	Male	45.1	20.7±4.16	18.2±4.02	2.67±1.16	19.4	1.00
	Female	NC	26.5±11.1	22.2±11.7	3.81±1.58	NC	3.00
	Combined	45.1	23.6±8.45	20.2±8.53	3.24±1.44	19.4	3.00
RDC-9864	Male	1210±216	1100±228	1100±228	43.8±12.1	12.5±3.50	13.0
	Female	1310±151	1210±154	1210±154	53.7±17.1	12.7±3.89	13.0
	Combined	1260±184	1150±192	1150±192	48.7±14.9	12.6±3.49	13.0
RDC-3954	Male	477±215	442±191	442±191	18.2±8.09	10.5±2.06	16.0
	Female	642±246	606±255	606±255	30.5±19.6	11.3±1.62	16.0
	Combined	559±234	524±229	524±229	24.4±16.5	10.9±1.79	16.0
RDC-5792	Male	1670±323	1390±307	1390±307	51.9±18.6	16.8±6.44	16.0
	Female	1810±179	1550±155	1550±155	61.1±16.2	14.9±4.62	16.0
	Combined	1740±257	1470±244	1470±244	56.5±17.1	15.8±5.38	16.0

*Median T_{max} is shown.
NC = not calculated; insufficient data.

[Table excerpted from NDA 207533 submission; study AT-3317-22]

Studies to evaluate the distribution of aripiprazole lauroxil were not conducted. Intravenous administration of the drug is not possible due to suspension formulation; therefore its volume of distribution is unknown.

Metabolism:
Aripiprazole lauroxil is converted to aripiprazole after intramuscular administration. Aripiprazole is subsequently metabolized primarily to dehydro-aripiprazole. Since the metabolism of aripiprazole is well established, this review focuses on the conversion of aripiprazole lauroxil to aripiprazole and the intermediate, N-hydroxymethyl aripiprazole, which is formed during the process. In vitro metabolism studies using microsomal or hepatocyte preparations were not conducted (b) (4)

The in vitro stability of aripiprazole lauroxil and the intermediate, N-hydroxymethyl aripiprazole, was evaluated in plasma from rats, dogs and humans (study 702-02912-02). Two concentrations of aripiprazole lauroxil (77 and 777 nM) were incubated with plasma from rat, dog or human at 37°C. The stability of aripiprazole lauroxil (RDC-3317) and formation of aripiprazole (RDC-9864) and the intermediate, N-hydroxymethyl aripiprazole (RDC-5792), was monitored over a 24 hour period. In rat plasma, the intermediate was formed and could be measured (higher than aripiprazole lauroxil and aripiprazole) at the first time point of 10 minutes. This was most likely due to high esterase activity in rat plasma and the rapid conversion of aripiprazole lauroxil to N-hydroxymethyl aripiprazole. The conversion of aripiprazole lauroxil to the intermediate and subsequent release of the N-hydroxy group to form aripiprazole was independent of concentration in rat plasma. The mean half-life of aripiprazole lauroxil in rat plasma in vitro was 31 minutes. Aripiprazole was stable in rat plasma over the 24 hour incubation time. In contrast, when using dog and human plasma, there was no appearance of either the N-hydroxymethyl aripiprazole intermediate or aripiprazole in vitro, but aripiprazole lauroxil was stable over the 24 hour incubation. The sponsor proposed that this is due to the low levels of esterases in dog and human plasma, and conversely rats have high plasma esterase activity.

Figure 3: Incubation of aripiprazole lauroxil in rat plasma at 37°C (777 nM)

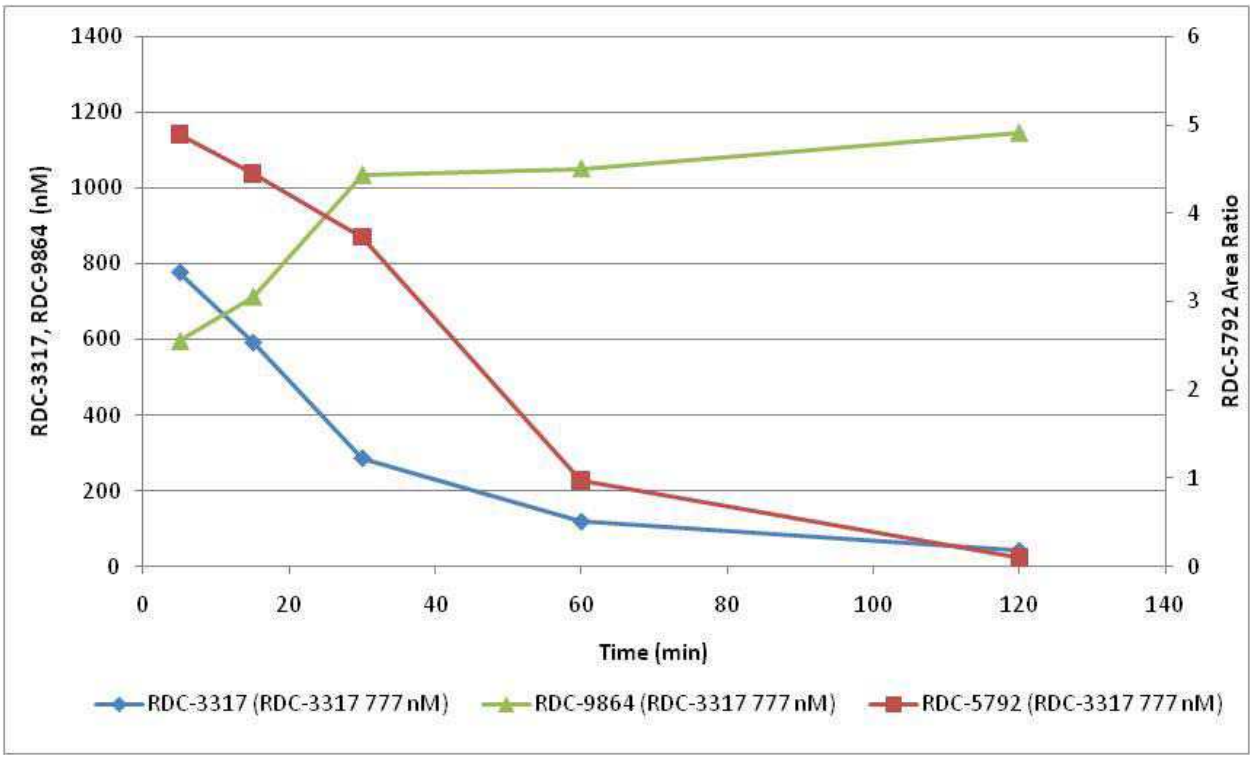


Figure 4: Incubation of aripiprazole lauroxil in dog plasma at 37°C (777 nM)

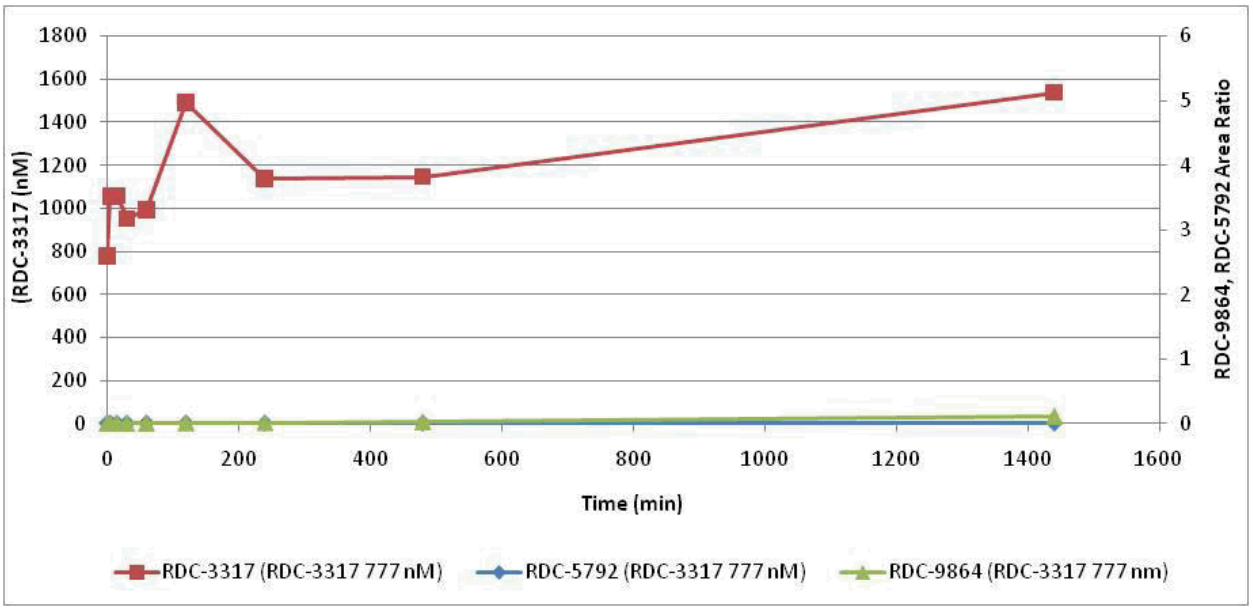


Figure 5: Incubation of aripiprazole lauroxil in human plasma at 37°C (777 nM)

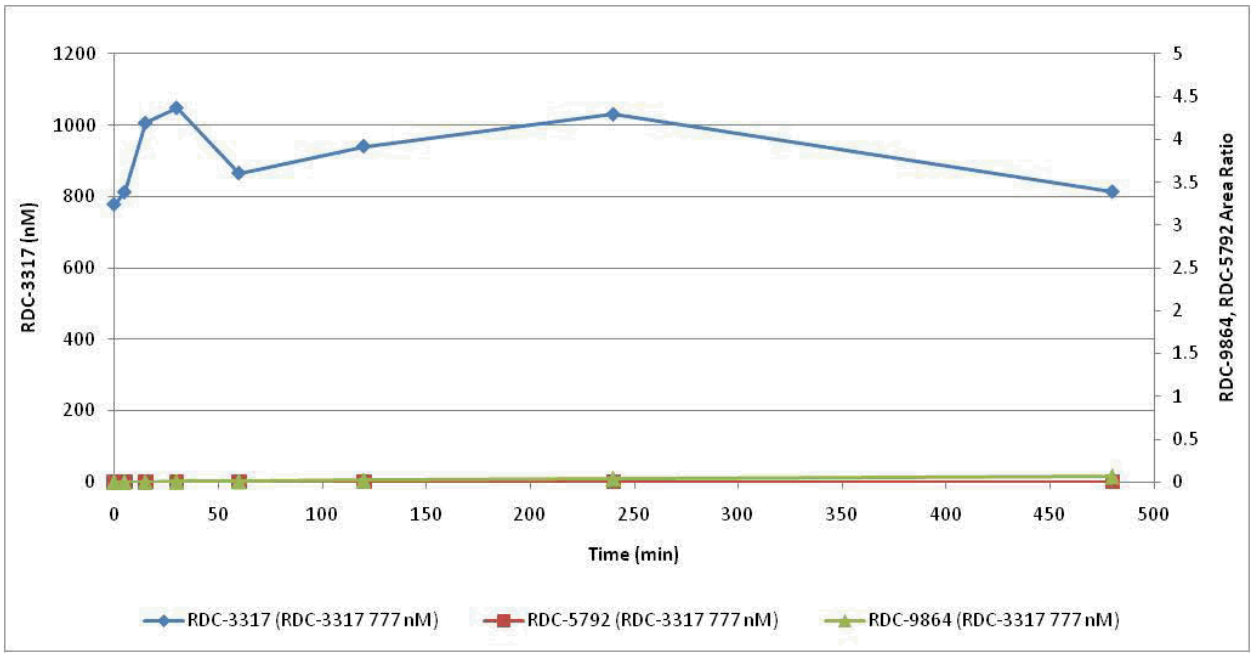
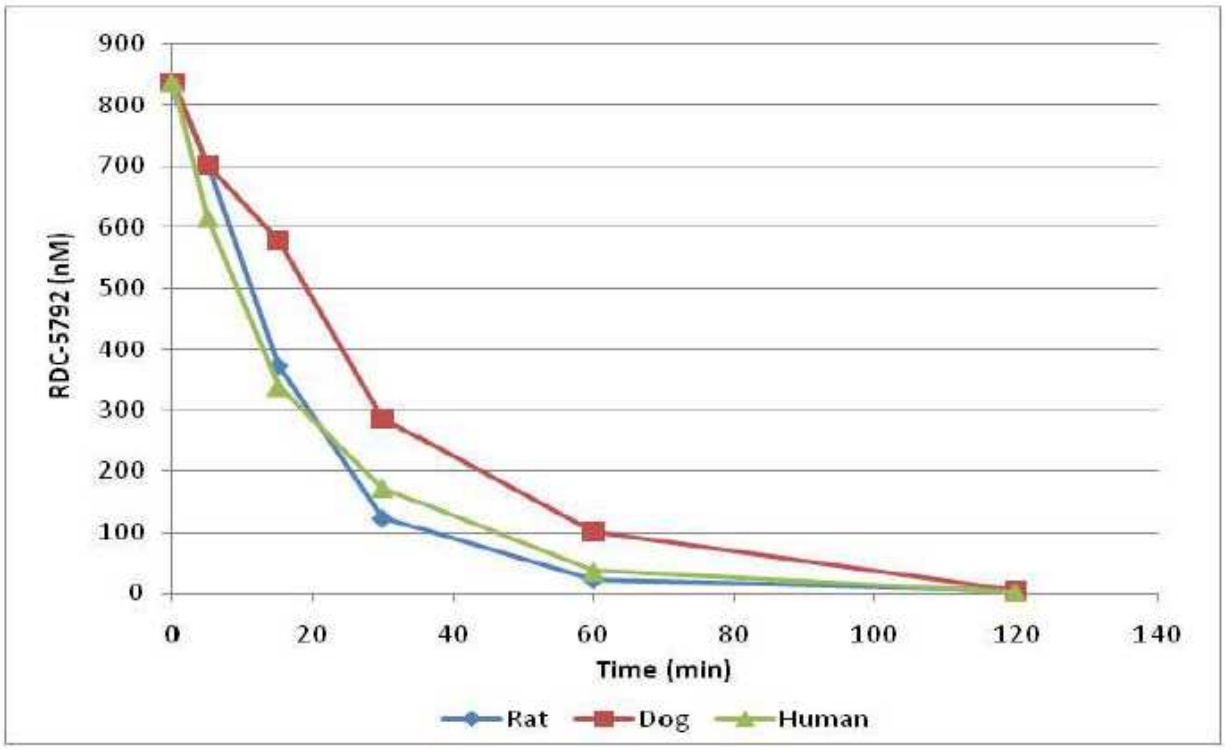


Figure 6: Plasma stability of N-hydroxymethyl aripiprazole (873 nM) in rat, dog and human plasma at 37°C



[Above graphs excerpted from NDA 207533 submission; study 702-02912-02]

The in vitro stability of N-hydroxymethyl aripiprazole (873 nM initial concentration) was also evaluated in rat, dog and human plasma (last graph). The half-life of N-hydroxymethyl aripiprazole in rat, dog and human plasma at 37°C ranged from 12-17 minutes with first-order correlation through at least 4 half-lives. The half-life of N-hydroxymethyl aripiprazole in a pH 7.0 aqueous buffer at 37°C was also measured to be 19 minutes which supports a non-enzymatic hydrolysis mechanism of conversion.

N-hydroxymethyl aripiprazole is formed in human plasma after intramuscular administration, although to a lesser extent than that in rats and dogs. The maximum concentrations of N-hydroxymethyl aripiprazole reported in human plasma from clinical trials across all dose groups were achieved by approximately 3 to 13 days after administration of aripiprazole lauroxil. The mean AUC_{tau} was 332.9, 454.4, and 471.8 day*ng/mL following the fourth dose (approximately at steady state) for the 441, 662, and 882 mg dose groups, respectively. Exposure to N-hydroxymethyl aripiprazole in humans was approximately 8.5-11.3% of the exposure to aripiprazole, and values would be even lower if compared to total drug-related material. The maximum exposure level of N-hydroxymethyl aripiprazole in dogs (whole blood) observed at the highest intramuscular dose of 1400 mg aripiprazole equivalents/animal in the 9-month study was $AUC_{225-252}$ = 1160/1400 ng.day/ml in males and females, respectively, at 28-days following the last (9^{th}) dose. This is 5.7/6.8-fold (males/females) greater than the levels observed in clinical trials (471.8 ng.day/ml in plasma), after dividing by a conversion factor of 0.435 to adjust for differences between plasma and whole blood exposures in humans and dog. The highest exposure of N-hydroxymethyl aripiprazole in the 6-month repeat dose study in rats provides a margin of 2.3/4.2 (males/females) compared to the maximum clinical exposure. Therefore, N-hydroxymethyl aripiprazole has been adequately covered in nonclinical species. The following tables were reviewer generated.

Table 12: Exposure levels (AUC) after single intramuscular dose of aripiprazole lauroxil (ng.day/ml)

	Rat (M/F)	Dog	Human
AL	1.16 (combined)	43.3	NC
NHA	821/1380	897	57.4
ARP	418/683	600	487
dARP	51.3/57.4	461	119

AUC values represent the 28 or 34-day period following first dose (AUC_{0-28} for rats and dogs AUC_{0-34} for humans)

Table 13: Exposure levels (AUC) after repeat intramuscular dosing of aripiprazole lauroxil (ng.day/ml)

	Rat (M/F)	Dog	Human
AL	2.89 (combined)	8.25	NC
NHA	1100/1960	1280	472
ARP	659/1420	835	5559
dARP	60.1/103	749	1700

Data taken from 6-month rat study (AT-3317-14), 9-month dog study (AT-3317-13), and clinical study (ALK9072-002): highest dose values reported for rat: 70 mg ARP equiv./animal and dog: 1400 mg ARP equiv./animal, human: 882 mg AL (600 mg ARP equiv.)
AUC values represent the 28-day period following the last dose (rat: $AUC_{141-168}$, dog: $AUC_{225-252}$, human: AUC_{118})
Whole blood samples used for rat and dog, plasma for human
Values for dog and human are combined sexes
NC = Not calculated (due to minimal/non-quantifiable)

Excretion:
Dedicated excretion studies were not conducted with aripiprazole lauroxil, however results from in vitro metabolism/stability and toxicokinetic studies suggest that the primary route of elimination of aripiprazole lauroxil is metabolism. Aripiprazole lauroxil is metabolized via esterase cleavage to N-hydroxymethyl aripiprazole and lauric acid, and then undergoes conversion to aripiprazole, via hydrolysis, and releases formaldehyde.

Urine or feces measurements of aripiprazole or any analytes was not conducted in any species.

Lauric acid is a fatty acid is eliminated by the fatty acid degradation pathway similar to other fatty acids in the body. B-oxidation of fatty acids occurs in the mitochondria matrix, resulting in the production of acetyl-CoA, which then enters the citric acid cycle. Formaldehyde is rapidly cleared in humans. Metabolic clearance occurs either by oxidative metabolism to form formic acid which is then eliminated in the urine, or it is further metabolism to carbon dioxide. Formaldehyde can also be incorporated into other molecules in vivo or can react with proteins, amino acids, DNA or RNA as part of the one carbon pool.

The elimination pathway of aripiprazole was characterized during the development of oral aripiprazole. Aripiprazole is primarily excreted in feces in rats, monkeys and humans.

5.2 Toxicokinetics

Tables of PK values are included in the review of toxicity studies in section 6.2 below.

6 General Toxicology

Toxicology studies using aripiprazole lauroxil were conducted at doses up to those maximally feasible based on physiochemical limitations of the formulation and maximum acceptable intramuscular dose volumes/sites of administration in rats, dogs, and rabbits. The maximum feasible dose for a given species increased over the course of nonclinical development due to increases in allowable dose volumes by the sponsor's Institutional Animal Care and Use Committees based on favorable tolerability and/or higher drug loads of aripiprazole lauroxil in newer formulations.
All doses of aripiprazole lauroxil used in nonclinical studies were administered as aripiprazole free base equivalent doses, and were corrected for aripiprazole lauroxil molecular weight (which is 1.473× greater than the molecular weight of aripiprazole). Aripiprazole lauroxil dose levels were also set to fixed doses in milligrams (mg) and not milligrams/kilogram (mg/kg) and were administered in a fixed volume.

It is noted that monkeys were used as the non-rodent species in aripiprazole toxicology studies supporting the safety of oral aripiprazole tablet (NDA 21-436), however the current sponsor selected dogs due to increased muscle mass in this species, and therefore, the ability to assess local tolerability in multi-dose studies at higher doses than would have been feasible in monkeys. Rats were used as the rodent species in toxicology studies for both oral aripiprazole and for aripiprazole lauroxil.

An amendment to the final study report for all pivotal toxicity study reports was included in the NDA submission. The amendment stated that "*a GLP exception has been added to indicate that the test article was not characterized following GLP procedures, but was instead characterized in accordance with standard operating procedures and accepted industry practices for non-Good Manufacturing Practices (GMP) material.*" An

information request was sent to the sponsor to provide further information on this exception. The sponsor responded on September 10, 2014 in SDN 3. They indicated that the test article was stated as non-GMP material because the (b) (4) manufacturing process had not been fully qualified prior to being used to manufacture the toxicology material. They also provided documentation of the procedures for characterization and stability testing of toxicology test articles. They concluded that the GLP exception had no impact on the studies because the toxicology test articles were well-characterized and the procedures were consistent with CFR section 58.105 (test and control article characterization). This reviewer considered the sponsor's response to be acceptable and that the GLP exception did not impact the study data.

All tables in the following toxicity study sections are excerpted from the individual study reports in the sponsor's NDA submission.

6.1 Single-Dose Toxicity

GLP single intramuscular dose toxicity studies were conducted in rats and dogs with 1- and 2-month recovery periods.

In the single-dose rat study (AT-3317-04), Sprague-Dawley rats (20/sex/group) were administered single intramuscular (i.m.) injections of aripiprazole lauroxil at doses of 0, 10, 20 or 60 (2 x 30) mg aripiprazole equivalents/animal in a volume of 0.2 ml/injection to one hindlimb. The high dose was divided into two 30 mg doses, one to each hindlimb. The control group was administered a single i.m. injection of the vehicle, (b) (4) % (b) (4) % Tween 20, (b) (4) % sodium chloride (b) (4) mM phosphate (b) (4) Half of the rats were sacrificed 1-month after dosing, while the remaining 10 rats/group were sacrificed 2-months following dosing to evaluate reversibility of any findings. Toxicity findings at the 1-month necropsy were limited to local reactions at the injection site at all doses in both males and females. The local reactions at the injection site were characterized as mild tan focus/foci observed macroscopically and minimal to moderate granulomas observed microscopically. The findings were observed at all dose levels in both males and females, but the incidence and severity was clearly dose-related. At the 2-month necropsy, similar macroscopic findings were only observed in a few high dose animals. However, similar microscopic findings of granulomas were still observed at all dose levels in both males and females, but the incidence and severity was decreased, indicating partial reversibility. No toxicity, including local injection site reactions and granulomas, were observed in any rats administered the vehicle control. The injection site local reactions were clearly drug-related since they were dose-related in both incidence and severity and were not observed in any control animals. Exposure levels, AUC, could not be calculated for aripiprazole lauroxil at any dose level or for dehydro-aripiprazole at 10 and 20 mg, due to only few samples with detectable levels in whole blood. The high dose was considered the NOAEL based on the absence of any damage to surrounding muscle myofibers and evidence of partial reversibility.

In the single-dose dog study (AT-3317-05), beagle dogs (6/sex/group) were administered single i.m. injections of aripiprazole lauroxil at doses of 0, 100, 300 or 1000 (2 x 500) mg aripiprazole equivalents/animal in a volume of 2 ml/injection to one

hindlimb for the control, 100 and 300 mg groups and 3.33 ml/injection site for the 1000 mg group. The high dose was divided into two 500 mg doses, one to each hindlimb. The control group was administered a single i.m. injection of the vehicle, (b) (4)% (b) (4)% Tween 20, (b) (4)% sodium chloride, 5.9 mM phosphate (b) (4) Half of the dogs were sacrificed 1-month after dosing, while the remaining 3 dogs/group were sacrificed 2-months following dosing to evaluate reversibility of any findings. Additional safety pharmacology endpoints included a functional observational battery (FOB), respiratory endpoints (rate, tidal volume and minute volume), and cardiovascular endpoints (qualitative and quantitative ECG parameters) at pre-study, during week 2 and prior to necropsy.
Toxicity findings were limited to clinical signs and local reactions at the injection sites. The observed clinical signs were related to i.m. dosing of the test article and consisted of impaired hindlimb function, swelling at the injection site, and a decrease in locomotor activity in the functional observational battery conducted on day 14. The decrease in locomotor activity was most likely related to the impaired hindlimb function due to the i.m. injection. A nodule was observed in one high dose female and a mild hypersensitivity reaction was observed in one mid dose male. Local injection site reactions at the 1-month necropsy consisted of accumulations of foreign material observed macroscopically and mild to severe granulomas observed microscopically in almost all drug-treated animals. The severity was dose-related. At the 2-month necropsy, macroscopic findings at the injection site were only observed in the high dose animals. Granulomas were still observed at all dose levels at the 2-month necropsy although the incidence and severity was decreased indicating partial reversibility. There were no effects on any respiratory or cardiovascular endpoints. The high dose was considered the NOAEL based on the absence of any damage to adjacent muscle myofibers and evidence of partial reversibility. Aripiprazole lauroxil, aripiprazole and dehydro-aripiprazole were quantifiable at all dose levels in dog whole blood samples.

It should be noted that a different vehicle was used in the single-dose toxicity studies than that of the final to be marketed clinical formulation. The clinical formulation, containing sorbitan monolaurate, was used in all subsequent repeat-dose toxicity studies. At the time the single-dose toxicity studies in rats and dogs were conducted, validated analytical methods were not available to measure the N-hydroxymethyl aripiprazole intermediate. However, methods became available to measure exposure levels of the intermediate in subsequent repeat-dose toxicity studies.

6.2 Repeat-Dose Toxicity

GLP repeat dose intramuscular toxicity studies were conducted in rats (4-month and 6-month with 1- and 2-month recovery periods each) and in dogs (4-month with 1- and 2-month recovery periods and 9-month with 1- and 4-month recovery periods). In all studies, aripiprazole lauroxil was administered once a month.

In the rat 4-month study (AT-3317-10), Sprague-Dawley rats (15/sex/group) were administered once monthly i.m. injections of vehicle 1 ((b) (4)% sorbitan monolaurate, (b) (4)% polysorbate 20, (b) (4)% sodium chloride, (b) (4)% sodium

phosphate monobasic dehydrate, (b) (4)% sodium phosphate dibasic anhydrous, and (b) (4)% water), vehicle 2 which contained the same excipients as vehicle 1 but a higher amount of sorbitan monolaurate ((b) (4)%) and polysorbate 20 ((b) (4)%) and lower amounts of water (b) (4)%), or aripiprazole lauroxil (10, 20, or 60 mg [2x30 mg] aripiprazole equivalents/animal). Vehicle 1 was used to formulate aripiprazole lauroxil and vehicle 2 was used to gain additional safety data on sorbitan monolaurate. It should be noted that no control was used that did not contain sorbitan monolaurate, therefore all animals received sorbitan monolaurate which makes for assessing potential toxicity due to sorbitan monolaurate alone not possible. 10 rats/group were sacrificed 1-month after the fourth dose and the remaining 5 rats/group were sacrificed 2-months following the last dose. Both vehicle 1 and 2 and the 10 and 20 mg/animal groups received treatment in one hindlimb in a 0.2 ml volume, and the monthly injections were rotated between both hindlimbs. The high dose group, 60 mg/animal, received injections to both hindlimbs (30 mg/injection) in a 0.2 ml volume. Satellite animals were used for toxicokinetic analysis.

There were no signs of systemic toxicity in any of the drug-treated groups or in either of the vehicle groups. Local toxicity at the injection site(s) was observed in all drug-treated groups and also at a low incidence in the vehicle control group 2 ((b) (4)% SML). Discoloration at the injection site(s), which correlated with granulomas observed microscopically, was observed at and near the injection sites in all drug-treated groups. The incidence was dose-related with respect to frequency and severity, and was present at both the 1- and 2-month necropsies. There were no adverse reactions observed in the vehicle 1 group (b) (4)% SML), however granulomas were seen in the vehicle 2 group ((b) (4)% SML) at the 1-month necropsy, although at a very low frequency. There was no NOEL for local toxicity at the injection sites, although the findings were not considered adverse as there was no toxicity to surrounding muscle tissue. The NOAEL for systemic toxicity was the highest dose (60 mg aripiprazole equivalents/animal).

In the dog 4-month study (AT-3317-09), beagle dogs (3-5/sex/group) were administered once monthly i.m. injections of vehicle 1, vehicle 2, or aripiprazole lauroxil (100, 300, or 1200 mg [2x600 mg] aripiprazole equivalents/animal) for 4 months. The vehicles used in this study were identical to those used in the 4-month rat study and also in the 6-month rat and 9-month dog studies. Both vehicle 1 and 2 and the 100 and 300 mg/animal groups received treatment in one hindlimb in a volume of 2 ml (aripiprazole lauroxil) or 4 ml (controls), and the injections were rotated between the left and right hindlimbs. The high dose group received treatment in both hindlimbs (600 mg each hindlimb) in a volume of 4 ml. Three dogs/group were sacrificed 1 month following the last dose and the remaining 2 dogs/group in the vehicle 1 and the 300 and 1200 mg/groups were sacrificed 2-months following the last dose. Safety pharmacology endpoints included a functional observational battery (FOB) conducted pretest and during week 2 and pulmonary function (respiratory rate, tidal volume and minute volume) at pretest and on 1 or 2 days following the second dose. There were no

drug-related effects in any FOB or pulmonary function assessments.
There was no evidence of any systemic toxicity in any of the drug-treated groups or in either vehicle group. Mild hypersensitivity reactions were observed in two high dose females. A few high dose animals had decreased activity and slightly impaired hindlimb function after the first dose. Nodules were noted on the hind limbs of one mid and 2 high dose males which lasted up to 20 weeks following injection (time of the last assessment). Macroscopic findings of white discoloration at the injection sites were observed in all drug-treated animals and were still present at the 2-month necropsy. The macroscopic findings correlated with granulomas observed microscopically at the injection sites in all drug-treated groups. The granulomas were still present at the 2-month necropsy, showing a lack of full reversibility. Minimal myofiber degeneration was observed in only one animal; therefore the toxicological significance is unknown. Macroscopic findings of white discoloration was also observed at the injection sites of 1/3 males and 1/3 females from the vehicle 2 group containing (b) (4)% SML. Granulomas were observed microscopically in 1/3 males and 3/3 females in the vehicle 2 group (all minimal in severity with the exception of one high dose female with moderate severity). The sponsor did not include the vehicle 2 group in the 2-month necropsy to look at reversibility of this finding. The observation of granulomas in the vehicle 2 group suggests a local inflammatory reaction to excipient SML at (b) (4)% concentration, however the frequency was less than that of the drug-treated groups and there were no findings in the vehicle 1 group containing (b) (4)% SML. There were no drug-related findings in any of the safety pharmacology assessments. There was no NOEL for local toxicity at the injection sites, although the findings were not considered adverse as there was no toxicity to surrounding muscle tissue. The NOAEL for systemic toxicity was the highest dose (1200 mg aripiprazole equivalents/animal).

Granulomas were also observed in drug-treated animals in the single-dose toxicity studies in rats and dogs in which a different vehicle, not containing sorbitan monolaurate, was used indicating that the injection site reactions (granulomas) are mainly due to the drug, aripiprazole lauroxil itself, and not an interaction of the drug with the vehicle.

Study title: RDC-3317: A 6-Month Intramuscular Toxicity Study in Rats with 1- and 2-Month Recoveries

The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek. The current reviewer agrees with Dr. Chalecka-Franaszek's findings and an abbreviated review is included below. For the full review, see Dr. Chalecka-Franaszek's review in DARRTS under IND 107,249.

Study no.:	AT-3317-14
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 15, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 (RDC-3317; extended release ester of aripiprazole), lots 100-01475 (purity 98.01%) and 100-01477 (purity 98.21%).

Key Study Findings

- One male in the vehicle 2 group was found dead on Day 21; no cause of death was determined.
- Drug-related macroscopic findings of mild tan discoloration at the injection sites were noted in male and female rats at all dose levels at 1-month post-last dose necropsy. No macroscopic findings were observed at the injection sites at 2-month post-last dose necropsy, indicating reversibility.
- Minimal to moderate granulomas were observed microscopically at the injection sites at 1- and 2-month post-last dose necropsies in all drug-treated animals. The incidence and severity of granulomas was dose-related. Granuloma was also observed in one female at 1-month post-last dose necropsy from the vehicle 2 group. The severity of the granulomas was decreased at the 2-month post-last dose necropsy as compared to the 1-month necropsy, indicating partial reversibility. Based on the absence of damage to the adjacent myofibers, the granuloma formation was not considered adverse by the sponsor.

NOAEL = 70 mg arip.eq./animal (35 mg/site) (102.9 mg aripiprazole lauroxil/animal) Associated mean aripiprazole lauroxil $AUC_{0\text{-tlast}}$ and C_{max} (after the 6^{th} dose) values were 138 ng•day/mL and 0.413 ng/mL, respectively, for males and females combined. The $AUC_{0\text{-tlast}}$ and C_{max} values for other analytes at the NOAEL were 4410 and 7990 ng•day/mL and 29.2 and 62.4 ng/mL (males and females, respectively) for aripiprazole, 389 and 591 ng•day/mL and 2.64 and 4.85 ng/mL (males and females, respectively) for dehydro-aripiprazole; and 7020 and 12100 ng•day/mL and 45.9 and 92.6 ng/mL (males and females, respectively) for N-hydroxymethyl aripiprazole.

Methods

Doses:	0, 0, 10, 20, and 70 mg (2x35 mg/site) aripiprazole equivalents (arip.eq.)/animal Aripiprazole lauroxil dose = 1.47x (14.7, 29.4, 102.9 mg aripiprazole lauroxil/animal)
Frequency of dosing:	Once per month on six separate occasions (Days 1, 29, 57, 85, 113, and 141)
Route of administration:	Intramuscular injection; LD and MD were dosed in alternating hind limbs; Vehicle 1, Vehicle 2, and HD animals were administered the test article in two injections/dose using both hind limbs (for the HD at 35 mg/site for a total dose of 70 mg arip.eq./animal)
Dose volume:	0.2 or 0.21 mL/site
Formulation/Vehicle:	Vehicle 1: (b) (4)% sorbitan monolaurate (SML), (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water
Species/Strain:	Rat/CD® [Crl:CD®(SD)]
Number/Sex/Group:	20/sex in the Vehicle 1, MD and HD groups; 15/sex in the Vehicle 2 and LD groups
Age:	Approximately 6 weeks of age at study initiation
Weight:	Males 242 to 285 g, females 174 to 222 g
Satellite groups:	The first 15 animals/group were maintained on study for a 1-month post-last dose recovery period. The last five animals (Vehicle 1, MD, HD groups) were maintained on study for a 2-month post-last dose recovery period. TK groups: 4/sex/Vehicle 1 group; 7/sex/LD, MD and HD groups; none for the Vehicle 2 group
Unique study design:	An additional objective of the study was to evaluate the tolerability of a second vehicle (Vehicle 2), which contained higher concentrations of SML and polysorbate 20 than those in the vehicle (Vehicle 1-Control) used to formulate aripiprazole lauroxil (Vehicle 2: (b) (4)% SML, (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water
Deviation from study protocol:	In the opinion of this reviewer, none of the protocol deviations affected the quality or integrity of the study.

Observations and Results

Mortality

All animals were observed for morbidity, mortality, and injury at least twice daily. There were no test article-related deaths. One male in the vehicle 2 group (animal number 1034) was found dead on Day 21. The cause of death could not be determined because no significant macroscopic or microscopic findings were observed in this animal.

Clinical Signs

Cage-side observations were conducted twice daily. A detailed clinical examination of each animal was performed weekly. Swelling of the hind limb was noted in several animals administered MD and HD of aripiprazole lauroxil in weeks 1 to 20 (number of times observed/total number of animals affected: 16/7 in HD males, 1/1 in MD females, and 2/2 in HD females) but not later during the study. According to the Sponsor, these may have been related to the injection site procedure but a clear dose-response relationship was not evident. Therefore, this finding was considered incidental. However, this reviewer concluded that the swelling of the hind limbs was test article-related because it was observed only in the MD and HD animals, with an increased incidence at the HD. Moreover, skin was discolored (brown) in several MD and HD animals (number of times observed/total number of animals affected: 24/9 in MD males, 16/6 in HD males, 1/1 in MD female, and 2/2 in HD females). The toxicological significance of this observation is unclear. There were no adverse clinical signs in the vehicle 1 and vehicle 2 groups.

Body Weights

Body weights were measured and recorded prior to dose administration and weekly during the study. Body weight tended to be lower (although not statistically significant) in HD males during study. Statistical significance ($p<0.05$) was reached only in Week 7. This effect correlated with decrease in food consumption. There were no differences in body weights between the vehicle 1 and vehicle 2 groups.

Food Consumption

Food consumption was lower by 6-14% in the HD males compared to the vehicle 1 group during Weeks 7-17 and during Weeks 25-28, although not always statistically significant. Although they were test article-related, the magnitude of these changes was small. There were no differences in food consumption between the vehicle 1 and vehicle 2 groups. Food consumption was measured and recorded weekly.

Ophthalmoscopy

There were no test article-related ophthalmic findings.
Examinations were conducted on all animals pre-test and on main-study animals prior to the 1-month post-last dose necropsy on Day 170.

ECG not conducted

Hematology

There were no test article-related effects among hematology parameters. Coagulation parameters: HD females had minimal (+4%; 0.67 sec) prolongation in the prothrombin time that was statistically significant. However, this finding was considered incidental

based on its small magnitude and lack of similar findings in males. There were no differences in hematology and coagulation parameters between the vehicle 1 and vehicle 2 groups.
Clinical pathology evaluations were conducted on designated main-study animals (14-15/sex/group) at the 1-month post-last dose necropsy (Day 171). An adequate battery of hematology and coagulation parameters was evaluated, no pre-dose samples were taken.

Clinical Chemistry

There were no test article-related clinical chemistry findings. There were no differences in clinical chemistry parameters between the vehicle 1 and vehicle 2 groups and all values for both vehicles were within the historical control ranges.
Clinical chemistry evaluations were conducted on designated main-study animals (14-15/sex/group) at the 1-month post-last dose necropsy (Day 171), no pre-dose samples were taken. An adequate battery of clinical chemistry parameters was evaluated including creatine kinase (total and MM, MB, and BB isoenzymes).

Urinalysis

Volume, specific gravity and pH were evaluated. There were statistically significant decreases in the urine volume in the vehicle 2, LD male, and MD male groups, when compared to the vehicle 1 group, and corresponding increases in the specific gravity in these groups. However, these changes in the test article groups were considered incidental based on the lack of dose-dependence and the lack of similar findings in females and the values were within the historical control range. A toxicological significance of differences between the vehicle 1 and vehicle 2 group is unclear based on the lack of correlating histopathology.

Gross Pathology

Necropsy examinations were performed on main-study animals at the scheduled 1- and 2-month post-last dose necropsies (Days 171 and 199, respectively). Tissues and organs collected, weighed, and processed using standard procedures with H&E staining. An adequate battery of tissues and organs were examined including the injection sites (intramuscular [distal b, distal, middle, and proximal (left and right)], and skeletal muscle (biceps femoris). Bone marrow smears (2) were collected and held for potential analysis (but were not examined). Four sections of brain were examined (cerebrum, midbrain, cerebellum, medulla/pons).

Test article-related macroscopic findings were observed only at the injection sites. Mild tan discoloration was observed at the left and right injection sites at all dose levels, with a dose-related increase in the incidence, as shown in the sponsor's table below. In addition, one HD female had minimal tan focus/foci at the injection site.

<u>1-month post-last dose necropsy</u>

Test Article-related Macroscopic Observations – 1-Month Recovery										
Dose level: Group	1		2		3		4		5	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	15	15	15[a]	15	15	15	15	15	15	15
Injection site, left, intramuscular										
discoloration, tan										
- mild	0	0	0	0	5	8	10	7	15	15
Injection site, right, intramuscular										
discoloration, tan										
- mild	0	0	0	0	11	13	13	13	15	15
focus/foci, tan										
- minimal	0	0	0	0	0	0	0	0	0	1

M – Male
F – Female
1 – Vehicle 1-Control
2 – Vehicle 2
3 – 10 mg aripiprazole equivalents/site
4 – 20 mg aripiprazole equivalents/site
5 – 35 mg aripiprazole equivalents/site (70 mg/animal group)

[a]Includes one animal that died on study.

Tan discoloration and foci at the injection sites correlated microscopically with test article-related granulomas. There were no differences in macroscopic observations between the vehicle 1 and vehicle 2 groups. No test article-related macroscopic findings were present at the 2-month post-last dose necropsy (Day 199), indicating reversibility of these effects.

Organ Weights

Organ weights were recorded for main-study animals at the 1- and 2-month post-last dose necropsies. Mean absolute and/or relative to body and brain weight of the pituitary was statistically significantly decreased in the vehicle 2, MD, and HD male groups; the absolute weight was 10%, 10%, and 21% lower, respectively, when compared to the vehicle 1 group, at the 1-month post-last dose necropsy. Mean kidney weight (relative to body weight) was 10% lower in the HD females compared to the vehicle 1 group. These findings were considered incidental based on the absence of a microscopic correlate and the presence of findings in one sex only. Except for the pituitary weight decrease, there were no other differences organ weights between the two vehicle groups. No test article-related organ weight findings were present at the 2-month post-last dose necropsy.

Histopathology

Microscopic examination of fixed H&E stained paraffin sections was performed on protocol-designated sections of tissues for main-study animals at the 1- and 2-month post-last dose necropsies. The slides were examined by a board-certified veterinary pathologist. To capture the intramuscular injection sites, four sections (proximal, middle, and two distal) of the muscle of both hindlimbs (in the region of the biceps femoris) were trimmed and processed for microscopic examination in all groups.

Adequate Battery: Yes
Peer Review: Yes
Histological Findings:
Granulomas were observed at the injection sites in all test article-treated groups at both the 1- and 2-month post-last dose necropsies. The number and size of granulomas increased with the increasing aripiprazole lauroxil dose. Therefore, granulomas observed in this study are aripiprazole lauroxil -related. There was some evidence of partial reversibility at the 2-month post-last dose necropsy since the overall severity was reduced when compared to the 1-month post-last dose necropsy. However, the lack of full reversibility of injection site granulomas following long recovery period in this study indicates a potential safety issue and requires monitoring in clinic. The following detailed description of granulomas was provided by the Sponsor:

"*The severity of the granuloma formation ranged from minimal to moderate. The granulomas were typical of a response to foreign material and were characterized by focal to multifocal aggregates of granulomatous inflammation that spread along fascial planes. The inflammation was typified by accumulations of multinucleated giant cells admixed with lesser numbers of macrophages and lymphocytes. The multinucleated giant cells frequently contained clear intracytoplasmic acicular clefts or irregular foci that were interpreted to represent uptake of the test article material. Macrophages within affected areas rarely contained golden-brown pigment consistent with iron that was indicative of prior hemorrhage in the region. Granulomas occasionally contained variably-sized central foci of necrosis, and the granulomas of one female treated with 20 mg aripiprazole equivalents/site had minimal to mild foci of central mineralization. Based on the absence of any damage to the adjacent myofibers, granuloma formation was not considered adverse".*

Granuloma formation also occurred in the vehicle 2 group at 1-month post-last dose necropsy. The presence of granuloma in the vehicle 2 group may indicate that this vehicle, containing (b) (4)% of the excipient SML, was not as well-tolerated as the vehicle 1, containing (b) (4)% of this excipient. However, the incidence and severity of the granuloma observed in the vehicle 2 group was very low (1/15 females, graded minimal), therefore, according to this reviewer, is of negligible toxicological significance.

Degeneration/necrosis of individual myofibers was observed in few males; however the finding was considered consistent with background findings in the muscle and skin or related to trauma associated with injection procedures. There was also a very low incidence of similar findings in females. This reviewer agrees with the sponsor's conclusion.

1-month post-last dose necropsy

Test Article-related Microscopic Observations – 1-Month Recovery											
Dose level: Group		1		2		3		4		5	
Sex		M	F	M	F	M	F	M	F	M	F
Number Examined		15	15	15[a]	15	15	15	15	15	15	15
Injection site, intramuscular, proximal, left											
Granuloma		0	0	0	0	7	8	6	7	15	14
	-minimal	0	0	0	0	1	6	4	4	0	3
	-mild	0	0	0	0	6	2	2	3	12	7
	-moderate	0	0	0	0	0	0	0	0	3	4
Injection site, intramuscular, middle, left											
Granuloma		0	0	0	1	12	13	12	10	15	14
	-minimal	0	0	0	1	5	10	4	8	0	1
	-mild	0	0	0	0	7	3	8	2	11	8
	-moderate	0	0	0	0	0	0	0	0	4	5
Injection site, intramuscular, distal, left											
Granuloma		0	0	0	0	7	13	13	10	15	15
	-minimal	0	0	0	0	5	9	4	6	3	0
	-mild	0	0	0	0	2	4	9	3	10	11
	-moderate	0	0	0	0	0	0	0	1	2	4
Injection site, intramuscular, distal b, left											
Granuloma		0	0	0	0	6	6	13	13	15	15
	-minimal	0	0	0	0	2	5	2	8	6	2
	-mild	0	0	0	0	4	1	11	5	8	9
	-moderate	0	0	0	0	0	0	0	0	1	4

M – Male
F – Female
1 –Vehicle 1-Control
2 –Vehicle 2
3 – 10 mg aripiprazole equivalents/site
4 – 20 mg aripiprazole equivalents/site
5 – 35 mg aripiprazole equivalents/site (70 mg/animal group)

[a]Includes one animal that died on study.

Test Article-related Microscopic Observations – 1-Month Recovery											
Dose level: Group		1		2		3		4		5	
Sex		M	F	M	F	M	F	M	F	M	F
Number Examined		15	15	15[a]	15	15	15	15	15	15	15
Injection site, intramuscular, proximal, right											
Granuloma		0	0	0	0	7	13	6	1	14	13
	-minimal	0	0	0	0	5	8	3	1	3	3
	-mild	0	0	0	0	2	5	3	0	9	9
	-moderate	0	0	0	0	0	0	0	0	2	1
Injection site, intramuscular, middle, right											
Granuloma		0	0	0	0	12	13	13	9	15	13
	-minimal	0	0	0	0	2	8	6	5	0	1
	-mild	0	0	0	0	10	5	4	4	12	5
	-moderate	0	0	0	0	0	0	3	0	3	7
Injection site, intramuscular, distal, right											
Granuloma		0	0	0	1	14	15	15	13	15	15
	-minimal	0	0	0	1	4	7	5	6	0	1
	-mild	0	0	0	0	10	8	10	6	12	11
	-moderate	0	0	0	0	0	0	0	1	3	3
Injection site, intramuscular, distal b, right											
Granuloma		0	0	0	0	14	14	13	15	14	15
	-minimal	0	0	0	0	3	7	3	3	2	4
	-mild	0	0	0	0	11	7	10	11	10	6
	-moderate	0	0	0	0	0	0	0	1	2	5

M – Male
F – Female
Group 1 –Vehicle 1-Control
Group 2 – Vehicle 2
Group 3 – 10 mg aripiprazole equivalents/site
Group 4 – 20 mg aripiprazole equivalents/site
Group 5 – 35 mg aripiprazole equivalents/site (70 mg/animal group)

[a]Includes one animal that died on study.

2-month post-last dose necropsy

Granulomas were still present in the mid and high dose male and female groups, 2-months following the last injection, however the severity levels were slightly less than compared to the 1-month necropsy, indicating an incomplete and very slow recovery process. It is noted that the low dose male and female groups were not evaluated microscopically at the 2-month necropsy.

Test Article-related Microscopic Observations – 2-Month Recovery						
Dose level: Group	1		4		5	
Sex	M	F	M	F	M	F
Number Examined	5	5	5	5	5	5
Injection site, intramuscular, proximal, left						
Granuloma	0	0	2	1	3	2
-minimal	0	0	2	1	2	1
-mild	0	0	0	0	1	1
Injection site, intramuscular, middle, left						
Granuloma	0	0	3	4	4	5
-minimal	0	0	3	4	2	1
-mild	0	0	0	0	1	4
-moderate	0	0	0	0	1	0
Injection site, intramuscular, distal, left						
Granuloma	0	0	4	3	5	5
-minimal	0	0	4	2	4	1
-mild	0	0	0	1	1	3
-moderate	0	0	0	0	0	1
Injection site, intramuscular, distal b, left						
Granuloma	0	0	4	3	4	5
-minimal	0	0	3	3	1	1
-mild	0	0	1	0	3	4

M - Male
F – Female
1 –Vehicle 1-Control
4 – 20 mg aripiprazole equivalents/site
5 – 35 mg aripiprazole equivalents/site (70 mg/animal group)

Test Article-related Microscopic Observations – 2-Month Recovery						
Dose level: Group	1		4		5	
Sex	M	F	M	F	M	F
Number Examined	5	5	5	5	5	5
Injection site, intramuscular, proximal, right						
Granuloma						
-minimal	0	0	2	1	1	2
Injection site, intramuscular, middle, right						
Granuloma	0	0	3	1	4	3
-minimal	0	0	3	1	1	2
-mild	0	0	0	0	3	1
Injection site, intramuscular, distal, right						
Granuloma	0	0	3	4	5	5
-minimal	0	0	3	4	0	2
-mild	0	0	0	0	5	3
Injection site, intramuscular, distal b, right						
Granuloma	0	0	5	5	4	5
-minimal	0	0	4	4	2	1
-mild	0	0	1	1	2	4

M - Male
F – Female
1 –Vehicle 1-Control
4 – 20 mg aripiprazole equivalents/site
5 – 35 mg aripiprazole equivalents/site (70 mg/animal group)

There were no other test article-related histopathology findings. There were no differences in microscopic observations between the two vehicle control groups except granuloma formation described above.

Several other microscopic findings were observed in several tissues/organs across all dose groups, including both vehicle groups, in a non-dose-dependent manner. The sponsor attributed all of these findings to be incidental background findings. The findings are clearly not related to aripiprazole lauroxil, as there was no dose-dependent effect. However, without a negative control not containing SML, it is difficult to determine whether or not the findings are attributed to SML.

A review of submitted historical control data (study no. 700-02313 document no. 700-02797-01) conducted by the current reviewer, for animals of this strain and similar age showed that all of the other microscopic findings (besides those at the injection site) observed across all dose groups including both vehicles were found in the historical control datasets. In addition, there was no dose effect observed for microscopic findings between vehicle 1 and 2, which contained different amounts of excipient, SML, further suggesting that the findings are incidental and not related to SML. If the findings were related to SML a higher incidence would be expected in vehicle 2, which contains (b) (4)% SML compared to vehicle 1 which only contains (b) (4)% of SML. Therefore, this reviewer agrees with the sponsor that the other non-injection site microscopic findings are incidental background findings and not drug or vehicle related.

Special Evaluation

None

Toxicokinetics

Blood samples were collected from cohorts of 3 treated TK animals/sex/group for determination of concentrations of aripiprazole lauroxil, aripiprazole dehydro-aripiprazole, and N-hydroxymethyl aripiprazole in whole blood. From the LD, MD and HD animals, blood was collected pre-dose on Day 1, at 24 hours post-dose on Day 2, and on Days 4, 9, 14, 17, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, and 168. In addition, blood was collected from the MD and HD animals on Days 175, 182, 189, and 196. Samples were also collected from the Vehicle 1 group animals at 24 hours post-dose on Day 2 and on Days 35, 70, 112, 140 and 168.

Low but measurable concentrations of aripiprazole lauroxil were present in whole blood samples from male and female rats in the Vehicle 1 group on Days 35 and 70. According to the sponsor, the test article was detected in the blood possibly due to contamination during sample processing or analysis since no other analytes were found.

Exposure levels were highest for N-hydroxymethyl aripiprazole > aripiprazole > dehydro-aripiprazole > aripiprazole lauroxil in rats following i.m. administration of aripiprazole lauroxil and the rank order was similar after the first and ninth doses. Aripiprazole lauroxil was not always measurable in rats, especially at the low and mid dose levels. Systemic exposure to aripiprazole lauroxil was similar in males and females; however exposure to aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole was higher in females than in males. Overall exposure to aripiprazole lauroxil was similar across all dose levels (when measurable). Overall exposure to N-hydroxymethyl aripiprazole and aripiprazole increased roughly dose proportional and exposure to dehydro-aripiprazole increased much greater than dose proportional. Systemic exposure levels (AUC and C_{max}) were only slightly higher (< 2-fold) following the ninth dose compared to the first dose for aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole. T_{max} values following the first and ninth doses ranged between 9-21 days for all analytes, with the exception of aripiprazole lauroxil in which

T_{max} values could only be calculated in the high dose group and ranged between 2-14 days.

Table 7: Mean Toxicokinetic Parameters for Aripiprazole Lauroxil, Aripiprazole, Dehydro-aripiprazole and *N*-hydroxymethyl aripiprazole in Male and Female Rats following Repeat Administration of Aripiprazole Lauroxil

			Dose 1			Dose 6			Overall	
Compound	**Dose[a] (mg/ animal)**	**Sex**	**C_{max} (ng/mL)**	**t_{max}[b] (day)**	**AUC_{0-28} (day•ng/mL)**	**C_{max} (ng/mL)**	**t_{max} (day)**	**$AUC_{141-168}$ (day•ng/mL)**	**$AUC_{0-tlast}$ (day•ng/mL)**	**AUC_{0-196} (day•ng/mL)**
Aripiprazole Lauroxil	10	Male	0	NC	0	0	NC	0	149	NA
		Female	0	NC	0	0	NC	0	140	NA
		Mean	0	NC	0	0	NC	0	144	NA
	20	Male	0	NC	0	0	NC	0	129	134
		Female	0	NC	0	0	NC	0	130	136
		Mean	0	NC	0	0	NC	0	130	135
	70	Male	0.660	2.00	0.990	0.827	14.0	5.79	148	151
		Female	0.887	2.00	1.33	0	NC	0	127	133
		Mean	0.773	2.00	1.16	0.413	14.0	2.89	138	142
Aripiprazole	10	Male	3.50	14.0	62.3	5.08	14.0	97.6	588	NA
		Female	6.22	9.0	103	8.01	14.0	165	1010	NA
		Mean	4.86	11.5	82.5	6.55	14.0	131	797	NA
	20	Male	7.47	9.0	133	12.8	14.0	221	1290	1290
		Female	13.3	17.0	230	19.9	14.0	413	2480	2480
		Mean	10.4	13.0	182	16.4	14.0	317	1890	1890
	70	Male	24.7	14.0	418	29.2	21.0	659	4410	4410
		Female	39.7	14.0	683	62.4	14.0	1420	7990	7990
		Mean	32.2	14.0	550	45.8	18.0	1040	6200	6200

Table 7: Mean Toxicokinetic Parameters for Aripiprazole Lauroxil, Aripiprazole, Dehydro-aripiprazole and *N*-hydroxymethyl aripiprazole in Male and Female Rats following Repeat Administration of Aripiprazole Lauroxil (Continued)

			Dose 1			Dose 6			Overall	
Compound	Dose[a] (mg/ animal)	Sex	C_{max} (ng/mL)	t_{max}[b] (day)	AUC_{0-28} (day•ng/mL)	C_{max} (ng/mL)	t_{max} (day)	$AUC_{141-168}$ (day•ng/mL)	$AUC_{0-tlast}$ (day•ng/mL)	AUC_{0-196} (day•ng/mL)
Dehydro-aripiprazole	10	Male	0	NC	0	0.493	14.0	3.45	NC	NA
		Female	0	NC	0	0	NC	0	NC	NA
		Mean	0	NC	0	0.247	14.0	1.73	NC	NC
	20	Male	0.347	9.00	1.73	0.460	14.0	3.22	NC	NC
		Female	0.853	17.0	10.1	1.00	14.0	13.0	81.5	83.3
		Mean	0.600	13.0	5.94	0.732	14.0	8.10	81.5	83.3
	70	Male	3.01	14.0	51.3	2.64	14.0	60.1	389	392
		Female	3.08	14.0	57.4	4.85	14.0	103	591	593
		Mean	3.05	14.0	54.4	3.75	14.0	81.7	490	492
N-hydroxy-methyl aripiprazole	10	Male	7.15	9.0	123	10.8	14.0	180	999	NA
		Female	13.9	9.0	228	11.1	14.0	265	1760	NA
		Mean	10.5	9.0	176	10.9	14.0	222	1380	NA
	20	Male	14.4	9.0	258	15.1	14.0	316	2000	2000
		Female	25.7	17.0	460	27.1	14.0	557	3730	3730
		Mean	20.0	13.0	359	21.1	14.0	437	2860	2860
	70	Male	48.7	14.0	821	45.9	21.0	1100	7020	7020
		Female	74.6	17.0	1380	92.6	14.0	1960	12100	12100
		Mean	61.7	15.5	1100	69.2	18.0	1530	9540	9540

[a] Administered at two sites (35 mg/site)
[b] Median values presented for t_{max}
NA = Not applicable; samples were not collected after 168 days; NC = Not calculated; insufficient data

Dosing Solution Analysis

Homogeneity and concentrations of the formulations were adequate (the relative standard deviation was <2.0% for homogeneity of suspensions and within ± 10% of nominal for concentrations of suspensions).

Study title: RDC-3317: A 9-Month Intramuscular Toxicity Study in Dogs with 1- and 4- Month Recoveries

The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek. The current reviewer agrees with Dr. Chalecka-Franaszek's findings and an abbreviated review is included below. For the full review, see Dr. Chalecka-Franaszek's review in DARRTS under IND 107,249.

Study no.:	AT-3317-13
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 15, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 (RDC-3317; extended release ester of aripiprazole), lots 100-01475 (purity 98.01% with several impurities) and 100-01477 (purity 98.21% with several impurities).

Key Study Findings

- Transient impaired hind limb/function and/or swelling were observed in all groups with the incidence significantly greater in the mid and high dose groups.
- Several animals, including controls, had hypersensitivity reaction (hives, swelling, redness) that developed shortly after administration of the first and/or second dose. This reaction may be associated with administration of (b) (4) (polysorbate 20) to dogs.
- Dose-dependent minimal to severe white foci were observed macroscopically at the injection sites in all drug-treated groups. The severity slightly decreased at 4-month post-dose necropsy.
- Granulomas were observed at the 1-month post-last dose necropsy in all drug-treated groups and were still present in all animals at 450 and 700 (1400 mg/animal) mg arip.eq./site at the 4-month post-last dose necropsy. There was a minimal decrease in severity at the 4-month post-last dose necropsy compared to the 1-month post-last necropsy, indicating slow reversibility.
- No significant differences in study parameters were noted between the vehicle 1 and vehicle 2 groups.

NOAEL = 1400 mg (700 mg/site) (arip.eq.)/animal (2058 mg aripiprazole lauroxil/animal) Associated mean combined gender $AUC_{0\text{-tlast}}$ and $C_{max(9)}$ values of 272 day.ng/mL and 1.19 ng/mL for aripiprazole lauroxil, 8980 day.ng/mL and 37.4 ng/mL for aripiprazole; 6290 day.ng/mL and 41.0 ng/mL for dehydro-aripiprazole, and 11500 day.ng/mL and 57.0 ng/mL for N-hydroxymethyl aripiprazole, respectively.

Methods

Doses:	0, 0, 100, 450, and 1400 mg (2x700 mg/site) aripiprazole equivalents (arip.eq.)/animal Aripiprazole lauroxil dose = 1.47x (147, 661.5, 2058 mg aripiprazole lauroxil/animal)
Frequency of dosing:	Once a month on nine separate occasions (Days 1, 29, 57, 85, 113, 141, 169, 197, and 225)
Route of administration:	Intramuscular (IM) injection
Dose volume:	4 mL/site (Vehicle 1 and 2), 2 mL/site (LD), 3 mL/site (MD), and 4 or 4.1mL/site (HD).
Formulation/Vehicle:	Vehicle 1 (control): (b) (4)% sorbitan monolaurate (SML), (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water)
Species/Strain:	Dog/Beagle
Number/Sex/Group:	Vehicle 1, MD, and HD groups: 6 animals/sex/group Vehicle 2 and LD groups: 4 animals/sex/group,
Age:	Approximately 5 to 5.5 months of age at study initiation
Weight:	Males: 6.75 to 9.25 kg; females: 5.30 to 8.05 kg at randomization
Satellite groups:	Following the dosing period, all animals were maintained for a 1-month period and 2 animals/sex receiving Vehicle 1, 450, and 1400 mg arip.eq./animal were maintained for a 4-month recovery period.
Unique study design:	An additional objective of the study was to evaluate the tolerability of a second vehicle (Vehicle 2), which contained higher concentrations of SML and polysorbate 20 than those in the vehicle (Vehicle 1-Control) used to formulate ALKS 9072 (Vehicle 2: (b) (4)% SML, (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water).
Deviation from study protocol:	In the opinion of this reviewer, none of the protocol deviations affected the quality or integrity of the study.

Observations and Results

Mortality

Observations for morbidity, mortality, and injury were conducted twice daily. There were no test article-related deaths.

Clinical Signs

Detailed clinical observations were conducted weekly. Several animals, including controls, had hypersensitivity reaction (hives, swelling, redness) that developed shortly after administration of the first and/or second dose. These animals were treated with diphenhydramine and the symptoms cleared. A few animals at the lower doses had mild symptoms that did not require treatment. The Sponsor did not consider hypersensitivity reactions as related to the test article administration since they occurred both in test article and control animals. Therefore, the Sponsor proposed that hypersensitivity may be associated with administration of (b) (4) (e.g. polysorbate 20) to dogs. The degree and incidence of hypersensitivity was most severe in the vehicle groups and HD group which received the greatest dose volumes (i.e., ~8 mL per monthly dose) and consequently the greatest amount of polysorbate 20. (b) (4) polysorbates, have been associated with hypersensitivity reactions in dogs and may provide an explanation for these findings.

Beginning with the third dose, all dogs were treated with hydroxyzine orally at approximately 30 minutes prior to dosing (prior to sedation) and with diphenhydramine IM within 5 minutes of dosing, as a preventative measure. No other adverse treatment-related clinical findings were noted.

Impaired hind limb/function and/or swelling were observed in Weeks 1 to 33 in the majority of dogs treated with the MD and HD as well as in the LD and vehicle control groups with the incidence lower than that in the MD and HD groups (except swelling in female dogs in the Vehicle 1 group). These findings were generally transient since they were observed only sporadically in Weeks 34 to 36. The impaired hind limb/function and/or swelling were considered non-adverse by the Sponsor, however due to the higher incidence in the MD an HD animals, a drug-related effect cannot be ruled out. The incidence of these findings in Weeks 1 to 33 is shown in the following Reviewer's table:

Observation	sex	Vehicle 1	Vehicle 2	LD	MD	HD
Limb function impaired	M	1/1	0/0	1/1	7/5	8/3
Swelling	M	4/3	2/2	0/0	5/2	8/5
Limb function impaired	F	5/3	2/1	7/2	23/6	26/5
Swelling	F	30/6	3/3	0/0	6/4	16/5

(Number of times observed/Total number of animals affected)

Body Weights

There were no adverse test article-related effects on body weight. However, mean group body weights were slightly greater in males in Vehicle 2 group during the dosing (~ after Day 80) and 1-month post-last dose periods when compared to Vehicle 1 group. This minor effect has no toxicological significance. Body weight was measured and recorded weekly.

Food Consumption

There were no adverse test article-related effects on food consumption. Statistically significant slight increases in food consumption were observed in Vehicle 2 males during the dosing period. This change was consistent with the trend for increased body weight in these animals. Food consumption was measured and recorded weekly.

Ophthalmoscopy

There were no adverse drug-related eye findings.
Eye examinations were conducted pretest and prior to the 1-month post-last dose necropsy by a certified veterinary ophthalmologist.

ECG

There were no adverse test article-related effects on the ECG parameters or blood pressure.
Electrocardiographic examinations and indirect blood pressure measurements were conducted pretest and prior to the 1-month post-last dose necropsy. The RR, PR, and QT intervals and QRS duration were measured, and the heart rate was determined. Corrected QT (QTc) interval was calculated using Fridericia's method. All tracings were evaluated and reported by a consulting veterinary cardiologist.

Reviewer's comment: There were statistically significant differences between the Vehicle 1 and Vehicle 2 groups, including 10% (4.4 msec) longer mean QRS duration in males at the 1 month post-last dose in the Vehicle 2 group when compared to Vehicle 1 group values ($p<001$). The QRS duration was 12% (5.1 msec) shorter in females in the Vehicle 2 group following 1-month post-last dose recovery period when compared to the Vehicle 1 female group values ($p<005$). The Sponsor did not discuss the toxicological significance of differences in the QRS duration between the Vehicle 1 and Vehicle 2 groups although the Vehicle 2 group was included to qualify the SML as a novel excipient for IM administration. This reviewer concluded that the observed differences in QRS duration among groups are not toxicologically significant due to a small magnitude of change and their presence pre-dose.

Hematology

There were no test article-related effects on hematology and coagulation parameters at 1-month post-last dose. A few statistical differences were observed that are not considered toxicologically significant due to a small magnitude of change consistent with normal physiological variation. The absolute reticulocyte count was 2.3-fold higher in the male Vehicle 2 group than that in the Vehicle 1 group following 1-month post-last dose recovery period. The toxicological significance of this finding is unclear, however it should be noted that the value was still within the historical control range. There were no other differences in the hematology or coagulation parameters between the two vehicle control groups. Values for most parameters were within the historical control range (or very close to it); and close to the pre-study values.
Blood samples for hematology and coagulation were collected from all animals pre-test and prior to the 1-month post-last dose necropsy. An adequate battery of parameters was evaluated.

Clinical Chemistry

There were no test article-related effects on clinical chemistry parameters, including creatine kinase isoenzymes, at 1-month post-dose. Although statistically significant differences were observed between groups, these are not considered toxicologically important due to a small magnitude of change consistent with normal physiological variation and that most values were within the historical control ranges.
Alkaline phosphatase was 1.8-fold higher in the male Vehicle 2 group than that in the Vehicle 1 group following 1-month post-last dose recovery period. Globulin level was also slightly increased and the A/G ratio was decreased in the male Vehicle 2 group (129% and 77%, respectively) when compared with the Vehicle 1 group. Total creatine kinase was 1.5-fold higher in the male Vehicle 2 group than that in the Vehicle 1 group following 1-month post-last dose recovery period, however there was a large standard deviation and the values were still within the historical control range. There were no other differences in the clinical chemistry parameters between the two vehicle control groups.
Blood samples for clinical pathology were collected from all animals pre-test and prior to the 1-month post-last dose necropsy. An adequate battery of clinical chemistry parameters was measured including total creatine kinase and creatine kinase isozyme levels (MM, MB, and BB).

Urinalysis

There were no test article-related effects on urinalysis parameters following 1-month post-last dose recovery period. There were no differences in these parameters between the two vehicle control groups.
Urine samples were collected from all animals pre-test and prior to the 1-month post-dose necropsy. Volume, specific gravity, and pH were measured.

Gross Pathology

Necropsy examinations were performed, organ weights were recorded, and tissues were microscopically examined for all animals designated for the 1- and 4-month post-last dose necropsy. All designated tissues were fixed in neutral buffered formalin, except for the eye/optic nerve and testes, which were fixed in a modified Davidson's fixative, and stained with H&E. Tissues and organs were collected, weighed, and examined. An adequate battery of tissues and organs were examined including the injection sites (left and right intramuscular), and skeletal muscle (biceps femoris). Bone marrow smears (2) were collected and held for potential analysis (but were not examined). Four sections of brain were examined (cerebrum, midbrain, cerebellum, medulla/pons).

1-month post-last dose necropsy: Macroscopically, minimal to severe white foci were observed at the injection sites in all test article administered groups. Their incidence and severity was dose-dependent. Approximately 50% animals were affected in the LD groups and all animals were affected in the MD and HD groups, as shown in the following Sponsor's table. There were no differences in macroscopic observations between the two vehicle control groups.

Test Article-related Macroscopic Observations – 1-Month Recovery										
Dose level: mg aripiprazole equivalents/site	Vehicle 1-Control		Vehicle 2		100		450		700	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	4	4	4	4	4	4	4	4	4	4
Injection site, left, intramuscular										
Focus/foci, white	0	0	0	0	2	3	4	4	4	4
-mild	0	0	0	0	2	2	3	1	1	1
-moderate	0	0	0	0	0	1	1	3	3	1
-severe	0	0	0	0	0	0	0	0	0	2
Injection site, right, intramuscular										
Focus/foci, white	0	0	0	0	2	2	4	4	4	4
-minimal	0	0	0	0	0	1	0	0	0	0
-mild	0	0	0	0	2	1	4	2	1	1
-moderate	0	0	0	0	0	0	0	2	3	1
-severe	0	0	0	0	0	0	0	0	0	2
M - Male F - Female										

4-month post-last dose necropsy: Macroscopically, the severity of the white foci decreased to mild to moderate (compared to minimal to severe at the 1-month post-dose necropsy) at MD and HD (the LD group was not necropsied after 4 months) as shown in the Sponsor's table below. There were no differences in macroscopic observations between the two vehicle control groups. Note: The white foci observed at both necropsies in the test article administered animals correlated to granulomas observed microscopically.

Test Article-related Macroscopic Observations – 4-Month Recovery						
Dose level: mg aripiprazole equivalents/site	Vehicle 1 - Control		450		700	
Sex	M	F	M	F	M	F
Number Examined	2	2	2	2	2	2
Injection site, left, intramuscular						
Focus/foci, white	0	0	2	2	2	2
-mild	0	0	2	2	2	1
-moderate	0	0	0	0	0	1
Injection site, right, intramuscular						
Focus/foci, white	0	0	1	1	2	2
-mild	0	0	1	1	2	1
-moderate	0	0	0	0	0	1
M - Male F - Female						

Organ Weights

Weighed organ are listed in the table above (*). There were no adverse test article-related adverse effects on organ weights at 1- and 4-month post last dose necropsies. Although changes in weights of some organs (thymus, lungs, pituitary, mandibular salivary gland, and spleen) were observed, they were not considered toxicologically relevant based on the low magnitude of change, lack of dose response, and absence of histopathology correlates. There were no differences in organ weights between the two vehicle control groups.

Histopathology

Adequate Battery: Yes
Peer Review: Yes
Histological Findings:
The white foci observed macroscopically correlated to granulomas observed microscopically at injection sites. Granulomas were noted at the 1-month post-last dose necropsy and were still present in all animals administered test article at 450 and 700 (1400 mg/animal) mg arip.eq./site at the 4-month post-last dose necropsy. There was a minimal decrease in severity at the 4-month post-last dose necropsy compared to the 1-month necropsy (minimal to moderate compared to minimal to severe, respectively), indicating slow reversibility. It is noted that the low dose male and female groups were not evaluated microscopically at the 4-month post-dose necropsy. Based on the absence of any damage to the adjacent muscular myofibers, granulomas were not considered adverse by the Sponsor. The incidence and severity of the injection site granulomas is shown in the following Sponsor's tables.

1-month post-last dose necropsy:

Test Article-related Microscopic Observations – 1-Month Recovery

Dose level: mg aripiprazole equivalents/site	Vehicle 1 - Control		Vehicle 2		100		450		700	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	4	4	4	4	4	4	4	4	4	4
Injection site, left, intramuscular										
Granuloma	0	0	0	0	3	4	4	4	4	4
-mild	0	0	0	0	3	2	2	1	1	0
-moderate	0	0	0	0	0	2	2	3	3	1
-severe	0	0	0	0	0	0	0	0	0	3
Injection site, right, intramuscular										
Granuloma	0	0	0	0	2	4	4	4	4	4
-minimal	0	0	0	0	0	1	0	0	0	0
-mild	0	0	0	0	2	2	3	1	0	0
-moderate	0	0	0	0	0	1	1	3	4	3
-severe	0	0	0	0	0	0	0	0	0	1

M - Male
F - Female

4-month post-last dose necropsy:

Test Article-related Microscopic Observations – 4-Month Recovery						
Dose level: mg aripiprazole equivalents/site	Vehicle 1 - Control		450		700	
Sex	M	F	M	F	M	F
Number Examined	2	2	2	2	2	2
Injection site, left, intramuscular						
Granuloma	0	0	2	2	2	2
-mild	0	0	2	0	2	1
-moderate	0	0	0	2	0	1
Injection site, right, intramuscular						
Granuloma	0	0	2	2	2	2
-minimal	0	0	1	1	0	0
-mild	0	0	1	1	0	0
-moderate	0	0	0	0	2	2
M - Male F - Female						

There were no other test article-related histopathology findings. There were no differences in microscopic observations between the two vehicle control groups. However, there were other non-injection site microscopic findings observed with comparable incidence in all groups, including controls, which the sponsor considered incidental background findings. (For a detailed listing of other microscopic findings, refer to the full review by Dr. Elzbieta Chalecka-Franaszek in DARRTS under IND 107,249.)

All animals in the study were exposed to the vehicle containing SML (either (b) (4) or (b) (4) %). Since the sponsor did not include a negative control group that did not contain the excipient, SML, it is difficult to assess the toxic potential of SML and if any of the non-injection site microscopic findings were directly related to SML. A thorough review of this laboratory's microscopic historical control data, conducted by this reviewer, (study no. 700-02313 document no. 700-02796-01) for animals of this strain and similar age showed that all of the other microscopic findings (besides those at the injection site) were found in the historical control datasets. Therefore, all other microscopic findings are considered to be incidental background findings and not related to either aripiprazole lauroxil or the excipient SML. There was also no dose effect observed for other microscopic findings between vehicle 1 and 2, further suggesting that the findings are incidental and not related to SML. If the findings were related to SML a higher incidence would be expected in vehicle 2, which contains (b) (4) % SML compared to vehicle 1 which only contains (b) (4) % of SML.

Special Evaluation

None

Toxicokinetics

Blood samples for determination of the whole blood concentrations of aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole were collected from designated animals at the following time points. From the LD, MD and HD animals, blood was collected on Days 1, 2, 4, 9, 14, 17, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168, 175, 182, 189, 196, 203, 210, 217, 224, 231, 238, 245, 252, 259, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, and 336. Samples were not collected from LD animals after 252 days. Samples collected beyond Day 252 in the MD and HD animals were from recovery animals only. Samples were collected from vehicle 1 group animals on Days 2, 35, 70, 112, 147, 182, 217 and 252; additional samples were collected from recovery animals only on Days 301 and 336.

Exposure levels were highest for N-hydroxymethyl aripiprazole > aripiprazole > dehydro-aripiprazole > aripiprazole lauroxil in dogs following i.m. administration of aripiprazole lauroxil and the rank order was similar after the first and ninth doses. There were no apparent gender differences in exposure levels for any of the four analytes. Overall exposure to aripiprazole lauroxil (C_{max} and AUC) increased much less than dose proportional, while overall exposure to N-hydroxymethyl aripiprazole and aripiprazole increased roughly dose proportional and exposure to dehydro-aripiprazole increased much greater than dose proportional. Exposure levels (AUC) were higher (< 2-fold) following the ninth dose compared to the first dose for aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole, however in contrast, exposure levels (AUC) for aripiprazole lauroxil were higher following the first dose; and were not even measurable in the LD and MD dose groups after the ninth dose. C_{max} values were similar for all analytes following the first and ninth doses. T_{max} values following the first and ninth doses ranged between 7-18 days for all analytes, with the exception of aripiprazole lauroxil (T_{max} values ranged between 7-28 days). This is in slight contrast to the single dose dog PK study, in which the T_{max} for aripiprazole lauroxil was ~3 days.

Table 15: Mean (±SD) Toxicokinetic Parameters for Aripiprazole Lauroxil, Aripiprazole, Dehydro-aripiprazole and *N*-hydroxymethyl aripiprazole in Male and Female Dogs Administered 9 Monthly Intramuscular Doses of Aripiprazole Lauroxil

			Dose 1			Dose 9			Overall	
Compound	Dose[a] (mg/ animal)	Sex	C_{max} (ng/mL)	t_{max}[b] (day)	AUC_{0-28} (day•ng/mL)	C_{max} (ng/mL)	t_{max} (day)	$AUC_{225-252}$ (day•ng/mL)	$AUC_{0-tlast}$ (day•ng/mL)	AUC_{0-336} (day•ng/mL)
Aripiprazole lauroxil	100	Male	4.58±0.182	28.0	16.0±0.639	0±0	NC	0±0	548±806	NA
		Female	4.71±0.131	28.0	16.9±1.27	0±0	NC	0±0	157±6.12	NA
		Mean	4.65±0.162	28.0	16.5±1.05	0±0	NC	0±0	353±567	NA
	450	Male	4.47±0.261	28.0	21.4±7.08	0±0	NC	0±0	173±33.0	166
		Female	4.57±0.419	28.0	26.9±8.5	0±0	NC	0±0	190±36.2	209
		Mean	4.52±0.337	28.0	24.1±8.00	0±0	NC	0±0	182±29.9	188±36.3
	1400	Male	5.77±1.83	16.0	41.9±109	0.807±0.915	7.00	6.21±6.69	252±52.9	235
		Female	4.85±0.231	28.0	44.6±6.79	1.56±1.43	7.00	10.3±9.98	292±61.7	281
		Mean	5.31±1.33	28.0	43.3±8.76	1.19±1.21	7.00	8.25±8.37	272±58.8	258±44.6
Aripiprazole	100	Male	2.53±1.06	15.5	33.6±14.9	3.01±0.897	14.0	68.9±22.3	746±212	NA
		Female	3.70±2.45	9.0	43.6±36.4	3.00±1.25	14.0	61.1±36.0	758±391	NA
		Mean	3.11±3.85	14.0	38.6±26.3	3.01±1.01	14.0	65.0±28.0	752±291	NA
	450	Male	12.1±3.62	14.0	198±58.6	10.8±3.69	7.0	247±82.8	3020±761	2820
		Female	14.4±6.07	14.0	231±95.6	12.6±3.72	7.0	284±72.3	3360±996	4500
		Mean	13.2±4.91	14.0	214±77.5	11.7±3.66	7.0	265±76.6	3190±864	3660±1120
	1400	Male	38.7±12.7	14.0	574±168	31.6±11.7	11.0	717±259	8530±2710	10700
		Female	39.3±26.7	17.0	625±391	43.2±17.4	18.0	953±470	9430±3760	12000
		Mean	39.0±20.0	15.5	600±288	37.4±15.4	14.0	835±382	8980±3160	11300±2560

Table 15: Mean (±SD) Toxicokinetic Parameters for Aripiprazole Lauroxil, Aripiprazole, Dehydro-aripiprazole and *N*-hydroxymethyl aripiprazole in Male and Female Dogs Administered 9 Monthly Intramuscular Doses of Aripiprazole Lauroxil (Continued)

			Dose 1			Dose 9			Overall	
Compound	Dose[a] (mg/ animal)	Sex	C_{max} (ng/mL)	t_{max}[b] (day)	AUC_{0-28} (day•ng/mL)	C_{max} (ng/mL)	t_{max} (day)	$AUC_{225-252}$ (day•ng/mL)	$AUC_{0-tlast}$ (day•ng/mL)	AUC_{0-336} (day•ng/mL)
Dehydro-aripiprazole	100	Male	0.498±0.995	14.0	6.21±12.4	0.793±0.919	11.0	13.2±15.5	122±83.4	NA
		Female	1.20±1.49	11.5	13.3±18.4	1.21±0.831	14.0	24.1±18.7	212±206	NA
		Mean	0.850±1.23	14.0	9.75±15.0	1.00±0.841	14.0	18.6±16.9	167±153	NA
	450	Male	6.68±3.33	14.0	105±50.5	7.61±4.55	7.0	162±93.2	1550±741	1220
		Female	9.09±5.46	15.5	135±84.7	7.76±2.93	14.0	172±56.8	1710±560	2170
		Mean	7.89±4.49	14.0	120±74.1	7.68±3.65	11.0	167±73.8	1630±632	1700±838
	1400	Male	20.5±7.00	14.0	313±78.9	18.9±6.50	7.0	411±177	4350±1500	5580
		Female	42.0±56.2	15.5	609±754	63.1±52.6	14.0	1090±749	8230±7010	13100
		Mean	31.2±39.8	14.0	641±534	41.0 ±42.5	11.0	749±628	6290±5240	9320±8360
N-hydroxymethyl aripiprazole	100	Male	4.70±3.53	14.0	73.6±47.0	5.47±2.02	14.0	125±41.0	1070±315	NA
		Female	6.32±2.87	9.0	86.6±41.4	5.90±2.98	14.0	122±68.5	1070±494	NA
		Mean	5.51±3.10	11.5	80.1±41.6	5.68±2.37	14.0	123±52.3	1070±384	NA
	450	Male	18.70±5.35	15.5	305±75.6	17.8±5.53	7.0	426±127	4090±787	4380
		Female	23.3±13.4	15.5	363±187	20.0±6.89	11.0	472±149	4240±1180	5400
		Mean	20.0±9.99	15.5	334±139	18.9±6.07	7.0	449±134	4170±960	4890±786
	1400	Male	57.1±19.4	14.0	858±207	53.3±19.1	7.0	1160±414	10800±3240	13800
		Female	59.0±25.6	15.5	936±320	60.7±20.8	7.0	1400±470	12000±3140	12700
		Mean	58.1±21.7	14.0	897±260	57.0±19.4	7.0	1280±441	11500±3130	13300±1510

[a] 100 and 450 mg/animal groups were administered the test article at one site, and the 1400

[b] Median presented for t_{max}

NA = not applicable. Where no SD is given, the mean is comprised of fewer than 3 observations.

Dosing Solution Analysis

Homogeneity and concentrations of the formulations were adequate (the relative standard deviation was <2.5% for homogeneity of suspensions and within ± 10% of nominal for concentrations of suspensions).

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek and summarized below.

Study title: Bacterial Reverse Mutation Assay

Study no.:	AT-3317-06
Study report location:	EDR: NDA SND 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 (RDC-3317), lot 100-01414, purity: 99.2%

Key Study Findings

Aripiprazole lauroxil did not cause a positive mutagenic response in any of the tester strains in either the presence or absence of rat liver S9 and is considered non-mutagenic under the conditions of this study.

Methods

Strains:	*Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A
Concentrations in definitive study:	Confirmatory assay: 50, 150, 500, 1500, and 5000 µg per plate
Basis of concentration selection:	Findings from the initial toxicity-mutation assay conducted at concentrations from 1.5 to 5000 µg per plate
Negative control:	Vehicle (acetone)
Positive control:	Without metabolic activation: 2-nitrofluorene (1.0 µg/plate) for TA98; sodium azide (1.0 µg/plate) for TA100 and TA1535; 9-aminoacridine (75 µg/plate) for TA1537; and methyl methanesulfonate (1000 µg/plate) for WP2 *uvr*A. With rat S9: 2-aminoanthracene at 1.0 µg/plate for TA98, TA1535, and TA1537, at 2.0 µg/plate for TA100, and at 10 µg/plate for WP2 *uvr*A
Formulation/Vehicle:	Solution/acetone
Incubation & sampling time:	Plates with the test article and appropriate controls were incubated for 48 to 72 hours before colony counting

Study Validity

Bacterial tester strains were treated in the absence and presence of an Aroclor-induced rat liver S9 activation system. The positive and solvent controls fulfilled the requirements for a valid test. All other criteria for a valid test were also met.

Results

In the initial toxicity-mutation assay, precipitate was observed beginning at 1500 or at 5000 µg per plate. No toxicity or positive mutagenic response was observed. In the confirmatory mutagenicity assay, precipitate was noted beginning at 1500 µg per plate. No toxicity or positive mutagenic response was observed. Aripiprazole lauroxil was concluded to be negative in the bacterial reverse mutation assay under the conditions of this study.

7.2 *In Vitro* Assays in Mammalian Cells

The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek and summarized below.

Study title: *In Vitro* Mammalian Chromosome Aberration Test

Study no.:	AT-3317-07
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 5, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 (RDC-3317), lot 100-01414, purity: 99.2%

Key Study Findings

Aripiprazole lauroxil was negative for the induction of structural and numerical chromosome aberrations both in the presence and absence of S9-activated test systems.

Methods

Cell line:	Human peripheral blood lymphocytes (HPBL) obtained from a healthy non-smoking 28-year-old adult female
Concentrations in definitive study:	Concentrations selected for analysis of chromosome aberrations were 62.5, 125, and 250 µg/mL without metabolic activation and 125, 250 and 500 µg/mL with metabolic activation.
Basis of concentration selection:	Precipitation of test article in the preliminary toxicity study (maximum concentration tested: 1000 mg/ml)
Negative control:	Vehicle (acetone)
Positive control:	Without metabolic activation: Mitomycin C With rat S9: Cyclophosphamide
Formulation/Vehicle:	Solution in vehicle/acetone
Incubation & sampling time:	See Sponsor's table below:

Treatment Condition	Treatment Time	Recovery Time	Dose levels (µg/mL)
Non-activated	4 hr	16 hr	62.5, 125, 250, 500
	20 hr	0 hr	62.5, 125, 250, 500
S9-activated	4 hr	16 hr	62.5, 125, 250, 500

Study Validity

HPBL were incubated with the test article in the absence and presence of the Aroclor induced rat liver S9 activation system. The positive and solvent controls fulfilled the requirements for a valid test (the percentage of structurally damaged cells in positive control group was statistically significant). All other criteria for a valid test were also met.

Results

Visible precipitate was observed in the treatment medium at all concentrations tested at the beginning of the treatment period. At the end of treatment, in the non-activated 4 and 20-hour treatment groups, visible precipitate was observed in the treatment medium at concentrations ≥ 250 µg/mL; lower concentrations were soluble. At the highest concentration evaluated microscopically for chromosome aberrations (250 µg/mL), mitotic inhibition was 6% and 17% for the 4 and 20-hour treatment groups, respectively, relative to the solvent control.

In the S9-activated 4-hour treatment group, visible precipitate was observed in the treatment medium at concentration of 500 µg/mL, while dose levels ≥ 250 µg/mL were soluble. At the highest concentration evaluated microscopically for chromosome aberrations (500 µg/mL) mitotic inhibition was 25%, relative to the solvent control.

The percentage of cells with structural or numerical aberrations in the test article-treated group was not significantly increased relative to solvent control at any dose level. Aripiprazole lauroxil is considered to be negative in the *in vitro* mammalian chromosome aberration test under the conditions of this study.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Not conducted with aripiprazole lauroxil.

7.4 Other Genetic Toxicity Studies

Genetic toxicity studies were conducted with excipient sorbitan monolaurate. See special toxicology study section 10 below.

8 Carcinogenicity

Carcinogenicity studies were not conducted with aripiprazole lauroxil since no preneoplastic lesions were observed in any nonclinical studies with aripiprazole lauroxil. This is consistent with FDA feedback from the end-of-phase 2 meeting. Lifetime carcinogenicity studies were conducted in mice and rats with oral aripiprazole under the NDA for Abilify. The sponsor has included those findings in the proposed label (see labeling section 1.3.3).

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek and summarized below.

Study title: RDC-3317: An Intramuscular Study of Fertility and Early Embryonic Development to Implantation in Male and Female Rats with a Toxicokinetic Evaluation

Study no.:	Sponsor Study No. AT-3317-19
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 22, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 (RDC-3317), lot 10-016-153, purity: total impurities (b) (4)%, single largest impurity (b) (4)%); Vehicle: contains (b) (4)% sorbitan monolaurate (SML), lot 210611-02

Key Study Findings

Changes in estrous cycles (persistent diestrus) were observed in females at all dose levels. In the high dose group females, slight increases in the number of corpora lutea per female, ovary weight and preimplantation loss were observed. In addition, mating, fertility and fecundity parameters were decreased. The high dose males had also lower mating and fertility indices.
The NOAEL for general toxicity in both sexes was the high dose of 98 (2x49) mg aripiprazole equivalents/animal. The NOAEL for the reproductive and fertility parameters was the medium dose of 33 mg aripiprazole equivalents/animal.

At the NOAEL for the reproductive and fertility parameters (33 mg/animal/dose), the $AUC_{0\text{-}56}$ values for males were 446, 19.7, and 729 ng·day/mL for aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole, respectively. For females, the $AUC_{0\text{-}29}$ were 207, 0, and 393 ng·day/mL for aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole, respectively.

Methods

Doses:	**0 (Vehicle), 12, 33, and 98 mg** (2x49 mg/site) aripiprazole equivalents (arip.eq.)/animal (Vehicle, LD, MD, and HD, respectively). Aripiprazole lauroxil dose = 1.47x (17.6, 48.5, 144 mg aripiprazole lauroxil/animal)
Frequency of dosing:	For all groups, males received injections on Days 1, 21, and 42; Females were injected once on Day 1
Dose volume:	Vehicle control group received the vehicle over two sites, once in each hindlimb, at 0.3 mL/site (total vol. 0.6 mL). LD and MD groups were administered 0.2 mL volume in one dose at one site. HD groups were administered 49 mg arip.eq. over two sites, once in each hindlimb, at 0.3 mL/site (total vol. 0.6 mL)
Route of administration:	Intramuscular injection
Formulation/Vehicle:	Suspension/Vehicle containing (b) (4)% SML (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water The test article was administered as a suspension of aripiprazole lauroxil in vehicle at a concentration of 241 mg/mL (164 mg aripiprazole equivalents/mL) for the 33 and 98 mg/animal/dose groups, or 88.2 mg/mL (60 mg aripiprazole equivalents/mL) for the 12 mg/animal group
Species/Strain:	Rat/CD® [Crl:CD®(SD)] ~ 8 (males) and 10 (females) weeks of age, weighing 325 to 381 g and 246 to 323 g, respectively
Number/Sex/Group:	25/sex/group
Satellite groups:	None
Study design:	Fertility and reproduction parameters in females: estrus cycle, tubal transport, implantation and development of preimplantation stages of the embryo. Fertility parameters in males: detection of functional effects on male fertility. TK analysis in both sexes. Males were dosed once every 3 weeks beginning 28 days prior to mating, and continuing until Day 42 (i.e., dosing on Days 1, 21, and 42). Females were dosed once on Day 1 (14 days prior to mating and corresponding to Day 14 of dosing in males). Males and females of the same treatment group were paired for mating up to 21 days, or until evidence of mating was observed. Mated females were euthanized on Gestation Day (GD) 13
Deviation from study	Deviations did not affect the integrity of the study.

protocol:

Observations and Results

Mortality

There were no treatment-related deaths.

Clinical Signs

There were no treatment-related clinical signs. Clinical examinations were conducted twice weekly during the study period, on each dosing day, and on the day of termination.

Body Weight

There were no changes in male body weight or body weight gain. Female body weight and body weight gain increased in HD females during the premating period, and transiently decreased during pregnancy. These slight changes correlated with changes in food consumption, and were not considered adverse.
Individual body weights were recorded twice weekly, at 3- and 4-day intervals. In addition, mated females were weighed on GD 0, 3, 6, 10, and 13.

Food Consumption

There were no changes in male food consumption. In females, slight changes in food consumption correlated with changes in body weight, as described above.
Food consumption was recorded twice weekly at 3- and 4-day intervals, except during the first 14 days of the pairing period.

Prolactin
Serum was collected from designated males on Day 56 for prolactin analysis.
There were no drug-related effects on prolactin in males at any dose level at the day 56 measurement. All values were considered to be within the acceptable range for biologic variation.

Toxicokinetics

Blood samples for toxicokinetic analysis of aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole were collected from the first 4 animals/group: from males and females on Days 1, 3, 7, 10, 14, 21, from females on Day 29, and from males on Days 23, 28, 35, 42, 44, 51, and 56. Validated LC/MS/MS method was used.

There was no systemic exposure to aripiprazole lauroxil in males or females.

Dose (mg aripiprazole equivalents/animal/dosing day)	0	12	33	98
Total Dose (mg/animal over duration of study)	0	36	99	294
Males Toxicokinetics:				
Number of Main Study Males for Toxicokinetics	4	4	4	4
RDC-3317 :				
C_{max} (ng/mL)	BLQ[a]	BLQ	BLQ	BLQ
AUC_{0-56} (day·ng/mL)	NC	NC	NC	NC
RDC-9864 (aripiprazole)				
C_{max} (ng/mL)	BLQ	4.86	14.2	47.7
AUC_{0-56} (day·ng/mL)	NC	182	446	1600
RDC-3954 (dehydro-aripiprazole)				
C_{max} (ng/mL)	BLQ	BLQ	0.980	6.25
AUC_{0-56} (day·ng/mL)	NC	NC	19.7	157
RDC-5792				
C_{max} (ng/mL)	BLQ	9.70	21.5	72.3
AUC_{0-56} (day·ng/mL)	NC	357	729	2510

Note: RDC-3317 doses are approximately 1.47× greater than aripiprazole-equivalent doses. GD = Gestation Day; BLQ = Below Limit of Quantitation (1 ng/mL); NC = Not Calculated; Placebo = ALKS 9072 Vehicle (containing (b) (4)% sorbitan monolaurate, (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, (b) (4)% water); RDC-3317 = *N*-lauroyloxymethyl aripiprazole; RDC-9864 = aripiprazole; RDC-3954 = dehydro-aripiprazole; RDC-5792 = *N*-hydroxymethyl aripiprazole

[a] All but one control samples were below the limit of quantitation for RDC-3317

Dose (mg aripiprazole equivalents/animal/dosing day)	0	12	33	98
Total Dose (mg/animal over duration of study)	0	12	33	98
Females				
Number of Main Study Females for Toxicokinetics	4	4	4	4
RDC-3317 :				
C_{max} (ng/mL)	BLQ	BLQ	BLQ	BLQ
AUC_{0-29} (day·ng/mL)	NC	NC	NC	NC
RDC-9864 (aripiprazole)				
C_{max} (ng/mL)	BLQ	5.98	11.0	38.1
AUC_{0-29} (day·ng/mL)	NC	108	207	712
RDC-3954 (dehydro-aripiprazole)				
C_{max} (ng/mL)	BLQ	BLQ	BLQ	3.08
AUC_{0-29} (day·ng/mL)	NC	NC	NC	50.4
RDC-5792				
C_{max} (ng/mL)	BLQ	11.7	20.3	69.9
AUC_{0-29} (day·ng/mL)	NC	210	393	1210

Dosing Formulation Analysis

Homogeneity and concentration of dose formulations were found to be within the acceptance range.

Necropsy

Pregnant females were euthanized on GD 13 and complete necropsies were conducted. Sperm was collected for motility, concentration, and morphology analysis. The following reproductive organs and tissues were collected, weighed, and preserved for both sexes: epididymides, ovaries, testes, prostate, seminal vesicle with coagulating glands, uterus (both horns) with cervix, vagina, gross lesions, and injections sites.

Macroscopic findings included observation of tan, foreign material at the injection sites, which is expected to be the test article.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.): There were 1, 0, 2, and 6 females (N=25/group) that were not pregnant in the control, LD, MD, and HD groups, respectively. Test article related findings included changes in estrous cycles (persistent diestrus of ≥ 6 days) at all doses (22/25, 4/25 and 7/25 females in the LD, MD and HD groups, respectively). There were no control animals with ≥ 6 consecutive days of diestrus.

Test article related findings in the HD females included significantly decreased mean number of cycles (1.8 cycles), in comparison to controls (2.6 cycles) during the 15 day premating period, lower mating, fertility and fecundity indices (88, 76, and 86.4%, respectively, in comparison with control values of 100, 96 and 96%, respectively), increased mean number of corpora lutea per female (18.9 vs.16.5 in control), slightly increased pre-implantation loss (13.11%/animal vs. 8.63%/animal in control), and increased mean ovary weight (116% of control).
There were no test article related effects on implantation sites, viable embryos, or postimplantation loss.

The HD males had lower mating (72% vs. 100% in the control group) and fertility (64% vs. 96% in the control group). These differences were statistically significant compared to controls, and related to treatment with ALKS 9072. The percent abnormal sperm (predominately detached heads) in HD males was slightly, but significantly, increased (5.82% vs. 3.70% abnormal in controls). However, this was primarily due to one male. This finding, although likely test article-related, was not considered adverse due to small magnitude. Epididymal sperm counts and sperm motility were comparable to controls. There were no treatment-related changes in testes, epididymides, and prostate or seminal vesicle weights.

9.2 Embryonic Fetal Development

The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek and summarized below.

Study title: RDC-3317: An Intramuscular Study for Effects on Embryo-Fetal Development in Rats with a Toxicokinetic Evaluation

Study no.:	AT-3317-20
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 14, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 (RDC-3317), lot 10-016-153, purity: total impurities (b) (4) %, single largest impurity (b) (4) %)

Key Study Findings

An accumulation of the test article at the injection site in most of the treated animals was evident and was similar to macroscopic findings observed in previous rat studies. No (or minimal) drug related effects. The NOAEL for maternal and developmental toxicity with aripiprazole lauroxil in rats was 98 mg aripiprazole equivalents/animal. This dose was associated with an aripiprazole $AUC_{GD3-GD20}$ of 298 ng·day/mL, dehydro-aripiprazole $AUC_{GD3-GD20}$ of 22.5 ng·day/mL, and N-hydroxymethyl aripiprazole AUC_{GD3-}

$_{GD20}$ of 564 ng·day/mL. The C_{max} values at the NOAEL were 31.0, 2.83, and 58.7 ng/mL for aripiprazole, dehydro-aripiprazole and N-hydroxymethyl aripiprazole, respectively.

Methods

Doses:	aripiprazole lauroxil doses: **0 (Vehicle), 12, 33, or 98 mg** aripiprazole equivalents (arip.eq.)/animal (Vehicle, LD, MD, HD, respectively) Aripiprazole lauroxil dose = 1.47x (17.6, 48.5, 144 mg aripiprazole lauroxil/animal)
Frequency of dosing:	Single dose on gestation Day 3; Vehicle and HD (98 mg aripiprazole eq./animal) were administered at two sites (49 mg/site), once in each hindlimb; LD and MD were administered at one site
Dose volume:	Vehicle and HD: 0.3 mL/site; LD and MD: 0.2 mL/site
Route of administration:	Intramuscular injection
Formulation/Vehicle:	Suspension/Vehicle containing (b) (4)% sorbitan monolaurate (novel excipient), (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water
Species/Strain:	Rat/CD® [Crl:CD®(SD)]; 12 weeks of age
Number/Sex/Group:	25 female rats /group weighing 218 to 275 g
Satellite groups:	None
Study design:	This study was designed to examine the developmental toxicity study in rats following administration of a single intramuscular dose of ALKS 9072 up to 98 mg aripiprazole equivalents/animal. Moreover, this study was conducted to address toxicity of the novel excipient sorbitan monolaurate (SML). Groups: doses/animal No. 1: (vehicle with (b) (4)% SML only) No. 2: 12 mg arip. eq./animal No. 3: 33 mg arip. eq./animal No. 4: 98 mg arip. eq./animal Animals received a single dose on GD 3, and were euthanized on GD 20. There is no control group for vehicle not containing the new excipient SML. Historical control data are included in study report. Prior to dosing, and least weekly thereafter, the injection sites in main-study animals were shaved and marked with indelible marker at least weekly. Care was taken within the demarcated area to avoid injection more than once into exactly the same injection site.
Deviation from study protocol:	Deviations did not affect the integrity of the study

Observations and Results

Mortality

All animals were observed for morbidity, mortality, and injury twice daily. All animals survived to scheduled necropsy.

Clinical Signs

There were no test article related clinical signs, however daily clinical observations were not conducted. Animals were given a detailed clinical examination every three days from GD 3 through 20 (60 to 90 minutes postdose on GD 3).

Body Weight

There were no test article related effects on maternal body weight and body weight gain. Body weights were recorded on GD 0, 3, 6, 9, 12, 15, 18, and 20 for all animals.

Food Consumption

There were no test article related effects on food consumption. Food consumption was measured and recorded on body weight days.

Toxicokinetics

Blood samples for TK analysis of the aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole were collected from first 5 animals/group on GD 3, 6, 10, 14, and 20. Whole blood concentrations were analyzed using a validated LC/MS/MS method. C_{max}, T_{max}, AUC_{last} and $AUC_{GD3-GD20}$ for each of the four analytes were determined. All individual AUC_{last} values were identical to the corresponding individual $AUC_{GD3-GD20}$ values, and only $AUC_{GD3-GD20}$ values are presented in the report.

All individual whole blood aripiprazole lauroxil concentrations were below the LLOQ of 1 ng/mL. Systemic exposure ($AUC_{GD3-GD20}$ and C_{max}) increased with increasing dose for aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole. The exposure to N-hydroxymethyl aripiprazole was greater than that for aripiprazole and dehydro-aripiprazole at all dose levels. T_{max} all analytes occurred on either GD 14 or GD 20. It should be noted that GD 20 was the last time point for collection of blood for TK. These data are shown in the following Sponsor's tables:

Dose (mg aripiprazole equivalents/animal)	0	12	33	98
Maternal Females				
Toxicokinetics:				
Number of Main Study Animals for Toxicokinetics	5	5	5	5
RDC-3317 :				
C_{max} (ng/mL)	BLQ	BLQ	BLQ[a]	BLQ
$AUC_{GD\ 3\text{-}20}$ (day·ng/mL)	NC	NC	NC	NC
RDC-9864 (aripiprazole)				
C_{max} (ng/mL)	BLQ	5.97	8.86[a]	31.0
$AUC_{GD\ 3\text{-}20}$ (day·ng/mL)	NC	64.5	80.0[a]	298
RDC-3954 (dehydro-aripiprazole)				
C_{max} (ng/mL)	BLQ	BLQ	BLQ[a]	2.83
$AUC_{GD\ 3\text{-}20}$ (day·ng/mL)	NC	NC	NC	22.5
RDC-5792				
C_{max} (ng/mL)	BLQ	12.1	16.7[a]	58.7
$AUC_{GD\ 3\text{-}20}$ (day·ng/mL)	NC	128	141[a]	564

Note: RDC-3317 doses are approximately 1.47× greater than aripiprazole-equivalent doses. BLQ = Below Limit of Quantitation for analyte (1 ng/mL); GD = Gestation Day; Placebo = ALKS 9072 Vehicle (containing (b) (4)% sorbitan monolaurate, (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, (b) (4)% water); NC = Not Calculated; RDC-3317 = *N*-lauroyloxymethyl aripiprazole; RDC-9864 = aripiprazole; RDC-3954 = dehydro-aripiprazole; RDC-5792 = *N*-hydroxymethyl aripiprazole

[a] N=4 pregnant rats for 33 mg aripiprazole equivalents/animal toxicokinetics group.

Dosing Formulation Analysis

Samples for each level met the sample analysis acceptance criteria for accuracy and precision.

Necropsy

Animals were euthanized on gestation day 20 (GD 20), and subjected to a complete necropsy. Accumulation of the tan foreign material at the injection site in most of the treated animals was observed, but was similar to macroscopic findings observed in previous rat studies, and not considered adverse.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no test article related effects on the following parameters: gravid uterine weights, the total number of corpora lutea, implantations, early and late resorptions, sex, and viability of fetuses.

The pregnancy index was 76, 96, 80, and 96% in the Vehicle, LD, MD and HD, respectively. Since the lower pregnancy index occurred in the Vehicle and MD groups, the difference was not test article-related. A statistically significant increase in pre-implantation loss, in comparison to controls was observed in the MD group. However, the value (12.79%) was within the historical control range (4.66 to 17.90%) for this laboratory and, in the absence of a dose-response relationship, was considered unrelated to treatment.

Offspring (Malformations, Variations, etc.)

External, visceral, and skeletal examination were conducted for all, 50% and 50% fetuses in each litter, respectively. All malformations and variations were recorded.

Results: The Vehicle and LD groups had no external, visceral, or skeletal malformations. The overall incidence of litters and fetuses with malformations in the MD

and HD groups was slightly higher (two fetuses at each dose level) compared to the vehicle group. The overall incidence was considered unaffected by drug treatment. These data are shown below:

(b) (4) Study Number 825-061
RDC-3317: An Intramuscular Study for Effects on Embryo-Fetal Development in Rats with a Toxicokinetic Evaluation

Summary of External, Visceral, and Skeletal Malformations

Observation	0 mg/animal	12 mg/animal	33 mg/animal	98 mg/animal
No. Litters Evaluated	19	24	20	24
No. Fetuses Evaluated	240	296	246	294
Total Malformations				
No. Litters(%)	0 (0.0)	0 (0.0)	2 (10.0)	2 (8.3)
No. Fetuses(%)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.7)

Malformations, considered spontaneous, included external malformation (omphalocele) in one HD fetus (not seen in historical control data, low 4.2% litter incidence), two visceral variations (increased renal pelvic cavitation and undeveloped renal papillae) in one HD fetus (litter incidence of 4.2% was within recent historical control data), skeletal malformations of the forelimbs (short humerus), hind limbs (short femur), and misshapen scapula in one HD fetus, bent femur (hind limb malformation) in one MD fetus, and short femur (hind limb malformation) in another MD fetus (not observed in controls, and with the exception of the misshapen scapula have not been seen in recent historical control data, however, observed at a low frequency). These findings were not considered toxicologically relevant as they were either of a small incidence, not dose-related, and/or within the historical control dataset.

Study title: RDC-3317: An intramuscular study for effects on embryo-fetal development in rabbits with a toxicokinetic evaluation

Study no.:	AT-3317-21
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 1, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALKS 9072 drug product, lot no. 10-016-153, total impurities (b) (4) %, single largest impurity (b) (4) %)

Key Study Findings

Aripiprazole lauroxil was not teratogenic to rabbits. There was a slight transient decrease in maternal body weight at the high dose. Accumulation of test article was observed at the injection site of all test-article treated animals, without any adverse

effects on muscle tissue. There were no drug-related effects on any uterine parameter and no adverse toxicity to fetuses.
NOAEL for both maternal and fetal changes: 1968 mg aripiprazole equivalents/animal.
$AUC_{GD3\text{-}GD29}$ values at NOAEL for aripiprazole of 5740 ng.day/ml, dehydro-aripiprazole of 1620 ng.day/ml and N-hydroxymethyl-aripiprazole of 5040 ng.day/ml.

Methods

Doses:	0, 164, 492, 1968 mg/animal (Dose levels based on aripiprazole equivalents administered over the total duration of the study) Aripiprazole lauroxil dose = 1.47x (241, 723, 2893 mg aripiprazole lauroxil/animal)
Frequency of dosing:	Vehicle group (0): administered to 2 dose sites (once in each hindlimb) both on GD 3 and 10; 164 mg/animal group: administered to 1 dose site (1 hindlimb) on GD 3 only 492 mg/animal group: administered to 2 dose sites (once in each hindlimb) on GD 3 only 1968 mg/animal group: administered 984 mg/animal over 2 dose sites (once in each hindlimb) on GD 3 and 10
Dose volume:	1 ml/kg (low dose) 1.5 ml/kg (mid dose) 3.0 ml/kg (control and high dose)
Route of administration:	Intramuscular into 1 or both hindlimbs
Formulation/Vehicle:	Formulation: suspension of aripiprazole lauroxil in vehicle, 241 mg RDC-3317/mL (164 mg aripiprazole equivalents/mL) Control vehicle and drug vehicle: Lot no. 21061102: (b) (4)% sorbitan monolaurate, (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, and (b) (4)% water.
Species/Strain:	Timed-mated female Rabbit/New Zealand white from (b) (4) ~8.5 months old at receipt.
Number/Sex/Group:	23/group
Satellite groups:	NA
Study design:	Depending on the dose administered, animals either received one or two doses of the vehicle or test article to either one or both hindlimbs on GD 3 or GD 3 and GD 10. All animals were euthanized on GD 29 and a complete necropsy was performed. All fetuses were examined for

	external and visceral variations and malformations and processed for skeletal examinations.
Deviation from study protocol:	Several minor deviations were reported, but none that affected the outcome of the study or data integrity.

Observations and Results

Mortality

None

Clinical Signs

There were no drug-related clinical signs in any animals. A nodule, which corresponded to tan material related to the test article at necropsy, was observed in one mid dose animal on GD 9 until termination, and a nodule was also observed on GD 9 in one high dose animal, without any corresponding macroscopic finding.
Cageside exams were conducted twice daily. Detailed exams, in which animals were removed from the cages, were conducted on GDs 3, 6, 9, 10, 12, 15, 18, 21, 24, 27, and 29. On dosing days, GD 3 and/or 10, exams were conducted 60-90 minutes postdose.

Body Weight

Final maternal body weights, body weight gains, and gravid uterine weights in all drug-treated groups were comparable to the vehicle control group. However from GD 3-6, there was a statistically significant decrease in body weight gain at all dose groups compared to controls, 35 g and 0 g gain at 164 and 492 mg/animal, respectively and a 70 g loss at 1968 g/animal, compared to a 70 g gain in the vehicle control group. This decrease in body weight gain was considered drug-related. However, the effect was transient as an increase in body weight gain was observed in between GD 9-15 at 492 mg/animal and between GD 12-15 at 1968 mg/animal. Also, there was no overall (GD 0-29) difference in body weight gain between drug-treated groups and controls. The effects on body weight gain correlated with changes in food consumption during the corresponding time period. Body weights for all animals were measured and recorded on GD 0, 3, 6, 9, 12, 15, 18, 21, 25, and 29.

Food Consumption

There was no effect on food consumption at 164 or 492 mg/animal. At 1968 mg/animal, there was a significant decrease in food consumption between GD 3-6, 28% compared to controls. However this effect was transient as a significant increase in food consumption was observed in the same group between GD 15-18, 11% compared to controls. In addition, a slight increase in food consumption was also observed at 492 mg/animal between GD 15-18 of 9% compared to controls. These changes in food consumption correlated with changes in maternal body weight gain. Food consumption was measured daily, and was recorded on the corresponding body weight day.

Toxicokinetics

Blood samples (whole blood) were collected from the first 5 animals/group. Concentrations of aripiprazole lauroxil, aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole were analyzed. AUC values were calculated from GD3-GD29. The following table on blood sampling times is excerpted from the Sponsor's submission.

Blood Collection for Precipitated Whole Blood Concentration		
Dose Level [a](mg/animal)	**Study Interval**	**Interval**
0, 164, 492, and 1968	GD 3[b]	12 hours after dosing
0 and 1968	GD 10[b]	12 hours after dosing
0, 164, 492, and 1968	GD 6, 9[b], 12[b], 16, and 21[b]	At approximately the same time of day as the last dose
0, 164, 492, and 1968	GD 29	At necropsy; all animals at approximately the same time of day

[a] Dose levels based on aripiprazole equivalents administered over the total duration of the study.
[b]Blood samples were collected from controls at all timepoints for consistency among groups. Control samples were discarded following collection.

Results:

No measurable amount of any of the four analytes was present in the control samples. Data were insufficient (fewer than 3 consecutive non-zero whole blood concentrations or all whole blood concentration were below the lower limit of quantification) to measure any systemic exposure to aripiprazole lauroxil in any sample. T_{max} occurred on day 29 for all measurable analytes. Exposures increased with increasing dose and exposure to aripiprazole was greater than that of dehydro-aripiprazole and comparable to that of N-hydroxymethyl aripiprazole.

Dose (mg aripiprazole equivalents/animal/dosing day)	0	164	492	984
Total Dose (mg aripiprazole equivalents/animal)	0	164	492	1968
Maternal Females:				
Number of Pregnant Toxicokinetic Animals (First 5 Main Study)	5	5	3	5
RDC-3317[a]				
C_{max} (ng/mL)	BLQ	BLQ	1	5
$AUC_{GD\ 3\text{-}29}$ (day·ng/mL)	NC	NC	NC	NC
RDC-9864 (aripiprazole)[a]				
C_{max} (ng/mL)	BLQ	76	238	725
$AUC_{GD\ 3\text{-}29}$ (day·ng/mL)	NC	636	2100	5470
RDC-3954 (dehydro-aripiprazole)[a]				
C_{max} (ng/mL)	BLQ	19	76	229
$AUC_{GD\ 3\text{-}29}$ (day·ng/mL)	NC	176	625	1620
RDC-5792[a]				
C_{max} (ng/mL)	BLQ	53	180	528
$AUC_{GD\ 3\text{-}29}$ (day·ng/mL)	NC	558	1920	5040

Note: RDC-3317 doses are approximately 1.47× greater than aripiprazole-equivalent doses. BLQ = Below Limit of Quantitation (Approximately 1 ng/mL); GD = Gestation Day; Placebo = ALKS 9072 Vehicle (containing (b) (4)% sorbitan monolaurate, (b) (4)% polysorbate 20, (b) (4)% sodium phosphate monobasic dihydrate, (b) (4)% sodium phosphate dibasic anhydrous, (b) (4)% sodium chloride, (b) (4)% water); NC = Not Calculated; RDC-3317 = *N*-lauroyloxymethyl aripiprazole; RDC-9864 = aripiprazole; RDC-3954 = dehydro-aripiprazole; RDC-5792 = *N*-hydroxymethyl aripiprazole

[a] Group means are shown, rounded to the nearest whole number.

Dosing Solution Analysis

Homogeneity of all test article formulations was tested on GD 3 from the top, middle and bottom layers of the formulations and all formulations were within the acceptance criteria (± 15% recovery and ≤10% RSD). The average concentration from all dose formulations on GD 3 was 108% of nominal. No test article was detected in the vehicle control samples.

Necropsy

Tan material was observed in the muscle of the right and/or left hindlimbs at the injection sites in all of the aripiprazole lauroxil-treated animals from all dose groups. This material was not present in any control animals and was considered to be accumulated test article. There were no abnormalities in the muscle tissue, therefore the finding was not considered adverse. There were no other treatment-related macroscopic findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no drug-related effects. The pregnancy index and the number of females with viable fetuses were comparable across all dose groups and the vehicle control. All ovary and uterine parameters in the drug-treated groups were comparable to those in the vehicle treated group. All values for the vehicle control group were within the historical control range for this laboratory, indicating that the vehicle is not causing any significant toxicity.

Offspring (Malformations, Variations, etc.)

Fetal body weights (male, female and combined) were slightly, but not statistically significant, decreased in the high dose group compared to fetal body weights from control animals, but were still within the historical control range for the laboratory.

Summary of Fetal Body Weight Values, g

Endpoint			0 mg/animal	164 mg/animal	492 mg/animal	1968 mg/animal
Fetal Weight						
	Males	Mean	44.08 (42.81)	42.75 (43.02)	42.66 (43.65)	40.43 (40.48)
		SD	6.583	4.766	4.730	5.156
		N	20	21	19	22
	Females	Mean	43.50 (42.40)	41.80 (42.01)	40.84 (41.67)	40.68 (40.70)
		SD	4.864	3.388	4.003	4.220
		N	19	21	19	22
	Males + Females	Mean	43.89 (42.71)	42.50 (42.75)	41.77 (42.69)	40.81 (40.85)
		SD	5.380	3.971	3.995	4.380
		N	20	21	19	22

There was no overall difference in the total number of malformations or variations (external, visceral and skeletal) between any dose group including controls. A few external malformations were observed in each dose group including one control fetus, but only in one fetus in each of the groups. No external variations were observed in any of the fetuses. A few visceral malformations were observed in all treated groups including the vehicle group, however they were all considered incidental since they were only observed in 1-2 fetuses, not dose-related and/or most were also observed with a similar frequency in the historical control data. The visceral variations of subclavian

artery, retroesophageal and absent innominate artery were observed in 3 fetuses each from the mid dose group which is a slightly higher incidence than the historical control range, and not observed in any other group. However, since the findings were not observed in the high dose group, they are most likely not drug-related. A higher incidence of the visceral variation of absent right lung azygous lobe (13.9% of fetuses and 54.5% of litters) was observed in the high dose group compared to all other treatment groups and higher than that of the historical control data (7.8% of fetuses and 45.5% of litters). Various skeletal malformations and variations were observed in all treatment groups including controls, at similar incidences. The findings were not dose-related, were observed at a low frequency or similar to controls and either very close to or within the historical control range for this laboratory. Therefore, the skeletal changes were not considered to be drug-related.
All values for the vehicle control group were within the historical control range for this laboratory, indicating that the vehicle is not causing any significant toxicity.

9.3 Prenatal and Postnatal Development

A prenatal and postnatal development study was not conducted with aripiprazole lauroxil. Data from animal studies with oral aripiprazole are included in the label (excerpted from the Abilify® label).

10 Special Toxicology Studies

Safety assessment of excipient sorbitan monolaurate:
Studies conducted by the sponsor using sorbitan monolaurate (SML) included an Ames bacterial gene mutation assay, in vitro chromosomal aberration and an in vivo micronucleus assay (see review of studies below). All general and reproductive toxicology studies included a vehicle control group containing SML. The 4-month rat and dog and the 6-month rat and 9-month dog studies utilized two vehicle control groups, one containing (b) (4)% and the other (b) (4)% SML. It should be noted that a negative control not containing SML was n cluded in any of the studies. In addition to the sponsor conducted studies, the sponsor also submitted a “SML White Paper” entitled “A summary of the safety, absorption, distribution, metabolism and excretion of sorbitan monolaurate and sorbitan fatty acid esters” (report no. 700-02313-06). This report included the chemical characteristics of SML and a summary of nonclinical toxicology studies with SML from both published literature and sponsor directed studies. The white paper also included historical control data for rats and dogs of the same strain and similar age from the laboratory in which the toxicity studies were conducted (body weight, food consumption, clinical pathology, urinalysis, ophthalmology findings, organ weight, and histopathology) in order to aid in assessing the safety of SML in the 4-month rat and dog and 6-month rat and 9-month dog repeat-dose toxicology studies since a negative control not containing SML was not included in those studies.

During the end of phase 2 meeting on September 15, 2011, the sponsor was informed that a hERG channel assay would need to be conducted for SML. An assay was not conducted and this reviewer submitted an information request to the sponsor asking

them to provide a scientific justification for not conducting a hERG channel assay. The sponsor's response was submitted on November 25, 2014 in SDN 7. The sponsor stated that (b) (4) The sponsor has evaluated the effects of SML on QT_c in vivo in the 4-month and 9-month toxicity studies in dogs, as evaluated in the vehicle control groups. There were no significant effects on QT_c values in the vehicle control groups comparing predose to post-dose values. This reviewer considers the sponsor's nonclinical evaluation of the cardiovascular effects of SML to be adequate and there are no significant adverse findings.

Study title: Bacterial Reverse Mutation Assay
The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek and summarized below.

Study no.:	Sponsor's Study No. AT-3317-15
Study report location:	(b) (4)
Conducting laboratory:	(b) (4)
Date of study initiation:	June 22, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sorbitan monolaurate (SML; also known as (b) (4)), lot no. T11141VAL, purity: certificate of analysis indicates several components of the SML mixture (see below)

Key Study Findings

Sorbitan monolaurate tested in the Ames test using standard method did not induce positive mutagenic responses with any of the tester strains, in either the presence or absence of S9 metabolic activation. Therefore, under the conditions of this study, SML was considered to be negative in the bacterial reverse mutation assay.

Methods

Strains:	*Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A
Concentrations in definitive study:	15, 50, 150, 500, 1500 and 5000 µg/plate
Basis of concentration selection:	Initial toxicity-mutation assay used to establish the dose-range
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	With S9: for all strains 2-aminoanthracene; Without S9: for strain TA98: 2-nitrofluorene, for strains TA100, TA1535: sodium azide, for strain TA1537: 9-aminoacridine, and for strain WP2*uvr*A: methyl methanesulfonate.
Formulation/Vehicle:	Solution in vehicle/DMSO
Incubation & sampling time:	Plates were incubated with the test article and controls for ~ 48 to 72 hours at 37±2°C

Study Validity

Sorbitan monolaurate was tested in the presence and absence of Aroclor-induced rat liver S9. The assay was performed using the plate incorporation method, and five concentrations of test article along with appropriate vehicle control and positive controls plated in triplicate. However, uniformity, concentration, and stability of the test article were not determined. The Sponsor indicated that a method was not available. Therefore, the interpretation of the data was based on nominal dose levels, and not on the actual formulated test article concentrations. However, toxicity and precipitate in the assay demonstrated that the system was dosed up to the required regulatory dose level.

Results

Precipitate was observed at 5000 µg per plate. Toxicity, as reductions in revertant counts, was observed beginning at 1500 or at 5000 µg per plate with most test conditions. No positive mutagenic responses were observed with any of the tester strains, in either the presence or absence of S9 activation. In conclusion, under the conditions of this study, sorbitan monolaurate was considered to be negative in the bacterial reverse mutation assay.

Study title: *In Vitro* Mammalian Chromosome Aberration Test
The following study was reviewed by Dr. Elzbieta Chalecka-Franaszek and summarized below.

Study no.:	Sponsor's Study No. AT-3317-16
Study report location:	EDR, NDA SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 13, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sorbitan monolaurate (known also as (b) (4) , lot no. T11141VAL, purity: certificate of analysis indicates several components of the test article mixture (see Certificate of Analysis for the Ames test above)

Key Study Findings

SML was negative for the induction of structural and numerical chromosome aberrations, in both non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

Methods

Cell line:	Human peripheral blood lymphocytes (HPBL)
Concentrations in definitive study:	35 to 750 µg/mL for both the non-activated, and the S9-activated 4-hour exposure groups, and from 25 to 500 µg/mL for the non-activated 20-hour exposure group
Basis of concentration selection:	Preliminary toxicity test
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	Mitomycin C for the non-activated test system, cyclophosphamide for the activated test system
Formulation/Vehicle:	Sorbitan monolaurate in DMSO
Incubation & sampling time:	Cells were treated for 4 and 20 hours in the non-activated test system, and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation.

Study Validity

The chromosome aberration assay was performed using standard procedures by exposing duplicate cultures of HPBL to 7 concentrations of the test article, as well as positive and solvent controls. The dividing cells were harvested at approximately 20 hours from the initiation of treatment. Mitotic Index reduction at highest dose scored

(100 µg/mL) was 11%, 32%, and 17% for 4 and 20 hours in the non-activated test system; and for 4 hours in the S9-activated test system, respectively. The highest dose level evaluated was the lowest precipitating dose level. Two additional lower dose levels were included in the evaluation. The positive and solvent controls fulfilled the requirements for a valid test. [redacted] (b) (4) has determined the identity, strength, purity (of all components, as indicated on the Certificate of Analysis) and composition or other characteristics to define the test article and the stability of the test article.

Results

The percentage of cells with structural or numerical aberrations in the test article-treated groups was not significantly increased, relative to solvent control at any dose level. Therefore, sorbitan monolaurate was concluded to be negative for the induction of structural and numerical chromosome aberrations.

Study title: Genotoxic assessment of sorbitan monolaurate following subcutaneous administration: rat bone marrow micronucleus assay

Study no:	AT-3317-17
Study report location:	EDR: NDA SDN 1
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	September 8, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sorbitan monolaurate (SML) ([redacted] (b) (4)) (CAS # 1338-39-2), lot no. T11141VAL, Density = 1.1 g/ml

Key Study Findings

SML did not produce a significant increase in the number of micronuclei in rat bone marrow under the conditions that this assay was performed.

Methods

Doses in definitive study:	0, 500, 1000, 2000 mg/kg/day
Frequency of dosing:	Once daily for 3 consecutive days
Route of administration:	Subcutaneous It is not possible to administer SML via the intramuscular route to rats (b) (4) . Therefore the subcutaneous route was chosen to permit dosing of the neat test article to a limit dose of 2000 mg/kg/day.
Dose volume:	1.82 ml/kg (for negative control and high dose), 0.46 ml/kg and 0.91 ml/kg for low and mid dose, respectively
Formulation/Vehicle:	SML was tested neat. (b) (4) (density of 1.1 gml)
Species/Strain:	Rats/Sprague-Dawley from (b) (4) Males and females (7 weeks old at dose administration) were used for dose range-finding phase. Males only were used (9 weeks old at dose administration) were used for definitive phase.
Number/Sex/Group:	6 males/group. An additional 6 males/group were dosed with 2000 mg/kg/day SML to serve as replacements in the event of mortality. Since no mortality occurred these animals were not used to assess genotoxicity.
Satellite groups:	NA
Basis of dose selection:	A dose range-finding assay was conducted in both males and females to assess for toxicity.

Group/Treatment (SC)	Dose volume*	Number of Animals/Sex
Test Article: Sorbitan Monolaurate		
1/500 mg/kg/day	0.46 mL/kg	3
2/1000 mg/kg/day	0.91 mL/kg	3
3/ 2000 mg/kg/day	1.82 mL/kg	3

SC = subcutaneous
*The dose volume was based on the density of sorbitan monolaurate (1.1 g/mL).

Negative control:	Sodium chloride for injection, saline (0.9% w/v)
Positive control:	Ethyl methanesulfonate (EMS) 200 mg/kg/day (volume of 10 ml/kg). EMS was administered by oral gavage on study day 2 (~24 hrs prior to bone marrow collection) and on study day 3 (~4 hrs prior to bone marrow collection).

Study Design:
A dose range-finding assay was conducted in both male and female rats at doses of 500, 1000, and 2000 mg/kg/day. No mortality occurred and all animals appeared normal, therefore a high dose of 2000 mg/kg/day was selected for the definitive assay and only male rats were used.

To determine if sorbitan monolaurate had any effect on erythropoiesis, an indicator of bone marrow cytotoxicity, the proportion of polychromatic erythrocytes to total of 1000 erythrocytes (PCEs/ECs ratio) was measured for each animal and treatment group.

Study Validity

The negative and positive control values were all within the historical control range for this laboratory. The positive control induced a significant increase in the number of MPCEs (micronucleated polychromatic erythrocytes) compared to the negative control, validating the assay procedures.

Results

All animals in definitive assay treated with the negative control and all 3 doses of sorbitan monolaurate appeared normal, without any noted clinical signs. All positive control animals had diarrhea after the second dose and before bone marrow collection. There was no significant effect on body weight in any group.
None of the sorbitan monolaurate dose groups produced a significant increase in MPCEs compared to the negative control group; all values were comparable to the negative control values. The EMS group did produce a significant increase in MPCEs compared to the negative control group. Sorbitan monolaurate at 1000 and 2000 mg/kg/day produced a slight decrease in the PCE/EC ratio (both caused a 15% decrease compared to control). The Sponsor noted that “reductions of this magnitude suggest that sorbitan monolaurate was bioavailable but that it did not markedly inhibit erythropoiesis”. This conclusion appears reasonable.
Under the conditions of this assay, sorbitan monolaurate was found to be non-genotoxic.

11 Integrated Summary and Safety Evaluation

Aristada™ (aipiprazole lauroxil) is an extended-release injectable suspension being developed for the treatment of schizophrenia to be administered via the intramuscular route. The sponsor submitted a 505(b)(2) NDA for aripiprazole lauroxil and is also relying on the Agency’s previous findings of safety and effectiveness for oral aripiprazole (NDA 21-436) for the treatment of schizophrenia.

Pharmacology
The efficacy of aripiprazole lauroxil is most likely due to aripiprazole and aripiprazole-related active metabolites. Aripiprazole lauroxil binds to similar dopamine and serotonin receptor subtypes as aripiprazole in vitro (D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2c}). However, the binding affinities were lower for aripiprazole lauroxil compared to aripiprazole for the majority of receptor subtypes and there was no measurable functional activity (agonistic or antagonistic), with the exception of weak agonist activity at the 5-HT_{1A} receptor.

Safety pharmacology
Safety pharmacology assessments (cardiovascular, neurofunctional and pulmonary) were incorporated into the single-dose, 4-month repeat-dose, and 9-month

(cardiovascular only) repeat- dose toxicology studies in dogs. There were no aripiprazole lauroxil-related findings in any of the safety pharmacology assessments with the exception of a significant decrease in locomotor activity in female dogs in the single-dose study; however this finding may be due to impaired hindlimb function due to the intramuscular injection. A hERG channel assay was conducted with aripiprazole lauroxil and showed a similar inhibition of the hERG channel as compared to aripiprazole (EC_{50s} of 0.22 µM and 0.289 µM, respectively).

Pharmacokinetics

Aripiprazole lauroxil is a covalently bonded modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. After intramuscular administration, aripiprazole lauroxil is converted to the active moiety, aripiprazole. In vivo conversion occurs by dissolution of the aripiprazole lauroxil (b) (4) from the injection site followed by hydrolysis, generating lauric acid and the novel intermediate, *N*-hydroxymethyl aripiprazole (which is the new chemical entity). The covalently bonded hydroxymethyl group on the intermediate is then converted to aripiprazole via water-mediated hydrolysis generating aripiprazole and formaldehyde. Aripiprazole is then metabolized primarily to dehydro-aripiprazole. Aripiprazole lauroxil was not routinely measured after intramuscular administration to rats, while it was consistently measured in dogs, however to a greater extent after a single dose compared to repeat dosing. Aripiprazole lauroxil was not measurable in human plasma. N-hydroxymethyl aripiprazole was routinely measured in rats, mainly at high doses, and in dogs and rabbits at all dose levels after intramuscular administration of aripiprazole lauroxil. In contrast, N-hydroxymethyl aripiprazole was not consistently measurable in human plasma, and when measurable, levels were very low. Exposure levels to the active moiety, aripiprazole, and the main aripiprazole metabolite dehydro-aripiprazole, were very low in rats and dogs after intramuscular administration of aripiprazole lauroxil. Exposure levels of aripiprazole and dehydro-aripiprazole were higher in humans than in rats and dogs after intramuscular administration of aripiprazole lauroxil. For this reason, the sponsor relied on FDA's previous findings of safety for aripiprazole and aripiprazole-related metabolites in nonclinical studies. The T_{max} of aripiprazole lauroxil averaged about 3 days following intramuscular administration, while the T_{max} for aripiprazole, N-hydroxymethyl aripiprazole, and dehydro-aripiprazole was ~2 weeks after administration. Half-lives of all analytes were ~14 days after a single administration.

General Toxicology

Single-dose and repeat-dose intramuscular toxicity studies were conducted in rats and dogs up to 6 and 9 months, respectively. Doses of 10, 20, and 70 mg (2x35 mg) aripiprazole equivalents/animal, which is equivalent to 14.7, 29.4, 102.9 mg aripiprazole lauroxil/animal, were used in the 6-month rat study; and doses of 100, 450, and 1400 mg (2x700 mg), which is equivalent to 147, 661.5, 2058 mg aripiprazole lauroxil/animal, were used in the 9-month dog study. Two vehicles were used in (b) (4) repeat-dose toxicity studies; vehicle 1 contained (b) (4) % sorbitan monolaurate (SML), (b) (4) % polysorbate 20, (b) (4) % sodium chloride, (b) (4) % sodium phosphate monobasic dihydrate, (b) (4) % sodium osphate dibasic anh us, and (b) (4) % water; and vehicle 2 containe e same excipients but higher amounts of SML ((b) (4) %) and polysorbate 20 (b) (4) %). The maximum

feasible dose was used in all studies based on the physiochemical properties of aripiprazole lauroxil and maximum allowable dosing volumes. These studies included toxicokinetic analyses of aripiprazole lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole and dehydro-aripiprazole. Maximal exposure of aripiprazole, *N*-hydroxymethyl aripiprazole, and dehydro-aripiprazole occurred about 14 days after administration of aripiprazole lauroxil in both rats and dogs, irrespective of dose level and repeat dosing. These studies did not reveal any systemic toxicity to aripiprazole lauroxil or the vehicles. Exposure levels to aripiprazole and dehydro-aripiprazole after intramuscular administration of aripiprazole lauroxil were much lower compared to exposure levels in toxicity studies with oral aripiprazole; therefore it is not unexpected that there was an absence of aripiprazole-related toxicities in these studies. However, the main toxicity observed in the intramuscularly administered aripiprazole lauroxil studies in both rats and dogs was local toxicity at the injection site. Dose-related injection site tissue reactions were observed in both rats and dogs and included macroscopic and microscopic findings of granulomatous inflammation and well as clinical signs in dogs of transient swelling and impaired limb function. Granulomas developed in both species at all dose levels which were dose-related in both frequency and severity. The sponsor considered them injection site tissue reactions to be indicative of a typical foreign body type reaction and this reviewer agrees with that conclusion. Granuloma formation was still present in all mid and high dose rats and dogs (low dose animals were not evaluated for reversibility) following a 2 month recovery period in rats and a 4 month recovery period in dogs. However, there was a decrease in the severity of the granulomas at the end of the recovery periods, indicating partial reversibility although very slow. According to the sponsor's proposed labeling, they considered that the local toxic effects (granulomatous inflammation) (b) (4) " This reviewer disagrees with their conclusion based on the lack of complete reversibility of the granulomas in the data provided; and this is reflected in this reviewer's proposed draft labeling in section 13.2

The NOAEL for systemic toxicity in the rat study was the highest dose of 102.9 mg aripiprazole lauroxil/animal, which is approximately 2 and 4 times the maximum recommended human dose (MRHD) of 882 mg aripiprazole lauroxil for males and females respectively, based on mg/m^2 basis. The NOAEL for systemic toxicity in the dog study was the highest dose of 2058 mg aripiprazole lauroxil/animal, which is approximately 8 and 10 times the MRHD for males and females respectively, based on mg/m^2 basis. Since exposure levels to aripiprazole lauroxil were not measureable in humans, safety margins compared to rats and dogs were >1 based on exposure (AUC). The systemic NOAEL values in the chronic rat and dog studies provide a safety margin of 2.3 and 4.2 for rats and 5.7 and 6.8 for dogs, males and females respectively, for the intermediate, N-hydroxymethyl aripiprazole, compared to the MRHD based on AUC.

Genotoxicity

Aripiprazole lauroxil was non-mutagenic in an in vitro bacterial Ames gene mutation assay and non-clastogenic in an in vitro chromosomal aberration assay using human peripheral blood lymphocytes. This is in contrast to findings reported with aripiprazole, in which aripiprazole and a metabolite (2,3-DCPP) were clastogenic in an in vitro

chromosomal aberration assay using Chinese hamster lung cells both with and without metabolic activation, and the metabolite produced an increase in numerical aberrations in the absence of metabolic activation. A possible explanation for these differences is that concentrations of aripiprazole formed in vitro in the assay testing aripiprazole lauroxil were not high enough to exert any toxic effects, under the conditions that those assays were performed. The concentrations of aripiprazole lauroxil used in the in vitro genetox studies were limited (b) (4). In addition, different test systems were used in each of the in vitro chromosomal aberration assays. A definitive explanation by the sponsor was not provided, however aripiprazole lauroxil was not genotoxic.

Reproductive Toxicity

Intramuscular administration of aripiprazole lauroxil to rats and rabbits during the period of organogenesis was not teratogenic. Doses of 12, 33, and 98 mg (2x49 mg) aripiprazole equivalents/animal, which is equivalent to 17.6, 48.5, 144 mg aripiprazole lauroxil/animal, were administered to timed-pregnant rats on gestation day 3. There were no drug-related maternal findings, with the exception of macroscopic findings of tan discoloration at the injection sites. There was no evidence of any fetal toxicity; all malformations observed in fetuses were either not dose-related, of low incidence, and/or were within the historical control ranges. Doses of 164, 492 (246x2 sites), and 1968 mg (492 mg x2 sitesx2 doses) aripiprazole equivalents/animal, which is equivalent to 241, 723, 2893 mg aripiprazole lauroxil/animal, were administered to timed-pregnant rabbits on gestation day 3 or gestation days 3 and 10 (high dose only). There were no adverse drug-related maternal findings; however there was a slight transient decrease in maternal body weight at the high dose and accumulation of test article was observed at the injection site(s) of all test-article treated animals, without any adverse effects on muscle tissue. There were no drug-related effects on any uterine parameter and no adverse toxicity to fetuses. The NOAEL for both maternal and fetal toxicity was the highest dose in both the rat and rabbit embryo-fetal development studies. The lack of any aripiprazole-lauroxil-related adverse effects on embryo-fetal development is in contrast to findings with oral aripiprazole. However, this is not unexpected as the exposure levels to aripiprazole achieved after i.m. administration of aripiprazole lauroxil to rats and rabbits are less than those after oral or i.v. administration of aripiprazole to rats and rabbits. For this reason, animal data describing the adverse effects of aripiprazole on reproduction and fertility found in the label for Abilify® are incorporated into the label for aripiprazole lauroxil. It is emphasized that the API (aripiprazole) is the same and therefore, the findings should be the same; the difference being the formulation and delivery of the API. A fertility study was conducted with intramuscular administered aripiprazole lauroxil to male rats (3 doses on days 1, 21, and 42) and female rats (one dose 2 weeks prior to mating) at doses of 12, 33, 98 mg (49 mgx2 sites) aripiprazole equivalents/animal, which is equivalent to 17.6, 48.5, 144 mg aripiprazole lauroxil/animal. Aripiprazole-lauroxil-related toxicities were observed which were not previously reported with oral aripiprazole. These included changes in male fertility parameters and impairments in overall fertility at the high dose, and persistent diestrus at all doses for females along with slight increases in the number of corpora lutea, ovary weight and preimplantation loss in high dose females. The NOAEL for

general toxicity in both sexes was the high dose, while the NOAEL for reproductive and fertility parameters was the mid dose of 33 mg aripiprazole equivalents/animal. In all reproductive toxicity studies with aripiprazole lauroxil, a separate group of animals were treated with the vehicle used to formulate the aripiprazole lauroxil doses (vehicle 1), containing (b) (4)% SML.

Overall safety evaluation of novel excipient sorbitan monolaurate (SML) CAS# 1338-39-2:

Sorbitan monolaurate (SML) is a partial ester of lauric acid with sorbitol and its mono- and di-anhydrides, sorbitan and isosorbide, respectively, and is an excipient used in the aripiprazole lauroxil drug product at (b) (4)% w/v. SML has been used as an excipient in previously approved drug products, however it has not been used in any parentally administered drug products and is therefore considered novel for intramuscular administration.

A negative control group not containing SML was not included in any of the general toxicity studies in order to accurately assess the safety of SML used in the vehicle control groups and used to formulate all aripiprazole lauroxil drug groups. However, the sponsor did provide historical control data for all parameters including clinical pathology and histopathology for comparison. In addition, predose values were taken for most parameters including ECGs, clinical chemistry, hematology, and urinalysis in the 9-month dog study (not in the 6-month rat study) in order to compare effects before and after dosing with the vehicles containing SML. A few of the studies in the historical control data set were from either intramuscular or subcutaneous administration studies. In those studies, granulomas and inflammation at the injection sites was observed. All of the other histopathological findings observed in both vehicle control groups from the rat and dog repeat-dose toxicity studies were also observed, and at similar frequencies, in the historical control data sets. The systemic-related incidental findings observed in the vehicle 1 control group, which contained (b) (4)% SML, from the rat and dog repeat-dose toxicity studies were also observed, and at similar frequencies, in the vehicle 2 group, which contained (b) (4)% SML, indicating no SML dose-related effects. In addition, safety pharmacology assessments (neurofunctional, pulmonary and cardiovascular) were included for all groups (including vehicle groups) in the 4-month repeat-dose dog study and 9-month (cardiovascular assessments only) repeat-dose dog toxicity study in order to evaluate any adverse effects of SML. There were no adverse effects on any safety pharmacology assessments in dogs treated with the vehicle containing SML. Overall, there were no signs of systemic toxicity due to SML in the vehicle control groups. There was a low incidence of granulomas/granulomatous inflammation observed at the injection sites in vehicle 2 group animals, containing (b) (4)% SML, in the 6-month rat study. A similar low incidence was also observed in vehicle groups animals from both the 4-month rat and dogs studies, but not in the 9-month dog study. The incidence and severity was very low. As with the aripiprazole lauroxil-related granulomas/granulomatous inflammation, they were not considered adverse. Injection site tissue reactions were not observed in any vehicle 1 group animals which contained (b) (4)% SML in any of the repeat-dose toxicity studies, providing a clear NOEL value. SML was found to be non-genotoxic in a complete genetox battery.

In addition to the sponsor generated studies assessing the safely of SML, the sponsor submitted a “SML white paper” (study 700-02313) which included all historical control data, and published data on the toxicity of SML (including toxicity studies with SML in rats, monkeys, and hamsters via the oral route in the diet). There are no published studies on SML administered via the intramuscular route.

Based on the totality of information, the amount of SML in the aripiprazole lauroxil drug product (b) (4) % w/v) does not appear to pose a substantial risk to humans when administered intramuscularly at the maximum recommended human dose of 882 mg Aristada.

The following table from the sponsor’s submission shows the amount of SML used in all nonclinical toxicity studies compared to the amount in the clinical drug product at the MRHD and the human equivalent dose multiples. There was no systemic toxicity to SML in any of the nonclinical studies and safety margins are >1 in all studies and as high as 19-fold. There was a very small incidence of local toxicity (granulomas) in a couple of control animals that received vehicle 2 containing (b) (4) % SML

Table 14: Nonclinical to clinical dose multiples of sorbitan monolaurate from sponsor generated repeat-dose and reproductive toxicity studies and human clinical study

Study	SML in Veh. or Form Dosed (% w/w)[a]	Dose Vol. (mL)	SML per Dosing Day (mg)[b]	Body Weight (kg)	SML Dose (mg/kg)	Dose Multiple (mg/kg)	SML Dose (mg/kg HED[c])	Dose Multiple (mg/kg HED)	Dose Multiple (mg/site)
4-Month Rat	0.5	0.2	1	0.456[d]	2.19	10	0.350	1.6	0.077
	1	0.2	2	0.456[d]	4.39	20	0.702	3.2	0.15
4-Month Dog	0.5	4	20	12.4[d]	1.61	7.4	0.871	4.0	1.5
	1	4	40	12.4[d]	3.23	15	1.74	8.0	3.1
6-Month Rat	0.5	0.4	2	0.534[d]	3.75	17	0.599	2.8	0.077
	1	0.4	4	0.534[d]	7.49	35	1.20	5.5	0.15
9-Month Dog	0.5	8	40	10.4[d]	3.85	18	2.08	9.6	1.5
	1	8	80	10.4[d]	7.69	35	4.15	19	3.1
Rat EFD	0.5	0.6	3	0.266[e]	11.3	52	1.80	8.3	0.12
Prelim Rabbit EFD	0.5	4	20	3.45[f]	5.80	27	1.86	8.6	0.77
Def Rabbit EFD	0.5	6	30	3.65[f]	8.22	38	2.63	12	1.2
Rat Fert (Male)	0.5	0.6	3	0.434[f]	6.91	32	1.11	5.1	0.12
Rat Fert (Female)	0.5	0.6	3	0.263[e]	11.4	53	1.83	8.4	0.12
4-Month Human	0.37	3.4	13	60[g]	0.217	--	--	--	--

Note: male body weights for general toxicology studies were used to provide the most conservative sorbitan monolaurate doses when expressed on a mg/kg basis; additionally, calculations were performed with non-rounded values.

Abbreviations: SML = sorbitan monolaurate; veh = vehicle; form = formulation; HED = human equivalent dose; EFD = embryofetal development; prelim = preliminary; def = definitive; fert = fertility and early embryonic development to implantation.

[a] Information for vehicles administered in 4-month rat (AT-3317-10), 6-month rat (AT-3317-14), 4-month dog (AT-3317-09), 9-month dog (AT-3317-13), rat EFD (AT-3317-20), preliminary rabbit EFD (AT-3317-18), definitive rabbit EFD (AT-3317-21), and rat fertility and early embryonic development to implantation (AT-3317-19) studies and the highest dose of drug product administered in ALK9072-002, ALK9072-003, ALK9072-003EXT, and ALK9072-003EXT2. Densities of nonclinical vehicles and the clinical formulation are 1 and 1.048 g/mL, respectively.

[b] Doses administered at 2 sites for all nonclinical studies except for 4-month rat and dog studies, where SML was administered at 1 dose site.

[c] mg/kg doses in rat, dog, and rabbit were converted to human equivalent doses by multiplying mg/kg values by 0.16, 0.54, and 0.32, respectively.

[d] Mean weekly male body weight over the treatment period in Vehicle 2 Group (b) (4) SML).

[e] Mean body weight at time of dosing for the vehicle control group (b) (4) % SML).

[f] Mean body weight over the treatment period for the vehicle control group (b) (4) % SML).

[g] Assumed body weight for calculation purposes.

[Table excerpted from NDA 207533 submission; toxicology written summary section]

(b) (4)

Safety Margins

The sponsor's summary tables below show the major findings in the chronic repeat-dose toxicity studies in rats and dogs (6 and 9-months in duration, respectively) and reproductive toxicology studies, along with exposure levels for all analytes (aripiprazole lauroxil, dehydro-aripiprazole, aripiprazole and N-hydroxymethyl aripiprazole) and the respective exposure margins compared to the maximum recommended human dose of 882 mg Aristada. It should be noted that in the label, safety margins for aripiprazole lauroxil were calculated based on mg/m^2 due to the lack of measurable exposure to aripiprazole lauroxil in human plasma. Exposure to aripiprazole lauroxil was higher after a single dose in dogs compared to multiple dosing. The values presented in the sponsor's table below were measured in dogs after the 6^{th} dose (see single-dose dog PK study for exposure levels after a single dose).

Table 15: Sponsor's table of noteworthy findings and exposure data from 6-month rat repeat-dose toxicity study

Study Type and Duration (Alkermes Reference No.)	Dose (mg)[a]	Dose Route	Noteworthy Findings	C_{max} (ng/mL) for M/F[b]	$AUC_{(141-168)}$ (ng*day/mL) in M/F[c]	Nonclinical to Clinical AUC Multiple (×) for M/F[d]
6-Monthly Administrations in Rats with 1- and 2-Month Post-Dose Necropsies (AT-3317-14)	10	IM	Granuloma/ granulomatous inflammation at injection sites	AL: NC/NC dARP: 0.493/NC ARP: 5.08/8.01 NHA: 10.8/11.1	AL: NC/NC dARP: 3.45/NC ARP: 97.6/165 NHA: 180/265	AL: NC/NC dARP: <0.01/NC ARP: 0.02/0.03 NHA: 0.38/0.56
	20	IM	Granuloma/ granulomatous inflammation at injection sites	AL: NC/NC dARP: 0.460/1.00 ARP: 12.8/19.9 NHA: 15.1/27.1	AL: NC/NC dARP: 3.22/13.0 ARP: 221/413 NHA: 316/557	AL: NC/NC dARP: <0.01/<0.01 ARP: 0.04/0.07 NHA: 0.67/1.2
	70 (35/site)	IM	Decreased body weight and food consumption in males, and increased body weight in females compared to controls; granuloma/ granulomatous inflammation at injection sites; NOAEL	AL: 0.827/NC dARP: 2.64/4.85 ARP: 29.2/62.4 NHA: 45.9/92.6	AL: 5.79/NC dARP: 60.1/103 ARP: 659/1420 NHA: 1100/1960	AL: >1/NC dARP: 0.04/0.06 ARP: 0.12/0.26 NHA: 2.3/4.2

AL = aripiprazole lauroxil (RDC-3317); dARP = dehydro-aripiprazole (RDC-3954); ARP = aripiprazole (RDC-9864); NHA = *N*-hydroxymethyl aripiprazole (RDC-5792)

Abbreviations: IM = intramuscular; M = male; F = female; NOAEL = no-observed adverse effect level; NC = not calculated (due to minimal/non-quantifiable exposure to analyte);

[a] Doses are in mg aripiprazole equivalents; doses of AL are approximately 1.47× greater given the molecular weights of AL (660.70 g/mole) and aripiprazole (448.39 g/mole). See Table 3 for dose-related details.

[b] C_{max} = greatest concentration of analyte following the last (6^{th}) dose.

[c] Reported AUC parameters reflect systemic exposure for the 28-day period following the last (6^{th}) dose using a validated bioanalytical assay for all analytes. Nonclinical AUC parameters reflect systemic exposure of analytes in whole blood.

[d] Values were calculated by dividing the nonclinical $AUC_{141-168}$ exposure parameter (whole blood) for each analyte by the corresponding clinical exposure AUC parameter (plasma) for the 28-day period following the 4^{th} dose in Study ALK9072-002. Clinical $AUC_{0-\tau}$ values for AL, dARP, ARP, and NHA were NC, 1700, 5559, and 471.8 ng*day/mL, respectively. Given $AUC_{0-\tau}$ 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.

Table 16: Sponsor's table of noteworthy findings and exposure data from 9-month dog repeat-dose toxicity study

Study Type and Duration (Alkermes Reference No.)	Dose (mg)[a]	Dose Route	Noteworthy Findings	C_{max} (ng/mL) in M/F[b]	$AUC_{(225-252)}$ (ng*day/mL) in M/F[c]	Nonclinical to Clinical AUC Multiple (×) in M/F[d]
9-Monthly Administrations in Dogs with 1- and 4-Month Post-Dose Necropsies (AT-3317-13)	100	IM	Granuloma/ granulomatous inflammation at injection sites	AL: NC/NC dARP: 0.793/1.21 ARP: 3.01/3.00 NHA: 5.47/5.90	AL: NC/NC dARP: 13.2/24.1 ARP: 68.9/61.1 NHA: 125/122	AL: NC/NC dARP: 0.01/0.02 ARP: 0.01/0.01 NHA: 0.61/0.59
	450	IM	Transiently impaired limb function and swelling; decreased food consumption in females; granuloma/ granulomatous inflammation at injection sites	AL: NC/NC dARP: 7.61/7.76 ARP: 10.8/12.6 NHA: 17.8/20.0	AL: NC/NC dARP: 162/172 ARP: 247/284 NHA: 426/472	AL: NC/NC dARP: 0.15/0.16 ARP: 0.05/0.05 NHA: 2.1/2.3
	1400 (700/site)	IM	Transiently impaired limb function and swelling; decreased food consumption in females; granuloma/ granulomatous inflammation at injection sites; NOAEL	AL: 0.807/1.56 dARP: 18.9/63.1 ARP: 31.6/43.2 NHA: 53.3/60.7	AL: 6.21/10.3 dARP: 411/1090 ARP: 717/953 NHA: 1160/1400	AL: >1/>1 dARP: 0.38/1.0 ARP: 0.14/0.18 NHA: 5.7/6.8

AL = aripiprazole lauroxil (RDC-3317); dARP = dehydro-aripiprazole (RDC-3954); ARP = aripiprazole (RDC-9864); NHA = *N*-hydroxymethyl aripiprazole (RDC-5792)

Abbreviations: IM = intramuscular; M = male; F = female; NOAEL = no-observed adverse effect level; NC = not calculated (due to minimal/non-quantifiable exposure to analyte);

[a] Doses are in mg aripiprazole equivalents; doses of AL are approximately 1.47× greater given the molecular weights of AL (660.70 g/mole) and aripiprazole (448.39 g/mole). See Table 3 for dose-related details.

[b] C_{max} = greatest concentration of analyte following the last (9^{th}) dose.

[c] Reported AUC parameters reflect systemic exposure for the 28-day period following the last (9^{th}) dose using a validated bioanalytical assay for all analytes. Nonclinical AUC parameters reflect systemic exposure of analytes in whole blood.

[d] Values were calculated by dividing nonclinical $AUC_{225-252}$ exposure parameter (whole blood) for each analyte by the corresponding clinical exposure AUC parameter (plasma) for the 28-day period following the 4^{th} dose in Study ALK9072-002. Subsequently, values were normalized to the clinical matrix to account for differences in whole blood to plasma analyte exposures in dogs as determined in Study AT-3317-22; this was done by dividing values by whole blood to plasma $AUC_{0\text{-}tlast}$ ratios for AL, dARP, ARP, and NHA (ie, 0.554, 0.643, 0.945, and 0.435, respectively). Clinical AUC values for AL, dARP, ARP, and NHA were NC, 1700, 5559, and 471.8 ng*day/mL, respectively. Given $AUC_{0\text{-}\tau}$ 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 17: Sponsor's table of noteworthy findings and exposure data from rat fertility and early embryonic development study

Study Type and Duration (Alkermes Reference No.)	Dose (mg)[a]	Dose Route	Noteworthy Findings	C_{max} (ng/mL) in M/F[b]	AUC (ng*day/mL) in M/F[c]	Nonclinical to Clinical AUC Multiple (×) in M/F[d]
Rat Fertility and Early Embryonic Development to Implantation (AT-3317-19)	12	IM	No significant parental toxicity; tan, foreign material at injection site at necropsy Estrous cycle changes (persistent diestrus); ↑ ovary weights	AL: NC/NC dARP: NC/NC ARP: 4.86/5.98 NHA: 9.70/11.7	AL: NC/NC dARP: NC/NC ARP: 182/108 NHA: 357/210	AL: NC/NC dARP: NC/NC ARP: 0.03/0.02 NHA: 0.76/0.45
	33	IM	No significant parental toxicity; tan, foreign material at injection site at necropsy Estrous cycle changes (persistent diestrus); NOAEL for reproductive and fertility parameters	AL: NC/NC dARP: 0.980/NC ARP: 14.2/11.0 NHA: 21.5/20.3	AL: NC/NC dARP: 19.7/NC ARP: 446/207 NHA: 729/393	AL: NC/NC dARP: 0.01/NC ARP: 0.08/0.04 NHA: 1.6/0.83
	98 (49/site)	IM	No significant parental toxicity; tan, foreign material at injection site at necropsy; NOAEL for generalized toxicity Estrous cycle changes (persistent diestrus, ↓ in mean number of cycles); ↑ ovary weights, ↑corpora lutea, and ↑ in copulatory interval; ↓ mating and fertility indices in both genders and ↓ fecundity index in females; ↑ percentage of abnormal sperm	AL: NC/NC dARP: 6.25/3.08 ARP: 47.7/38.1 NHA: 72.3/69.9	AL: NC/NC dARP: 157/50.4 ARP: 1600/712 NHA: 2510/1210	AL: NC/NC dARP: 0.09/0.03 ARP: 0.29/0.13 NHA: 5.3/2.6

AL = aripiprazole lauroxil (RDC-3317); dARP = dehydro-aripiprazole (RDC-3954); ARP = aripiprazole (RDC-9864); NHA = *N*-hydroxymethyl aripiprazole (RDC-5792)

Abbreviations: IM = intramuscular; M = male; F = female; NOAEL = no-observed adverse effect level; NC = not calculated (due to minimal/non-quantifiable exposure to analyte);

[a] Doses are in mg aripiprazole equivalents; doses of AL are approximately 1.47× greater given the molecular weights of AL (660.70 g/mole) and aripiprazole (448.39 g/mole). See Table 3 for dose-related details.

[b] C_{max} = greatest concentration of analyte over the course of the study regardless of the number of doses.

[c] $AUC_{0\text{-}56}$ and $AUC_{0\text{-}29}$ values in ng*day/mL are reported for males and females, respectively. Nonclinical AUC parameters were determined using a validated bioanalytical assay and reflect systemic exposure of analytes in whole blood.

[d] Values were calculated by dividing the nonclinical AUC exposure parameter (whole blood) for each analyte by the corresponding clinical exposure AUC parameter (plasma) for the 28-day period following the 4th dose in Study ALK9072-002. Clinical $AUC_{0\text{-}\tau}$ values for AL, dARP, ARP, and NHA were NC, 1700, 5559, and 471.8 ng*day/mL, respectively.

Table 18: Sponsor's table of noteworthy findings and exposure data from rat embryo-fetal development study

Study Type and Duration (Alkermes Reference No.)	Dose (mg)[a]	Dose Route	Noteworthy Findings	C_{max} (ng/mL) in F	$AUC_{(GD3\text{-}GD20)}$ (ng*day/mL) in F[b]	Nonclinical to Clinical AUC Multiple (×) in F[c]
Rat Embryofetal Development (AT-3317-20)	12	IM	No significant maternal or developmental toxicity; tan, foreign material at injection site at necropsy	AL: NC dARP: NC ARP: 5.97 NHA: 12.1	AL: NC dARP: NC ARP: 64.5 NHA: 128	AL: NC dARP: NC ARP: 0.01 NHA: 0.27
	33	IM	No significant maternal or developmental toxicity; tan, foreign material at injection site at necropsy	AL: NC dARP: NC ARP: 8.86 NHA: 16.7	AL: NC dARP: NC ARP: 80.0 NHA: 141	AL: NC dARP: NC ARP: 0.01 NHA: 0.30
	98 (49/site)	IM	No significant maternal or developmental toxicity; tan, foreign material at injection site at necropsy; NOAEL for maternal and developmental toxicity	AL: NC dARP: 2.83 ARP: 31.0 NHA: 58.7	AL: NC dARP: 22.5 ARP: 298 NHA: 564	AL: NC dARP: 0.01 ARP: 0.05 NHA: 1.2

AL = aripiprazole lauroxil (RDC-3317); dARP = dehydro-aripiprazole (RDC-3954); ARP = aripiprazole (RDC-9864); NHA = *N*-hydroxymethyl aripiprazole (RDC-5792)

Abbreviations: IM = intramuscular; F = female; NOAEL = no-observed adverse effect level; NC = not calculated (due to minimal/non-quantifiable exposure to analyte); GD = gestation day;

[a] Doses are in mg aripiprazole equivalents; doses of AL are approximately 1.47× greater given the molecular weights of AL (660.70 g/mole) and aripiprazole (448.39 g/mole). See Table 3 for dose-related details.

[b] Nonclinical AUC parameters were determined using a validated bioanalytical assay and reflect systemic exposure of analytes in whole blood.

[c] Values were calculated by dividing the nonclinical $AUC_{(GD3\text{-}GD20)}$ exposure parameter (whole blood) for each analyte by the corresponding clinical exposure AUC parameter (plasma) for the 28-day period following the 4th dose in Study ALK9072-002. Clinical $AUC_{0\text{-}\tau}$ values for AL, dARP, ARP, and NHA were NC, 1700, 5559, and 471.8 ng*day/mL, respectively.

Table 19: Sponsor's table of noteworthy findings and exposure data from rabbit embryo-fetal development study

Study Type and Duration (Alkermes Reference No.)	Dose (mg)[a]	Dose Route	Noteworthy Findings	C_{max} (ng/mL) in F[b]	$AUC_{(GD3-GD29)}$ (ng*day/mL) in F[c]	Nonclinical to Clinical AUC Multiple (×) in F[d]
Definitive Rabbit Embryofetal Development (AT-3317-21)	164	IM	No significant maternal or developmental toxicity; tan, foreign material at injection site at necropsy	AL: NC dARP: 19.0 ARP: 76.2 NHA: 53.5	AL: NC dARP: 176 ARP: 636 NHA: 558	AL: NC dARP: 0.10 ARP: 0.11 NHA: 1.2
	492	IM	No significant maternal or developmental toxicity; tan, foreign material at injection site at necropsy	AL: 0.553 dARP: 76.0 ARP: 238 NHA: 180	AL: NC dARP: 625 ARP: 2100 NHA: 1920	AL: NC dARP: 0.37 ARP: 0.38 NHA: 4.1
	1968	IM	No significant maternal or developmental toxicity; tan, foreign material at injection site at necropsy; decreased fetal body weights; NOAEL for maternal and developmental toxicity	AL: 5.39 dARP: 229 ARP: 725 NHA: 528	AL: NC dARP: 1620 ARP: 5470 NHA: 5040	AL: NC dARP: 0.95 ARP: 0.98 NHA: 10.7

AL = aripiprazole lauroxil (RDC-3317); dARP = dehydro-aripiprazole (RDC-3954); ARP = aripiprazole (RDC-9864); NHA = *N*-hydroxymethyl aripiprazole (RDC-5792)

Abbreviations: IM = intramuscular; F = female; NOAEL = no-observed adverse effect level; NC = not calculated (due to minimal/non-quantifiable exposure to analyte); GD = gestation day;

[a] Doses are in mg aripiprazole equivalents; doses of AL are approximately 1.47× greater given the molecular weights of AL (660.70 g/mole) and aripiprazole (448.39 g/mole). See Table 3 for dose-related details.

[b] C_{max} = greatest concentration of analyte over the course of the study regardless of the number of doses.

[c] Nonclinical AUC parameters were determined using a validated bioanalytical assay and reflect systemic exposure of analytes in whole blood.

[d] Values were calculated by dividing the nonclinical $AUC_{(GD3-GD29)}$ exposure parameter (whole blood) for each analyte by the corresponding clinical exposure AUC parameter (plasma) for the 28-day period following the 4th dose in Study ALK9072-002. Clinical $AUC_{0-\tau}$ values for AL, dARP, ARP, and NHA were NC, 1700, 5559, and 471.8 ng*day/mL, respectively.

[Above tables excerpted from NDA 207533 submission; toxicology written summary section]

12 Appendix/Attachments

Below is the computational toxicology report from CDER's Chemical Informatics Group for (b) (4).

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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

/s/

AMY M AVILA
04/30/2015

AISAR H ATRAKCHI
04/30/2015