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CLINICAL REVIEW

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(Proposed) Trade Name Aristada
Therapeutic Class Antipsychotic
Applicant Alkermes Inc.

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Dosing Regimen Suspension/ IM up to 6 weeks
Indication(s) Schizophrenia
Intended Population(s) Schizophrenia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approve.

1.2 Risk Benefit Assessment

Aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole) is a prodrug of aripiprazole. When given as an intramuscular (IM) injection, aripiprazole lauroxil converts to the N-hydroxymethyl aripiprazole, and then is likely non-enzymatically cleaved through water-mediated hydrolysis to form aripiprazole.

The applicant submitted a 505(b)(2) NDA. In a single, adequate and well-controlled, Phase 3 clinical trial, the applicant supported a demonstration that, when dosed at high (882 mg) and low (442mg) levels, aripiprazole lauroxil is safe and effective in schizophrenic patients. The applicant also relied on the Agency's previous findings of safety and effectiveness for the listed drug Abilify (aripiprazole) tablets (NDA 21436) to support the safety and effectiveness of the aripiprazole lauroxil product. The applicant submitted information to demonstrate sufficient similarity between the aripiprazole lauroxil product and the listed drug to justify reliance on the listed drug. The applicant submitted data that support an injection schedule for aripiprazole lauroxil of up to once every 6 weeks. The ability to dose every 6 weeks and the introduction of aripiprazole lauroxil in strengths for which aripiprazole injection is not available are benefits for individualized treatment. The suspension must be shaken prior to injection. Aristada can be injected in the deltoid muscle (441mg) or gluteal muscle (441, 662, or 882 mg).

Aripiprazole, which has been approved by the Agency since November 2002 as Ability (aripiprazole) tablets (NDA 21436), is well-known in regards to its efficacy and risk profile. Aripiprazole lauroxil has a unique risk profile because of N-hydroxymethyl aripiprazole, which exists for a short period of time and achieves only low level of systemic exposures at steady state. There is no evidence from the clinical program that the general side effect profile for the proposed aripiprazole lauroxil product differs from Abilify (aripiprazole) tablets (NDA 21436), the relied-upon listed drug (LD). Additionally, there is no evidence of a local toxicity where higher local exposures to N-hydroxymethyl aripiprazole are expected.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance will be adequate to manage the risk-benefit profile.

1.4 Recommendations for Postmarket Requirements and Commitments

CDRH reviewer recommends:

Within NDA 207533 Supplement 0015, submitted on April 1, 2015, the sponsor committed to performing ongoing stability analysis to assess mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports

2 Introduction and Regulatory Background

2.1 Product Information

Aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole) (ARISTADA) consists of aripiprazole covalently bonded to a lauroyloxymethyl ester through a carbon-nitrogen bond. In vivo conversion of aripiprazole lauroxil to aripiprazole is governed by dissolution of the drug particles from the injection site followed by hydrolysis, generating lauric acid and *N*-hydroxymethyl aripiprazole. The covalently bonded *N*-hydroxymethyl aripiprazole is then converted to aripiprazole following water-mediated hydrolysis, releasing aripiprazole and formaldehyde. The exposure of aripiprazole following injection of aripiprazole lauroxil is qualitatively similar to that following oral administration of aripiprazole tablets. Aristada is proposed to be available in three dose strengths (441, 662, or 882 mg) and to be administered by a health care professional once monthly (441, 662, or 882 mg) or every 6 weeks (for the 882 mg dose only). Aristada can be injected in the deltoid muscle (441mg) or gluteal muscle (441, 662, or 882 mg).

Aripiprazole lauroxil comes in a pre-filled single use syringe.

2.2 Currently Available Treatments for Proposed Indications

Several long acting injectable formulations exist for atypical antipsychotics (Risperdal Consta, Invega Sustenna, Abilify Maintena, Zyprexa Relprevv). Additionally, older generation depot formulations are available and use typical antipsychotic agents (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, and trifluoperazine).

2.3 Availability of Proposed Active Ingredient in the United States

Aripiprazole lauroxil is not available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

There are several well-known safety risks associated with the use of atypical antipsychotics. These risks include increased morbidity and mortality in elderly patients with dementia-related psychosis due to CVAs and all causes, neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension, leukopenia, neutropenia, and agranulocytosis, seizures, and potential cognitive and motor impairment.

Injectable medications generally come with a risk of local site reactions and dose dumping that can lead to post-injection delirium/sedation syndrome (PDSS).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Studies with aripiprazole lauroxil for treatment of schizophrenia were conducted under an Investigational New Drug Application (IND #107,249) submitted to the Division of Psychiatry Products on July 16, 2010 in sequence 0002. The proposed application was discussed at the pre-NDA Meeting held on May 19, 2014.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No significant issues or concerns regarding data quality or the integrity of the trial were noted in the course of the review.

3.2 Compliance with Good Clinical Practices

The applicant, Alkermes, states that its studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. In addition, Alkermes certified that the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act were not used in connection with this application.

The Division requested an OSI Consult for routine inspections which found no actions indicated. See detailed review by Jenn Sellers, MD (OSI).

3.3 Financial Disclosures

Alkermes submitted a form OMS No. 0910-0396 to certify that they have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Alkermes certified that it required each listed clinical investigator to disclose whether he or she had a proprietary interest in the proposed product or significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no investigator disclosed such interests. Alkermes also certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). See Module 1.3.4.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

According to review dated 4/22/15 by Sherita McLamore-Hines, Ph.D and Wendy Wilson-Lee, Ph.D., Aristada can be approved from a CMC perspective, pending labeling, resolution of the outstanding deficiencies (bulk hold stability, post-approval stability protocol) and information requests (clarification of terms) along with completion of the facilities inspections and reviews by the biopharmaceutics and CMC-microbiology team.

The deficiencies were addressed after their 4/22/15 review was submitted. Microbiology has been found acceptable

Ryan McGowan of CDRH reviewed the device on 5/4/2015 and found the information acceptable with the comment below:

The consulting reviewer recommends approval of the NDA in the context of device constituent parts for the combination product. The reviewer recommends one post-approval commitment, as described below:

In NDA 207533 Supplement 0015 that was submitted on April 1, 2015, the applicant committed to performing ongoing stability analysis to assess mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches. The applicant should submit evidence of completion of these activities to NDA annual reports.

4.2 Clinical Microbiology

Review pending.

4.3 Preclinical Pharmacology/Toxicology

A detailed preclinical toxicology review was performed by Amy Avila, Ph.D. and filed on April, 30, 2015. Her findings are summarized below. The no-observed-adverse-effect-level (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/m² 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/m² basis. Since exposure levels to aripiprazole lauroxil were not measurable 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 Ames gene mutation assay and non-clastogenic in an in vitro chromosomal aberration assay using human peripheral blood lymphocytes. This finding is in contrast to the finding described in the labeling for aripiprazole where it was found to be clastogenic in an assay using Chinese Hamster lung cells. Dr. Avila offers several possible explanations of this discrepancy detailed in her review.

Reproductive Toxicity

Intramuscular administration of aripiprazole lauroxil to rats and rabbits during the period of organogenesis was not teratogenic. Dose exposure levels were below the oral dosing and the aripiprazole lauroxil label should reflect the oral dosing finding reflected in the listed drug labeling.

Excipients and conversion products

Dr. Avila states;

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). 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.

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

Based on the totality of information, the amount of formaldehyde and lauric acid released during the conversion of aripiprazole lauroxil to aripiprazole does not appear to pose a substantial risk to humans at the levels described.

4.4 Clinical Pharmacology

The clinical pharmacology review was conducted by a team consisting of Praveen Balimane, Xiaofeng Wang, Kevin Krudys, Jeff Kraft, Christian Grimstein, Ping Zhao, Hao Zhu. Their analysis confirms that Aristada supplies adequate systemic aripiprazole within the established therapeutic range.

4.4.1 Mechanism of Action

Aripiprazole lauroxil consists of aripiprazole covalently bonded to a lauroyloxymethyl ester through a carbon-nitrogen bond. [REDACTED] (b) (4)

[REDACTED] Following IM injection, the product dissolves slowly and is then converted to *N*-hydroxymethyl aripiprazole and then is likely non-enzymatically cleaved through water-mediated hydrolysis to the parent-drug metabolite aripiprazole and formaldehyde. Based on data submitted by the applicant, the systemic exposure of aripiprazole following aripiprazole lauroxil administration is qualitatively similar to that following oral administration.

4.4.2 Pharmacodynamics

See Section 4.4.1 Mechanism of Action.

4.4.3 Pharmacokinetics

The Office of Clinical Pharmacology's findings are summarized below:

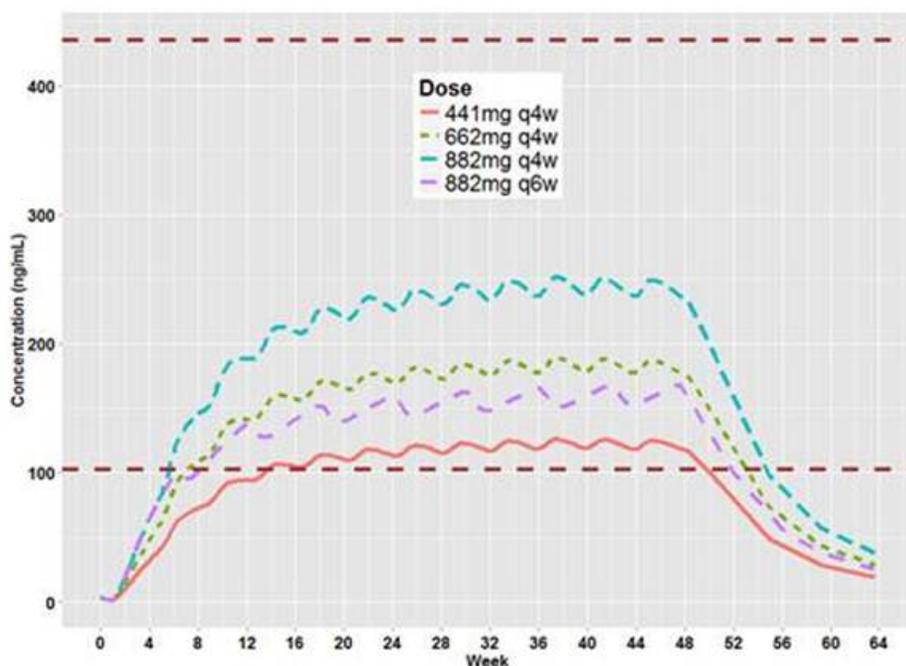
- An adequate link between aripiprazole lauroxil IM injection and the marketed aripiprazole oral tablet has been established.
- Aripiprazole lauroxil IM injection is efficacious in treating patients with schizophrenia.
- The dose levels and the dosing regimens proposed by the applicant are acceptable.
- The pharmacokinetic profile is sufficient to support a once monthly or once every 6 weeks dosing (for the 882 mg dose level). Due to significant low concentration of aripiprazole during the first 7-10 days post the first injection and the initial slow

rising phase of aripiprazole concentration, it is reasonable to include oral aripiprazole as a supplement for 21 days at the time of initiation of therapy with IM injection.

- Aripiprazole lauroxil can be administered through deltoid muscle for the 441 mg dose and via the gluteal muscle for all 3 dose levels (441 mg, 662 mg and 882 mg).
- Dose adjustments in CYP2D6 poor metabolizers and in patients receiving CYP2D6 and/or CYP3A4 modulators are recommended in Table 1.
- No evidence of dose dumping was observed in pharmacokinetic data collected in the clinical trials (single dose, multiple dose or pivotal efficacy study).

Labeling changes were proposed to Alkermes to reflect current presentations of this data. See page 3 of the Clinical Pharmacology Review submitted 8-22-2015.

Figure 1: Shows the simulated mean aripiprazole Concentration Time Profiles following 441 mg, 662 mg, and 882 mg Monthly and 882 mg every 6 weeks doses up to Steady State. The Lower Dash Line Represents the Mean Steady State Cmin following 10 mg Daily Oral Doses of Abilify Tablets and the Upper Dash Line Represents the Mean Steady State Cmax following 30 mg Daily Oral Doses of Abilify Tablets.



5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 Table of Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned/ Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase 1 studies							
PK/ Safety	ALK9072-001	Safety, tolerability, and PK	R/DB/PC	Oral aripiprazole, 10 mg, once daily for 5 days. Then, a single gluteal injection of AL	Total 40/32: AL 221 mg:10 AL 441 mg: 8 AL 588 mg: 8	Adult subjects with chronic stable schizophrenia	Single injection/ 1 month

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				(221, 441, or 588 mg); or Pbo (normal saline)	Pbo:6 Oral aripiprazole		
BA and BE	ALK9072-101	Safety, tolerability, and PK	R/OL	Cohort A: 2 sentinel subjects, single dose of AL 221 mg via deltoid muscle Cohort B: single dose of AL 441 mg via gluteal or deltoid muscle; 1:1 ratio	Total 46/46: AL 221 mg deltoid: 2 AL 441 mg deltoid: 22 AL 441 mg gluteal: 22	Adult subjects with chronic stable schizophrenia, or schizoaffective disorder	Single injection/ 1 month
PK/ Safety	ALK9072-002	Safety, tolerability, and PK	R/DB/PC	Oral aripiprazole 10 mg once daily for 5 days. Then 4 monthly gluteal injections of AL (441, 662, 882 mg); or, volumematched Pbo (INTRALIPID®)	Total 62/76: AL 441 mg:30 AL 662 mg:12 AL 882 mg:14 Pbo:20	Adult subjects with chronic stable schizophrenia	4 injections/ 4 months
PK/safety	ALK9072-102	Safety, tolerability and PK	R/DB/PC	4 monthly deltoid injections of AL 441 mg; or, volumematched Pbo (INTRALIPID®)	Total 29/53 AL: 20 PI: 9	Adult subjects with chronic stable schizophrenia	4 injections/ 8 months
Phase 3 studies							
Safety	ALK9072-003	Efficacy and safety	R/DB/PC	3 monthly gluteal injections of AL (441 or 882 mg); or, volume-matched Pbo (INTRALIPID®) Oral aripiprazole 15 mg (AL subjects) or matching oral Pbo (Pbo subjects) coadministered daily with AL for first 3 weeks after randomization	Total 540/623 randomized: AL 441 mg: 207 AL 882 mg: 208 Pbo: 208	Adult subjects with acute exacerbated schizophrenia	3 injections/ 3 months
Long-term Safety	ALK9072-003 EXT	Safety	OL and long term	Monthly gluteal injection of AL (441 or 882 mg) For subjects who participated in ALK9072-003, dose based on study	Total 500/478: De novo: 242 AL 441 mg: 110 (AL rollover 81; Pbo	Adult subjects with stable schizophrenia	13 monthly injections/ 1 year

				drug received in ALK9072-003. De novo subjects (ie, those who hadn't participated in ALK9072-003) received AL 882 mg. De novo subjects and subjects who received Pbo in ALK9072-003 were administered oral aripiprazole 15 mg for 21 days.	roll-over 29) AL 882 mg: 368 (de novo 242; AL rollover 100; Pbo roll-over 26)		
Long-term safety	ALK9072-003EXT2	Safety	OL long term safety (for subjects who completed treatment period in ALK 9072-003EXT)	Monthly gluteal injection of AL (441 or 882 mg); dose based on study drug received in ALK9072-003EXT	Total: Up to 300/13	Adult subjects with stable schizophrenia	13-32 monthly injections

5.2 Review Strategy

Efficacy data was reviewed in consultation with the biostatistics and clinical pharmacology groups. Additionally, the applicant submitted data comparing Aristada (aripiprazole lauroxil) and the listed drug, Abilify (aripiprazole) tablets, to establish that it is scientifically appropriate for Alkermes to rely on FDA's finding of safety and effectiveness for Abilify tablets for the approval of Aristada.

For safety, the ISS document was reviewed and case report forms submitted were examined. Aripiprazole lauroxil and its unique intermediate metabolites were considered for the possible cause for site reactions in review of the safety reports. Inspectors were alerted to proper recording of site reaction during their site inspections. The safety profile of aripiprazole in the listed drug for use in schizophrenia is well known and labeled for the listed drug and comparison of previously reported AEs was considered.

5.3 Discussion of Individual Studies/Clinical Trials

The safety of aripiprazole lauroxil over a dose range of 221 to 882 mg administered by IM injection was evaluated in the Phase 3 pivotal study ALK9072-003 and four Phase 1 studies (ALK9072-001, ALK9072-002, ALK9072-101, and ALK9072-102). Long-term safety was assessed using the data from 2 ongoing 52-week open-label extension studies (ALK9072-003EXT and ALK9072-003EXT2) using the cut-off date of 30 April 2014.

Because the applicant is relying, in part, on Agency previous finding of efficacy for Abilify tablets, the relied-upon listed drug, and the well-defined oral dosing range, the efficacy of Aristada was demonstrated in a single clinical study, in addition to well-designed PK studies.

6 Review of Efficacy

Efficacy Summary

Efficacy was established from one 12-week, phase 3 efficacy study **ALK9072-003**. In this study, two strengths of aripiprazole lauroxil (441 mg and 882 mg) were tested in 622 subjects with schizophrenia. Statistical significance and clinical meaningful improvement over the placebo was observed in both dosage groups.

This study is an adequate bridge to previous findings of efficacy for aripiprazole. Antipsychotic efficacy is due to constant blood level exposures at adequate levels. Oral tablet dosing for aripiprazole is up to 30 mg a day and trials for treating acute schizophrenia are usually 6-8 weeks duration. The dosing in this study is at the low dose (441 mg) and the high dose (882 mg) and for adequate duration to demonstrate that the efficacy is due to aripiprazole lauroxil's ability to sustain exposures in the therapeutic range after the oral aripiprazole tablet is discontinued. Due to the wide efficacy range and similar safety profile when compared to Abilify tablets, it was appropriate to test the high and lower doses to establish to upper and lower bounds of the efficacy range.

6.1 Indication

Treatment of Schizophrenia

6.1.1 Methods

Due to well established efficacy of the listed drug's aripiprazole, the metabolite of aripiprazole lauroxil, and sufficient bridging to the listed drug product, Abilify (aripiprazole tablets), the applicant was able to demonstrate efficacy in a single adequate, double-blind, placebo-controlled trial.

Design:

Patients who have never taken aripiprazole received oral aripiprazole 5 mg/day for two days before randomization; patients who have taken and tolerated aripiprazole previously were excluded from this requirement. Patients were randomized on day 1 in a 1:1:1 ratio to one of three IM treatment groups: placebo, aripiprazole lauroxil 441 mg, or aripiprazole lauroxil 882 mg (about 180/group). The injected volumes of the 441 and 882 doses are different (1.6 vs. 3.4 ml); therefore, patients randomized to placebo were further randomized in a 1:1 ratio to high or low volume placebo to maintain blinding. IM placebo will contain Intralipid®, a sterile fat emulsion containing soy oil, egg lecithin, and glycerol. The first IM dose was given on day 1 by gluteal injection with subsequent alternation between the right and left sides. In addition, patients received oral medication for the first three weeks after randomization: patients receiving aripiprazole lauroxil received oral aripiprazole tablets 15 mg/day and patients receiving IM placebo received matching placebo capsules. Blinding was maintained by over encapsulation of the aripiprazole tablets. Patients remained on the inpatient unit for at least 14 days after the first dose. The second IM dose was given on day 29 and the third and final IM dose was given on day 57 (28 -3/+7 days between these doses). The second and third doses were administered on an outpatient basis. Double-blind evaluations were continued for four weeks after the last IM dose, with the final treatment period assessment on day 85. Follow-up visits occurred on days 113 and 141.

Previous antipsychotic therapy, inducers or inhibitors of CYP3A4, inhibitors of 2D6, MAOI's, and mood stabilizers were prohibited during the trial. Unless specifically prohibited, patients taking a stable dose of an antidepressant for at least 30 days before screening was continued that therapy. Benzodiazepines, anticholinergics, and antihistamines were used to treat extrapyramidal symptoms.

Study population

Subjects enrolled in the study were 18-70 years of age who could understand protocol requirements and provided written informed consent. Subjects had a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria and were experiencing an acute exacerbation (hospitalized for <2 weeks if inpatient) or relapse with onset of less than 2 months prior to screening. Subjects were required to have (1) PANSS total score between 70 and 120 (inclusive), (2) a score of ≥ 4 (moderate or greater) for at least 2 of the 4 items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), or P6 (suspiciousness/persecution), and (3) a score of ≥ 4 on Clinical Global Impression – Severity (CGI-S) at screening and baseline.

Key exclusion criteria included DSM-IV-TR diagnosis other than schizophrenia, any clinically significant medical condition or neurological disorder, and any clinically significant abnormal laboratory test findings or electrocardiogram results at screening. Subjects with history of treatment resistance or inadequate clinical response to aripiprazole or suicide risk were excluded.

Endpoints:

The endpoint was a standard well validated measure of efficacy for psychosis in schizophrenia. The PANSS is a multi-item inventory of psychopathology. The PANSS is a 30-item rating scale specifically developed to assess both the positive and negative symptoms of patients with schizophrenia, as well as general. The PANSS total score is rated based on a structured clinical interview (SCI-PANSS) with the patient and supporting clinical information obtained from family, hospital staff, or other reliable informants.

This assessment provides scores in different subscales, including a positive syndrome, a negative syndrome, depression, a composite index, and general psychopathology. Each item is scored on a 7-point scale (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, and 7 = extreme).

6.1.2 Demographics

The study was well-balanced demographically.

A total of 623 subjects were randomized and 622 received at least one injection of IM study drug (aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo). A total of 360 subjects (58%) completed the 12-week treatment period.

Most study subjects were male (68%). The median age was 39 years old, with a range from 18-66 years. Overall, 47% of subjects were white, 40% were black, and 13% were Asian. Demographic and baseline characteristics were evenly distributed among the three treatment groups. The study was conducted in the US, Europe, and Asia.

6.1.3 Subject Disposition

A higher proportion of subjects completed treatment in the aripiprazole lauroxil treatment arms (63% and 65% of subjects in the 441 mg and 882 mg treatment groups, respectively), compared with placebo (46% of subjects). Detailed analysis is within the statistical review. The pattern does not appear to influence the analysis.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was specified as the change from baseline to Day 85 in PANSS total score. The primary efficacy analysis was carried out using an ANCOVA model with LOCF approach for the Full Analysis Set (FAS). The ANCOVA model included change from baseline to Day 85 in PANSS total score as the dependent variable, study region and treatment group as factors, and baseline PANSS total score as a covariate.

The PANSS, a multi-item inventory of psychopathology used to evaluate the effects of drug treatment in schizophrenia, was chosen as the primary efficacy parameter. The PANSS is a 30-item rating scale specifically developed to assess both the positive and negative symptoms of patients with schizophrenia, as well as general psychopathology. The PANSS total score is rated based on a structured clinical interview (SCI-PANSS) with the patient and supporting clinical information obtained from family, hospital staff, or other reliable informants.

The primary efficacy endpoint was change in PANSS total score from baseline to Day 85 using an ANCOVA model with LOCF imputation.

An unblinded interim analysis on the 271 subjects (50% of planned sample size) was conducted for sample size re-estimation only based on the conditional power. The results of the interim analysis were that the sample size was to remain as originally planned. The Cui, Hung, Wang (CHW) method together with Hommel procedure was used for controlling the Type 1 error rate due to the interim analysis and multiple comparisons. The Cui, Hung, Wang (CHW) method combined 2 independent statistical results with an equal weight ($\sqrt{0.5}$) from 2 stages. Stage 1 was based on the interim analysis population ($n=271$), and Stage 2 was based on the post-interim population ($n=325$). The subjects in the 2 stages did not overlap. Alkermes supplied table 1 shows the analysis results from ANCOVA model in each stage, in all subjects without applying the CHW method, and in all subjects with applying CHW method.

Using the CHW method, the LS mean difference (SE) compared to placebo was -10.9 (1.82) for the aripiprazole lauroxil 441 mg group, and -11.9 (1.81) for the aripiprazole lauroxil 882 mg group. For both aripiprazole lauroxil groups, the difference is statistically significant (test statistics against placebo and test statistics for the joint test were smaller than -1.96) and corresponds to $p < 0.001$.

Table 2 displays the change to baseline for PANSS total scores using the ANCOVA LOCF on the full analysis sets at multiple time points by visits.

Table 2: Change from baseline in PANSS Total Score, ANCOVA, LOCF (Full Analysis Set)

	Placebo (N=196)	Aripiprazole Lauroxil	
		441 mg (N=196)	882 mg (N=204)
Stage 1 (Interim Analysis subset)			
N	94	89	88
Baseline: Mean (SD)	94.1 (11.04)	93.0 (10.25)	91.1 (10.94)
Change from Baseline at Day 83: LS Mean (SE)	-9.7 (2.27)	-18.2 (2.26)	-19.7 (2.33)
LS Mean Difference against Placebo (SE)		-8.5 (2.50)	-10.0 (2.52)
Unadjusted p-value against placebo		<0.001	<0.001
Stage 2			
N	102	107	116
Baseline: Mean (SD)	93.7 (10.59)	92.3 (10.18)	92.0 (10.66)
Change from Baseline at Day 83: LS Mean (SE)	-10.6 (2.00)	-23.3 (1.97)	-23.7 (1.89)
LS Mean Difference against Placebo (SE)		-13.3 (2.63)	-13.7 (2.60)
Unadjusted p-value against placebo		<0.001	<0.001
All Subjects (without penalty)			
N	196	196	204
Baseline: Mean (SD)	93.9 (11.18)	92.6 (10.21)	92.0 (10.77)
Change from Baseline at Day 83: LS Mean (SE)	-9.8 (1.39)	-20.9 (1.39)	-21.8 (1.33)
LS Mean Difference against Placebo (SE)		-11.1 (1.84)	-12.0 (1.82)
Unadjusted p-value against placebo		<0.001	<0.001
Adjusted p-value against placebo		<0.001	<0.001
CHW Method: Combining Stage 1 & 2 (with penalty)			
Weighted LS Means Difference against Placebo (SE)	--	-10.9 (1.82)	-11.9 (1.81)
Test Statistics against Placebo	--	-3.931	-6.535
Test Statistics for Joint Test	-6.329		

Abbreviations: ANCOVA=analysis of covariance; CHW=Choi, Hung, and Wang; PANSS=Positive and Negative Syndrome Scale; LOCF=last observation carried forward; SD=standard deviation; SE=standard error.

Note: The independent statistical results from two stages are combined using the CHW method with a pre-specified equal weight (opt(0.1)). The superiority of a particular aripiprazole lauroxil group is claimed using a closed test strategy if the test statistics against placebo and the test statistics for joint test are smaller than or equal to -1.96 at the 0.05 significance level.

Source: A1R9072-003 CSR, Table 14.2.2.3.1

Table 3: Change from Baseline by visit in PANSS Total Score, ANCOVA, LOCF (full analysis set)

Visit Statistics	Placebo (N=196)	Aripiprazole Lauroxil	
		441 mg (N=196)	882 mg (N=204)
Baseline: Mean (SD)	93.9 (11.28)	92.6 (10.21)	92.0 (10.77)
Change from Baseline at Day 8: LS Mean (SE)	-5.2 (0.81)	-8.3 (0.81)	-8.9 (0.79)
P-values against placebo	-	0.004	<0.001
Change from Baseline at Day 15: LS Mean (SE)	-8.1 (1.07)	-13.0 (1.07)	-13.8 (1.04)
P-values against placebo	-	<0.001	<0.001
Change from Baseline at Day 22: LS Mean (SE)	-8.7 (1.19)	-16.5 (1.19)	-17.8 (1.16)
P-values against placebo	-	<0.001	<0.001
Change from Baseline at Day 29: LS Mean (SE)	-9.6 (1.26)	-17.8 (1.26)	-18.9 (1.23)
P-values against placebo	-	<0.001	<0.001
Change from Baseline at Day 57: LS Mean (SE)	-9.3 (1.32)	-19.7 (1.32)	-20.4 (1.29)
P-values against placebo	-	<0.001	<0.001
Change from Baseline at Day 85: LS Mean (SE)	-9.8 (1.39)	-20.9 (1.39)	-21.8 (1.35)
P-values against placebo	-	<0.001	<0.001

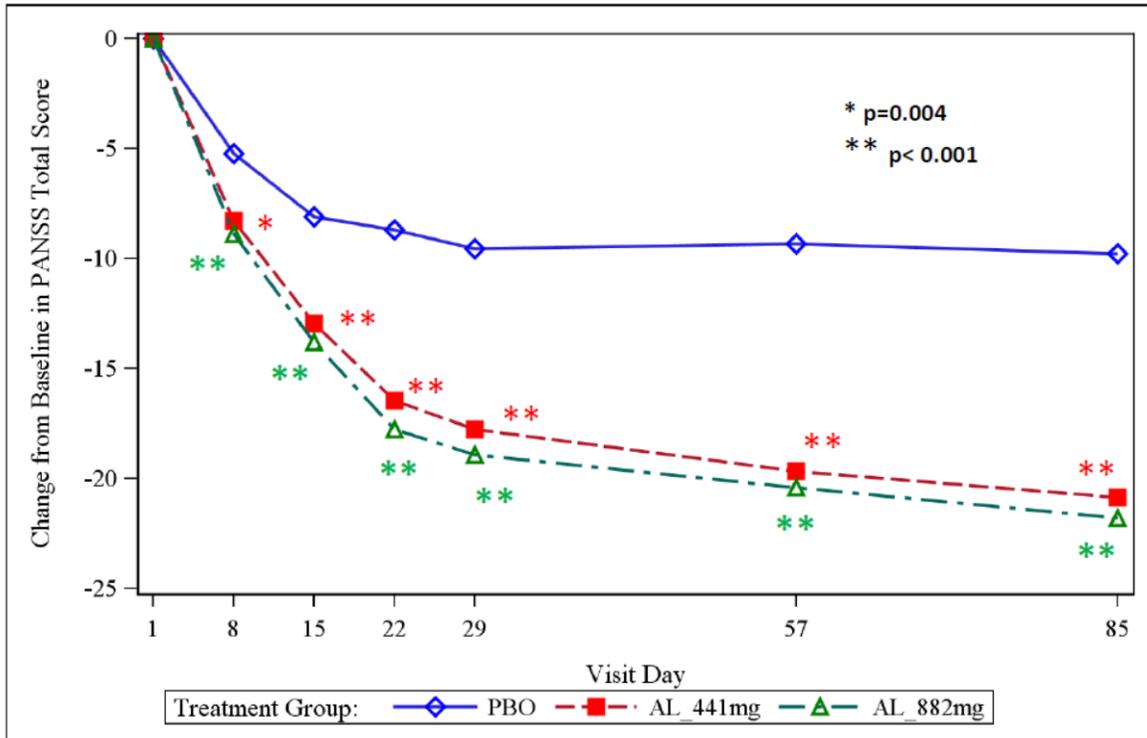
Abbreviations: ANCOVA=analysis of covariance; FAS=full analysis set; PANSS=Positive and Negative Syndrome Scale; LOCF=last observation carried forward; LS=least square; SD=standard deviation; SE=standard error.

Note: ANCOVA model using LOCF approach; dependent variable is change from baseline in PANSS total score with study region and treatment group as fixed effects and the baseline PANSS total score as a covariate.

Source: ALK9072-003 CSR, Table 14.2.2.3.1, Table 14.2.4.1.1

Figure 3 from the applicant's submission displays visually the continued symptom improvement after day 21 after the loss of the pharmacologic effect of the oral aripiprazole.

Figure 2 Change from Baseline in PANSS Total Score by Visit by ANCOVA LOCF Full Analysis Set)



Abbreviations: AL=aripiprazole lauroxil; ANCOVA=analysis of covariance; PBO=placebo; PANSS=Positive and Negative Syndrome Scale; LOCF=last observation carried forward
 Source: ALK9072-003 CSR, Table 14.2.2.3.1 and Table 14.2.4.1.1

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints support the primary findings. The CGI-I scale, used for the secondary efficacy assessment, is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) and measures the change from baseline in the overall severity of illness in the individual patient relative to his/her baseline.

Statistically significant improvement ($p < 0.05$) was seen for each aripiprazole lauroxil group compared to the placebo group at each post baseline visit.

6.1.6 Other Endpoints

The exploratory endpoints were looking at subscales and health outcome measures. The exploratory efficacy assessments included PANSS subscales (positive, negative, and general psychopathology), PANSS response, overall response, CGI-S, PSP,

subject retention, EuroQol Group health outcome measure (5 level) (EQ-5D-5L), and 36-item Short-Form health survey Version 2 (SF-36).

The PANSS positive subscale score is the sum of the 7 items (P1 to P7) of PANSS.

The PANSS negative subscale score is the sum of the 7 items (N1 to N7) of PANSS.

The PANSS general psychopathology subscale score is the sum of the 16 items (G1 to G16).

PANSS response is defined as $\geq 30\%$ decrease in PANSS total score.

Overall response is defined as $\geq 30\%$ decrease in PANSS total score or CGI-I score of 2 (much improved) or 1 (very much improved).

The CGI-S scale is a 7-point scale ranging from 1 (normal, not all ill) to 7 (among the most extremely ill patients) that measures the overall severity of the illness compared with the severity of illness in other patients the physician has observed.

The PSP scale is a 0-100 point that measures the personal and social performance.

All analyzes in secondary endpoints were supportive.

6.1.7 Subpopulations

Effect of demographic factors and study region in primary efficacy were evaluated. The change from baseline in PANSS total score at Day 85 was analyzed by age (<55 years, ≥ 55 years), gender (male, female), race (white, non-white), and study region (US, non-US). Subgroup analyses were carried out using an ANCOVA model with treatment group, subgroup of interest, and associated interaction term as factors and baseline PANSS score as a covariate.

No evidence of lack of efficacy was evident in the subpopulation analysis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is no significant difference in response rates for the different dosages at a population mean level. Despite this fact, it is well known that individual patients with schizophrenia respond to differing dosage levels and dosing in this population is individualized. There is a significantly large individual variance in the PK. Dosing equivalence was negotiated in labeling discussions with the applicant and described in detail the OCP reviews.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy of antipsychotics has been well established. There is no evidence of tolerance effects for aripiprazole lauroxil.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

There were no new safety findings for this 505(b)(2) application. The trials did not reveal any surprising injection site reactions due to aripiprazole lauroxil and *N*-hydroxymethyl aripiprazole.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The ISS included safety of aripiprazole lauroxil over a dose range of 221 to 882 mg administered by IM injection evaluated in the Phase 3 pivotal study ALK9072-003 and four Phase 1 studies (ALK9072-001, ALK9072-002, ALK9072-101, and ALK9072-102). Long-term safety was assessed using the data from 2 ongoing 52-week open-label extension studies (ALK9072-003EXT and ALK9072-003EXT2) using the cut-off date of 30 April 2014.

7.1.2 Categorization of Adverse Events

Coding of AEs was adequate. All AEs were coded using the MedDRA Dictionary; version 14.1 for Phase 3 studies and version 16.1 for the Phase 1 studies.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Comparative safety data was derived from the double blinded study but general safety was from combined studies described above.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At the EOP2 Meeting with the Food and Drug Administration (FDA) on September 15, 2011, it was agreed that the aripiprazole lauroxil safety database should include a minimum of 500 subjects exposed to at least 1 IM injection of aripiprazole lauroxil, 240 exposed to at least 3 IM injections, 140 exposed to at least 6 IM injections, and 50 subjects exposed to at least 12 IM injections of aripiprazole lauroxil.

Because of differences in study designs, dosages, and patient populations, the studies presented in the ISS document were organized into 2 groups as agreed in the pre NDA meeting as follows:

- Group 1 (subjects from the controlled study ALK9072-003; treatment groups are placebo, aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg)
- Group 2 (subjects from the long-term extension study, ALK9072-003EXT as of April 30, 2014 plus data for aripiprazole lauroxil rollover subjects from Study ALK9072-003). The treatment groups are aripiprazole lauroxil 441 mg (rollover subjects: placebo-441mg)

These requirements have been exceeded. As of the cutoff date of April 30, 2014, a total of 880 subjects had received at least 1 IM injection of aripiprazole lauroxil (Phase 1 and Phase 3 studies). Of these, 622 had received at least 3 IM injections, 276 had received at least 6 IM injections, and 66 had received at least 12 IM injections (applicant supplied Table 4).

Table 4: Summary of Overall Exposure to Aripiprazole Lauroxil Phase 1 and Phase 3

	Subjects Exposed ^a
Phase 1 Studies	
Single Dose Studies	72
Multiple Dose Studies	96
Total Phase 1	168
≥1 dose	168
≥3 dose	80
Phase 3 Studies	
Group 1 (ALK9072-003)	415
Group 2 (ALK9072-003EXT ^b)	478 (includes 181 aripiprazole lauroxil rollovers from Group 1)
Total Phase 3^c	
≥1 dose	712
≥3 doses	542
≥6 doses	276
≥12 doses	66
Overall Exposure to Aripiprazole Lauroxil (Phase 1-3)	
≥1 dose	880
≥3 doses	622
≥6 doses	276
≥12 doses	66

^a "Subjects Exposed" includes all subjects who received at least one dose of aripiprazole lauroxil

^b includes rollover subjects from ALK9072-003 plus extension study data as of 30 April 2014

^c Based on unique subjects from Group 1 and Group 2 (excluding 181 aripiprazole lauroxil rollovers)

Source: ISS Table 4

Because of differences in study designs, dosages, and patient populations, the studies presented in the ISS document were organized into 2 groups as agreed in the pre NDA meeting as follows:

- Group 1 (subjects from the controlled study ALK9072-003; treatment groups are placebo, aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg)
- Group 2 (subjects from the long-term extension study, ALK9072-003EXT as of 30 April 2014 plus data for aripiprazole lauroxil rollover subjects from Study ALK9072-003). The treatment groups are aripiprazole lauroxil 441 mg (rollover subjects: placebo-441mg and 441 mg-441mg) and aripiprazole lauroxil 882 mg (rollover subjects: placebo-882 mg and 882 mg-882 mg; de novo subjects: 882 mg).

Table 5: Summary of Aripiprazole Lauroxil Exposure Safety Population (Group 2)

Category	Aripiprazole Lauroxil 441 mg (N=110) n (%)	Aripiprazole Lauroxil 882 mg (N=368) n (%)	All Aripiprazole Lauroxil (N=478) n (%)
Duration of Exposure to IM Study Drug^a (days)			
Mean (SD)	250.8 (97.93)	184.4 (102.17)	199.6 (104.91)
Min – Max	29 – 464	29 – 475	29 – 475
Number of IM Injections, n (%)			
≥1 IM injection	110 (100.0)	368 (100.0)	478 (100.0)
≥2 IM injections	108 (98.2)	350 (95.1)	458 (95.8)
≥3 IM injections	107 (97.3)	340 (92.4)	447 (93.5)
≥4 IM injections	105 (95.5)	284 (77.2)	389 (87.0)
≥5 IM injections	97 (88.2)	225 (61.1)	322 (67.4)
≥6 IM injections	91 (82.7)	185 (50.3)	276 (57.7)
≥7 IM injections	85 (77.3)	160 (43.5)	245 (51.3)
≥8 IM injections	76 (69.1)	131 (35.6)	207 (43.3)
≥9 IM injections	52 (47.3)	97 (26.4)	149 (31.2)
≥10 IM injections	40 (36.4)	72 (19.6)	112 (23.4)
≥11 IM injections	31 (28.2)	56 (15.2)	87 (18.2)
≥12 IM injections	24 (21.8)	42 (11.4)	66 (13.8)
≥13 IM injections	17 (15.5)	26 (7.1)	43 (9.0)

^a Assumes 28 days of exposure per IM injection

Abbreviation: IM=intramuscular

Source: Tables 2.2.1.4 and 2.2.2.2

7.2.2 Explorations for Dose Response

In clinical trials, doses of aripiprazole lauroxil were expressed as aripiprazole equivalents of the listed drug. Doses of 221, 441, 588, 662, and 882 mg of aripiprazole lauroxil correspond to doses 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, of oral aripiprazole tablets, respectively.

Doses of 441mg and 882mg of aripiprazole lauroxil were tested in study -003 for efficacy. PK was examined in these studies and found to be within the therapeutic index.

All doses of aripiprazole lauroxil tested were found to be efficacious. There was little difference of dose response but the side effects also showed little dose response. Based on the data submitted, the upper dose of the listed drug's oral maximum dose

averaged PK is still above the projected top dose of the injectable in regards to mean PK.

7.2.3 Special Animal and/or In Vitro Testing

Routine animal testing was performed and preclinical results are described in the in detail in the toxicology review. The results were acceptable.

Local Tolerability or site reactions:

Of concern for the clinical program was the findings in the dog after repeat dosing. They included impaired limb function, swelling, and/or decreased activity. These findings were reported to be short lived typically resolving with 24 hours post dose without intervention. Microscopically, injection site findings in rats and dogs consisted of granuloma/granulomatous inflammation, which was anticipated following administration of a depot of foreign material (ie, foreign body reaction). Microscopic changes showed partial reversibility following a recovery period, and there was no evidence of aripiprazole lauroxil-related skeletal muscle injury; accordingly, injection site findings were not considered adverse.

7.2.4 Routine Clinical Testing

Routine clinical testing was included in the protocol as discussed in section 6.1.1. In general, it appears that clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No studies of drug metabolism or interactions were submitted with this NDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adequate evaluation of known side effects of drugs in this class was evaluated. These well-known risk factors are adequately described in the proposed label.

7.3 Major Safety Results

7.3.1 Deaths

Two of the SAEs were fatal; homicide by gunshot in 1 subject in the placebo group, and suicide following discontinuation from the study for worsening of schizophrenia in 1 subject in the aripiprazole lauroxil group.

7.3.2 Nonfatal Serious Adverse Events

SAEs were reported by 12 subjects in Group 1 (including one subject with an SAE during the follow-up period) and 10 subjects in Group 2. The rate of occurrence of SAEs was similar across treatment groups, and few were considered related to study drug or led to study discontinuation.

Convulsion was reported as an SAE in one subject who received aripiprazole lauroxil 882 mg; the event was considered probably not related to study drug by the investigator. The subject was subsequently discontinued from the study because of a TEAE of squamous cell carcinoma.

There were no reported cases of hypersensitivity/allergic reactions. There were no reported AEs of neuroleptic malignant syndrome (NMS), deep vein thrombosis or pulmonary embolism in either group. There was no reported AEs of Post injection Delirium/Sedation Syndrome (PDSS).

The incidence of suicidal ideation, suicidal and/or auto-aggressive behavior was low; suicidal ideation was reported as a TEAE in 1% of subjects in all 3 treatment groups in Group 1. One subject in Group 2 had an SAE of completed suicide. No additional TEAEs associated with suicidal ideation or suicidal behaviors were reported in Group 2. The events reported as TEAEs were also noted in the C-SSRS evaluation and no meaningful increases were noted with long-term exposure.

The SAEs reported did not reveal any new safety finding.

Table 6: Summary of Adverse Events in Phase 3 Studies, Safety Population (Group 1 and Group 2)

Category	Group 1			Group 2	
	Placebo (N=207) n (%)	Aripiprazole Lauroxil		Aripiprazole Lauroxil	
		441 mg (N=207) n (%)	882 mg (N=208) n (%)	441 mg (N=110) n (%)	882 mg (N=368) n (%)
Death	1 (0.5)	0	0	0	1 (0.3)
Any Serious Adverse Event (SAE)	4 (1.9)	3 (1.4)	4 (1.9)	0	10 (2.7)
SAE leading to Discontinuation	2 (1.0)	2 (1.0)	0	0	7 (1.9)
Any Related SAE	0	0	1 (0.5)	0	3 (0.8)
Any AE leading to Discontinuation	37 (17.9)	14 (6.8)	6 (2.9)	3 (2.7)	23 (6.3)
Any TEAE	129 (62.3)	122 (58.9)	119 (57.2)	46 (41.8) ^a	167 (45.4) ^a
Any Related TEAE	72 (34.8)	80 (38.6)	77 (37.0)	30 (27.3) ^a	105 (28.5) ^a
Any Severe TEAE	12 (5.8)	9 (4.3)	9 (4.3)	3 (2.7) ^a	12 (3.3) ^a

^a Excluding TEAEs reported in aripiprazole lauroxil subjects during the lead-in study, prior to the first IM injection in Study ALK9072-003EXT.

Note: In Group 1, one additional subject (119-016, aripiprazole lauroxil 882 mg group) reported an SAE (lung carcinoma, cell type unspecified, Stage IV) that led to discontinuation from study and one subject (717-001, placebo group) was discontinued due to schizophrenia during the follow-up period.

Source: [ISS Table 17](#)

7.3.3 Dropouts and/or Discontinuations

In Group 1, more subjects in the placebo group were discontinued due to adverse events [37 subjects (17.9%)] compared to the aripiprazole lauroxil 441 mg [14 (6.8%)] or aripiprazole lauroxil 882 mg group [6 (2.9%)]. Worsening of schizophrenia and/or psychotic disorder were the most common AEs contributing to discontinuation; no other AE led to discontinuation in more than 2 subjects in any treatment group.

In Group 2, adverse events led to discontinuation from the study for 26 subjects (5.4%). Many were de novo subjects (16 of the 26 subjects); worsening of schizophrenia was the most frequently reported AE leading to discontinuation. No other AE led to discontinuation in more than 2 subjects taking either dose of aripiprazole lauroxil.

7.3.4 Significant Adverse Events

Adverse events reflected well characterized events as reflected from the LD labeling.

7.3.5 Submission Specific Primary Safety Concerns

Injection site reactions:

Overall the injections were well tolerated. The 882mg group reported the most reactions. The reaction most cited was pain and decreased with successive injections. The mean duration was 3 days to 4.5 days in the placebo controlled study and 3.1 to 5.4 in the uncontrolled extension studies.

There were no TEAEs indicative of rhabdomyolysis. Reported events included elevations of creatine phosphokinase (CPK), pain and weakness without evidence of myopathy. There were no TEAEs of myoglobinuria or urinary occult blood. There were no observations of clinically significant muscle pathology.

Other SAEs:

Convulsion was reported as an SAE in one subject who received aripiprazole lauroxil 882 mg; the event was considered probably not related to study drug by the investigator. The subject was subsequently discontinued from the study because of a TEAE of squamous cell carcinoma.

There were no reported cases of hypersensitivity/allergic reactions. There were no reported AEs of neuroleptic malignant syndrome (NMS), deep vein thrombosis or pulmonary embolism in either group. There was no reported AEs of Post injection Delirium/Sedation Syndrome (PDSS).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A significant number of subjects in these studies had previous exposures to aripiprazole so the raters of side effects do not reflect a good pattern for treatment naive patients. The only treatment emergent adverse event in >5% of subjects and at least twice placebo was akathisia. This observation is consistent with previously observed adverse events in the LD labeling for aripiprazole (11.1%, 11.1%, and 3.9% of subjects in the aripiprazole lauroxil 441 mg group, 882 mg group, and placebo, respectively). Akathisia was reported more frequently in males than females and non-white than white subjects in each aripiprazole lauroxil group. The incidence was higher in obese and overweight subjects compared to subjects with normal BMI across all 3 treatment groups.

Other TEAEs with incidence $\geq 2\%$ occurring more frequently in both aripiprazole lauroxil groups than in the placebo group included injection site pain, weight increased, nausea, blood creatine phosphokinase (CPK) increased, sedation, and toothache.

Table 7: Treatment Emergent Adverse Events in > or equal 2% of Subjects in Any Treatment Group by System Organ Class and Preferred Term During Treatment Period, Safety Population (Group 1)

System Organ Class Preferred Term	Placebo (N=207) n (%)	Aripiprazole Lauroxil	
		441 mg (N=207) n (%)	882 mg (N=208) n (%)
Any treatment emergent adverse event	129 (62.3)	122 (58.9)	119 (57.2)
Gastrointestinal disorders			
Toothache	1 (0.5)	5 (2.4)	8 (3.8)
Nausea	4 (1.9)	6 (2.9)	7 (3.4)
Constipation	8 (3.9)	6 (2.9)	5 (2.4)
Diarrhoea	7 (3.4)	5 (2.4)	5 (2.4)
Dyspepsia	4 (1.9)	6 (2.9)	4 (1.9)
Dry mouth	5 (2.4)	2 (1.0)	0
General disorders and administration site conditions			
Injection site pain	4 (1.9)	7 (3.4)	10 (4.8)
Investigations			
Weight increased	1 (0.5)	6 (2.9)	5 (2.4)
Blood creatine phosphokinase increased	1 (0.5)	9 (4.3)	3 (1.4)
Weight decreased	5 (2.4)	1 (0.5)	2 (1.0)
Musculoskeletal and connective tissue disorders			
Neck pain	3 (1.4)	2 (1.0)	5 (2.4)
Nervous system disorders			
Akathisia	9 (4.3)	24 (11.6)	24 (11.5)
Headache	17 (8.2)	17 (8.2)	18 (8.7)
Sedation	3 (1.4)	4 (1.9)	5 (2.4)
Dizziness	6 (2.9)	2 (1.0)	2 (1.0)

Table 8: Treatment Emergent Adverse Events in > or equal to 2 % of Subjects in Any Treatment Group by System Organ Class and Preferred Term during treatment Period, Safety Population (group 1) Continued

System Organ Class Preferred Term	Placebo (N=207) n (%)	Aripiprazole Lauroxil	
		441 mg (N=207) n (%)	882 mg (N=208) n (%)
Psychiatric disorders			
Insomnia	24 (11.6)	20 (9.7)	25 (12.0)
Anxiety	14 (6.8)	6 (2.9)	11 (5.3)
Schizophrenia	22 (10.6)	12 (5.8)	5 (2.4)
Restlessness	4 (1.9)	6 (2.9)	4 (1.9)
Agitation	11 (5.3)	3 (1.4)	3 (1.4)
Psychotic disorder	9 (4.3)	2 (1.0)	2 (1.0)
Skin and subcutaneous tissue disorders			
Pruritus	5 (2.4)	1 (0.5)	2 (1.0)

Percentages are based on the number of Safety Population subjects in each treatment arm.

If a subject experiences more than one adverse event in a category, then the subject is counted only once in that category.

Source: [ALK9072-003 CSR Table 34](#)

7.4.2 Laboratory Findings

There were no clinically meaningful changes in renal, hepatic, electrolyte, or hematologic parameters. No subjects met criteria for Hy's Law.

There was no overall increase in prolactin concentrations. This fact may reflect the fact that most of these patients were not treatment naive.

Episodic elevations in CPK values did occur. In Group 1, 3 subjects (2 in the aripiprazole lauroxil 441 mg group, 1 in the placebo group) had CPK values >5000 U/L at any post baseline assessment. The CPK values trended toward normal at the last visit for the 2 aripiprazole treated subjects. For the placebo subject, the maximum CPK value was noted at the last visit and the subject was lost to follow up. CPK values >5000 U/L at any post baseline assessment were not observed for any subject in Group 2.

7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs observed in the study. Though, incidence of orthostatic hypotension, defined as an increase in heart rate ≥ 25

bpm within 3 minutes of standing and a reduction in systolic blood pressure ≥ 20 mm Hg, was low and similar across treatment groups in Group 1 and Group 2. No subjects in Group 1 and 1 subject (aripiprazole lauroxil 882 mg group) in Group 2 reported an AE of orthostatic hypotension.

7.4.4 Electrocardiograms (ECGs)

Changes from baseline in ECG parameters over time were generally small and not clinically meaningful; no consistent differences between treatment groups were noted in Group 1 or Group 2. The percentage of subjects with potentially clinically significant increases in QTcF intervals was small and similar across groups; no increase in rates was noted with longer term exposure.

7.4.5 Special Safety Studies/Clinical Trials

In the single dose and multiple dose aripiprazole lauroxil injection studies in either gluteal or deltoid muscle, injection site pain was more commonly reported in the deltoid in comparison to the gluteal site.

7.4.6 Immunogenicity

There were no observations of allergic reactions in the development program.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The dose dependent adverse events were expected for this class of medications. Sedation had a dose dependent increase. The placebo group had 1.4% and the 441 mg and 882 mg groups had 1.9 and 2.4%, respectively. Site injection pain also had a dose dependent increase from 3.4 to 4.3% which was most probably due to the volume difference. Mild dose dependent adverse effects were seen in headache 3.4 to 5.3%, weight gain 1.9 to 2.4%, nausea was 1.9 to 2.4% and anxiety 1.9 to 2.4%.

7.5.2 Time Dependency for Adverse Events

Akathisia median duration was 13 days for the placebo group, 15 days for 441 mg group, and 22 days for the 882 mg group.

7.5.3 Drug-Demographic Interactions

There was no drug-demographic interaction observed.

7.5.4 Drug-Disease Interactions

There is no drug-disease interaction observed.

7.5.5 Drug-Drug Interactions

Concomitant medication was consistent with the medications that would be taken by a typical patient population with schizophrenia. The most common concomitant medications were benzodiazepines, primarily lorazepam. DDI labeling information was detailed in the OCP reviews and is included in the labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no evidence of human carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

No data was obtained in these studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Aripiprazole lauroxil was not studied in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Aripiprazole lauroxil has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. Review of the TEAEs reported during the safety follow-up period for Study ALK9072-003 indicated no systemic withdrawal or rebound effects with aripiprazole lauroxil. There is no evidence of abuse potential for aripiprazole lauroxil.

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

There is no marketing experience with aripiprazole lauroxil. There is extensive postmarketing experience with aripiprazole, which has been approved by the Agency since November 2002 in the form of aripiprazole tablets and has been approved in generic form since April 2015.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

Labeling was negotiated and attached to the labeling review.

9.3 Advisory Committee Meeting

N/A

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

/s/

LUCAS P KEMPF
10/02/2015

MITCHELL V Mathis
10/02/2015