CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209830Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	Division of Psychiatry Products
Reviewer Name(s)	David H. Millis, MD
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Established/Proper Name	aripiprazole lauroxil
(Proposed) Trade Name	Aristada Initio
Applicant	Alkermes
Dosage Form(s)	intramuscular
Applicant Proposed Dosing Regimen(s)	675 mg single intramuscular injection
Applicant Proposed Indication(s)/Population(s)	initiation of treatment of schizophrenia with Aristada
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	initiation of treatment of schizophrenia with Aristada

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Aripiprazole lauroxil (proprietary name "Aristada") is an atypical antipsychotic developed by Alkermes, Inc. It has a combination of receptor activities, including partial agonist activity at D2 and 5HT1A receptors and antagonist activity at 5HT2A receptors. The molecule is a covalent modification of aripiprazole to form N-lauroyloxymethyl aripiprazole. The medication is administered by a healthcare professional by intramuscular (IM) injection.

Aripiprazole lauroxil (NDA 207533) received approval in the United States on October 5, 2015, for the treatment of schizophrenia. The dosing schedules approved at that time were 441 mg IM every four weeks, 662 mg IM every four weeks, and 882 mg IM every four or six weeks. Supplement 002, approved on June 5, 2017, added an additional dosing schedule of 1064 mg IM every eight weeks.

Because it takes several weeks for aripiprazole lauroxil to reach steady state blood levels, initiation of treatment currently requires starting the patient on oral aripiprazole at the same time as the first injection of aripiprazole lauroxil. The patient must continue taking oral aripiprazole daily for three weeks. At the end of the three-week period, the oral aripiprazole is discontinued, and treatment continues with aripiprazole injections given every four, six, or eight weeks. A limitation of this strategy is that it requires the patient's compliance with oral medication for the first 21 days of treatment. This can be problematic because patients considered for intramuscular medication tend to be those who have had difficulty with consistent compliance with oral medication.

With the current New Drug Application, the Applicant is seeking approval of a new formulation of aripiprazole lauroxil, in an effort to simplify the treatment-initiation regimen. The new formulation (proprietary name "Aristada Initio") is also given by intramuscular injection, but it has a smaller particle size than the original formulation. The smaller particle size accelerates the rate of dissolution, resulting in earlier appearance of circulating aripiprazole. The Applicant has proposed a treatment-initiation regimen which eliminates the need for 21 days of oral medication by giving a single intramuscular injection of Aristada Initio on the same day as the first intramuscular injection of Aristada.

Because Aristada Initio requires some time to reach a steady-state blood level, the requirement for oral medication at the beginning of treatment is not completely eliminated. However, the required oral medication is reduced to a single dose of oral aripiprazole at the beginning of treatment. Thus, the new proposed Aristada Initio treatment initiation regimen consists of three components:

1. Aristada Initio 675 mg, single injection, not repeated;
2. Aripiprazole 30 mg oral table, single dose, not repeated;
3. Aristada 441 mg, 662 mg, 882 mg, or 1064 mg, to be repeated every 4, 6, or 8 weeks.

Aristada Initio will be available in a single dose strength of 675 mg. The dose of Aristada Initio and the dose of oral aripiprazole given on the first day of treatment will be the same regardless of the dose of Aristada that is planned for the patient's ongoing maintenance treatment.

The Applicant has proposed a 505(b)(2) filing strategy for this NDA application. The reference drugs are oral aripiprazole (Otsuka Pharmaceuticals, NDA 021436, trade name "Abilify") and aripiprazole lauroxil (Alkermes, NDA 207533, trade name "Aristada"). The Applicant has submitted pharmacokinetic bridging data to demonstrate that aripiprazole exposures under the Aristada Initio initiation strategy are comparable to the exposures achieved under the current 21-day oral aripiprazole initiation strategy.

This application does not include additional efficacy studies. To support the new treatment initiation strategy, the Applicant has submitted data from three pharmacokinetic studies designed to identify a treatment initiation strategy that would provide adequate aripiprazole exposures while limiting the requirement for oral medication to a single dose.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend approval of this efficacy supplement, which requests approval of a new formulation of aripiprazole lauroxil for use in the initiation of treatment for schizophrenia. The submitted pharmacokinetic bridging analysis supports the assertion that a single intramuscular injection of Aristada Initio, combined with a single oral dose of aripiprazole 30 mg, provides aripiprazole exposures that are similar to the exposures provided by 21 consecutive days of oral aripiprazole. The safety issues identified for the new formulation are comparable to the safety issues that characterized the already approved formulation of aripiprazole lauroxil. No safety findings could be identified that would preclude approval of the new aripiprazole lauroxil formulation for the treatment of schizophrenia.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Schizophrenia is a serious psychiatric illness that typically continues throughout a patient's lifetime. The illness can have significant and disabling impact on the patient's social functioning. Treatment generally requires long-term treatment with antipsychotic medication. Ensuring consistent compliance with a schedule of daily oral antipsychotic medication is difficult for many patients. Intramuscular antipsychotic medication can help make compliance easier for the patient by eliminating the need for the patient to remember to take oral medication daily. Aristada is a long-acting intramuscular medication approved for the treatment of schizophrenia. However, it takes several weeks for the initial Aristada injection to reach steady-state blood levels. This requires that the patient take oral aripiprazole for 21 days after the first Aristada injection. There is a risk of inadequate treatment during these 21 days, since patients considered for long-acting intramuscular medication are often those who have had demonstrated difficulty in compliance with oral medication. The availability of an aripiprazole formulation that would eliminate the need for three weeks of oral medication would improve the likelihood that patients will maintain a consistent therapeutic level of medication during the first three weeks of treatment. The single required dose of oral aripiprazole can be given during the same office visit as the single intramuscular injection of Aristada Initio. The proposed new aripiprazole lauroxil formulation does not appear to be associated with any new risks that are not associated with the already-approved aripiprazole lauroxil formulation. Thus, the risk-benefit ratio is considered favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Schizophrenia is a chronic psychiatric condition • Treatment requires long-term use of antipsychotic medication • Poor treatment compliance can result in repeated hospitalizations	Schizophrenia is a chronic psychiatric condition characterized by psychotic symptoms, which may be persistent. Patients typically experience episodes of exacerbation of psychotic symptoms, which may cause sufficient impairment to require hospitalization. Voluntary compliance with a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		regular medication schedule is difficult for many patients. Periods of poor medication compliance can contribute to the relapse of psychotic symptoms.
Current Treatment Options	• Several medication options are currently available • Long-acting injectable medications are often considered for patients who have had problems with consistent adherence to daily oral medication • Tolerability of first-generation long-acting injectable antipsychotic medications may be limited by adverse events • Second-generation long-acting injectable antipsychotic medications have less severe neuromuscular adverse events • Second-generation long-acting injectable antipsychotic medications may require a period of several weeks of continued adherence to daily oral medication during the initiation of treatment	Several medication options are currently available, including both oral and long-acting injectable medications. Long-acting injectable medications are often considered for patients who have had problems with consistent adherence to daily oral medication. However, tolerability of first-generation long-acting injectable antipsychotic medications may be limited by adverse events. In particular, the neuromuscular adverse events often seen with first-generation antipsychotics can be very physically uncomfortable for patients, decreasing their willingness to continue the treatment regimen. Second-generation long-acting injectable antipsychotic medications have less severe neuromuscular adverse events. However, several of the second-generation long-acting formulations currently available take several weeks to reach a steady-state blood level. This requires a period of continued adherence to daily oral medication during the initiation of treatment. Patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		who do not take the oral medication consistently risk inadequate treatment and return of psychotic symptoms during the first few weeks of initiation of treatment with second-generation long-acting injectable antipsychotic medications.
Benefit	• eliminates the need for daily oral medication during the first three weeks of treatment with long-acting injectable medication, after a single dose of oral medication on the first day of treatment • provides systemic drug levels comparable to three weeks of oral medication	A treatment initiation regimen that requires regular compliance with oral medication brings a risk of inadequate treatment during the first three weeks of treatment with a long-acting injectable medication. Replacing the daily oral medication with an injection of a faster-acting medication formulation has the potential to improve compliance while maintaining adequate medication exposure.
Risk and Risk Management	• risk of common antipsychotic adverse effects remains • risk of patient discomfort due to the need for two injections at a single office visit • potential medication errors due to lack of clinician familiarity with the new initiation regimen	The Division has considered the potential for medication errors due to the lack of clinician familiarity with the new initiation regimen, and the similarity of the product names "Aristada" and "Aristada Initio." While the pharmacokinetic studies completed supported an Aristada Initio dose of (b) (4) the Division felt that there could be confusion with the (b) (4) mg dose of Aristada. We have worked with the Applicant to identify a different dose strength, 675 mg, which would be more easily

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		distinguishable from the (b) (4) dose of Aristada while providing e aripiprazole exposure during the treatment initiation period. The Division has recommended labeling text and packaging design elements to highlight the differences between Aristada and Aristada Initio.

1.4. Patient Experience Data

The three Phase 1 studies, B101, B102, and B103, were primarily designed to collect pharmacokinetic data. Patient experience data was limited to the safety assessment performed in each study, which included clinician-reported abnormal movement scales and clinician-reported assessments of suicidal ideation and suicidal behavior.

Table 1. Patient Experience Data Relevant to This Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	8.5.2, Abnormal Movement Scales; 8.5.3, Columbia-Suicide Severity Rating Scale
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a chronic and disabling psychiatric disorder characterized by disordered thinking, altered sensory perceptions, and deficits in social functioning. Psychosocial treatments such as individual supportive therapy, family therapy, occupational therapy, and structured daytime activities in a supervised setting are important components of a patient's treatment. However, the most disabling symptoms of schizophrenia typically do not resolve unless psychopharmacological treatment is initiated. Ongoing medication management over the patient's lifetime is required to prevent recurrence of symptoms. Current treatment guidelines recommend atypical antipsychotic agents as first-line treatment for schizophrenia.

2.2. Analysis of Current Treatment Options

Several oral atypical antipsychotics have been approved for the maintenance treatment of schizophrenia. These include risperidone, olanzapine, ziprasidone, aripiprazole, paliperidone, iloperidone, quetiapine, quetiapine extended-release, brexpiprazole, and asenapine. Atypical antipsychotics available as long-acting intramuscular preparations include risperidone microspheres, olanzapine pamoate, aripiprazole monohydrate, and paliperidone palmitate. The available preparations vary in the dose strengths available and in their duration of action. Currently, the intramuscular atypical antipsychotic with the longest dosing interval is paliperidone palmitate (proprietary name "Invega Trinza"), which is administered once every three months. This agent has been approved for the treatment of patients with schizophrenia who have been stabilized with once-monthly paliperidone palmitate (proprietary name "Invega Sustenna") for at least four months.

Important risks associated with the use of atypical antipsychotics include:

- Metabolic changes including hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain;
- Cerebrovascular events (e.g., stroke) and death in elderly patients with dementia-related psychosis;
- QT interval prolongation;
- Orthostatic hypotension and syncope;
- Neuroleptic malignant syndrome;
- Tardive dyskinesia;
- Leukopenia, neutropenia, and agranulocytosis.

Long-acting injectable antipsychotics carry the same risks as oral agents. Because an injectable agent cannot be withdrawn if the patient has intolerable adverse effects after administration, the typical clinical practice is to ensure tolerability and effectiveness of an oral agent before switching to an equivalent dose of the long-acting formulation of the same agent.

The long-acting injectable atypical intramuscular agents vary in the time required to achieve a therapeutic blood level. This may require continuing an oral antipsychotic for several weeks after the initial intramuscular injection. Aripiprazole lauroxil requires an overlap of three weeks with oral aripiprazole. Aripiprazole monohydrate requires a two-week overlap with oral aripiprazole. Risperidone microspheres require a three-week overlap with oral risperidone. Olanzapine pamoate does not require overlap with oral olanzapine. Paliperidone palmitate does not require overlap with oral paliperidone, but it does require two separate loading dose injections to be given during the first week. Paliperidone palmitate does not require overlap with an oral agent, but it does require that the patient has been receiving once-monthly paliperidone palmitate injections for at least four months.

One long-acting intramuscular atypical antipsychotic, olanzapine pamoate (proprietary name "Zyprexa Relprevv"), has a risk of a cluster of symptoms termed post-injection delirium/sedation syndrome (PDSS) characterized by sedation, confusion, dysarthria, somnolence, dizziness, ataxia, extrapyramidal symptoms, agitation, anxiety, and disorientation. Seizures and coma have occurred. The patient must be monitored by a health care professional for three hours after injection.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

To date, Aristada Initio is not approved for marketing in the United States. The Agency has not placed any specific limitations on the current or future development of Aristada Initio on the basis of safety information.

3.2. Summary of Presubmission/Submission Regulatory Activity

Aristada (aripiprazole lauroxil) was approved for the treatment of schizophrenia on October 5, 2015, in the dose strengths of 441 mg IM every four weeks, 662 mg IM every four weeks, and 882 mg IM every four or six weeks (NDA 207533). The dose strength of 1064 mg IM every two months was approved on June 5, 2017 (DNA 207533 S-002).

On September 9, 2015, a Type B End of Phase 2 meeting was held under IND 121179 to discuss

an NDA filing for Aristada Initio. Filing requirements discussed included the following:

1. a new NDA application, rather than a supplement;
2. the addition of a study arm to Study ALK9072-B102 for pharmacokinetic bridging to Aristada;
3. assessment of deltoid versus gluteal administration;
4. blood drawing in pharmacokinetic studies at the time of any SAEs to explore possible dose dumping.

A Pre-NDA meeting for Aristada Initio was held on May 4, 2017. The Agency agreed to submission of data specific only to Aristada Initio, with cross-referencing of safety and efficacy data from NDA 207533 for Aristada. The Agency agreed to cross-referencing the literature search for the IND 121179 Development Safety Update Report (DSUR) in place of a new literature search for the Aristada Initio NDA. The issue of possible filing as a supplement to the Aristada NDA was again discussed. The Agency did not agree to filing as a supplement to the NDA 207533, due to different release characteristics, the possibility of a different safety profile, and the possible need for a separate package insert to avoid practitioner confusion and medication errors. The Agency requested a separate use-related risk analysis, and not just a cross-reference to the human factors summary report completed for the Aristada NDA.]

3.3. Foreign Regulatory Actions and Marketing History

To date, Aristada Initio is not approved for marketing in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division did not request clinical site investigations in the course of the review of this NDA application.

4.2. Product Quality

A review of the NDA application was submitted by the Office of Pharmaceutical Quality on May 23, 2018. Key issues discussed in the OPQ review:

- While postmarketing reports of needle clogs have occurred with Aristada, OPQ feels that the smaller particle size for Aristada Initio reduces the risk of needle clogs for this product.

- Pre-approval inspection at the drug product manufacturing site was performed by OPQ team members from April 29, 2018 to May 4, 2018. The team found the manufacturing site to be in compliance with all relevant drug manufacturing regulations.
- The proposed product strength in the initial NDA submission was (b) (4) This raised concerns about possible medication errors due to the similarity with the proprietary name "Aristada," the use of the non-proprietary name "aripiprazole lauroxil" for both products, (b) (4) In the course of the review, OPQ discussed with the Applicant the possibility of changing the labeled strength. In response, the Applicant revised the dosage strength of Aristada Initio (b) (4) to 675 mg. OPQ feels that the change is scientifically justified, as the 675 mg strength is more in line with that used in the clinical studies. Additionally, the potential for patient harm would be reduced (b) (4). OPQ will consider additional measures during labeling negotiations, such as addition of a qualifier such as "submicron," "submicronized," or "nano-sized" to the non-proprietary name to further distinguish this product from Aristada.

OPQ has recommended the NDA application for approval.

4.3. Clinical Microbiology

No new clinical microbiology data was submitted with this application.

4.4. Nonclinical Pharmacology/Toxicology

A Nonclinical Pharmacology/Toxicology review of the NDA application was submitted on May 17, 2018. Key issues discussed in the Pharmacology/Toxicology review:

1. Nonclinical studies confirmed increased absorption in rats and dogs for ALKS 9072N compared to Aristada, including earlier T_{max} values and higher C_{max} values for circulating aripiprazole in rats and dogs after intramuscular administration of similar doses of ALKS 9072N and Aristada.
2. Dose-related local toxicity at the injection sites was observed at all dose levels in rats and dogs. Findings in both rats and dogs included swelling at the injection site, macroscopic findings of discoloration and swollen/thickened injection sites, and microscopic findings of granulomas and subacute/chronic inflammation. Findings in dogs included impaired limb function and microscopic mineralization. Increased severity of local injection site toxicity in repeat-dose toxicity studies may have been due to trauma associated with more frequent IM injections to the same muscle group. In addition, the ALKS 9072N dose used

in the animal studies ranged from 0.6 times to 14 times the maximum recommended human dose (MRHD) of 675 mg.

3. Hypersensitivity reactions (reddened skin, excessive scratching, facial swelling, and injected sclera) were observed in a few high-dose ALKS 9072N-treated dogs and in all control-treated dogs. Hypersensitivity reactions were observed at a higher frequency in control dogs administered the vehicle compared to high-dose ALKS 9072N-treated dogs. Therefore, the reactions were attributed to excipients in the vehicle, most likely polysorbate-20. The amount of polysorbate-20 in ALKS 9072N is higher than that of any FDA-approved drug product for intramuscular administration. However, the Applicant provided nonclinical data and information from published literature to adequately qualify the levels of polysorbate-20 in Aristada Initio. The reviewer recommends monitoring and possible labeling language for potential allergic reactions to polysorbate-20 in humans.

The Pharmacology/Toxicology review concludes that the nonclinical data submitted with the NDA application supports approval of the application.

4.5. Clinical Pharmacology

A review by the Office of Clinical Pharmacology (OCP) has been completed. The findings from this review are as follows:

- At the population level, the proposed dosing regimen of initiating Aristada with 675 mg of ALKS 9072N and a single 30 mg of oral aripiprazole is anticipated to produce a clinical response similar to that obtained from the currently approved initiation regimen of 21 days of oral aripiprazole.
- The proposed initiation regimen of ALKS 9072N 675 mg combined with a single 30 mg dose of oral aripiprazole results in aripiprazole exposures that are comparable to those achieved with the currently approved initiation regimen of 21 days of oral aripiprazole.
- Both the mean C_{max} and the $AUC_{0\text{-}28d}$ were comparable between the proposed initiation regimen using ALKS 9072N and the currently approved oral initiation regimen.
- The proposed dosage initiation with Aristada Initio is adequate for treatment initiation with all approved dose levels of Aristada.
- Aristada Initio is not recommended for use in patients who are known CYP2D6 poor metabolizers or who are taking CYP modulators (inhibitors of CYP3A4 or CYP2D6, or inducers of CYP3A4).
- Aristada Initio can be interchangeably dosed to either gluteal or deltoid muscle.
- No evidence of dose dumping was observed in pharmacokinetic data collected from

around 100 individual subjects across three different clinical trials.

OCP has concluded that there is sufficient clinical pharmacology information provided in the NDA application to support a recommendation for approval of Aristada Initio.

4.6. Devices and Companion Diagnostic Issues

A review by the Center for Devices and Radiological Health (CDRH) was submitted on March 7, 2018. CDRH reviewed the product labeling, the design of the pre-filled syringes in which the drug product will be distributed, and the design of the safety needles that will be included in the drug administration kit. Needles of different lengths will be included to provide a choice of needle based on the amount of subcutaneous tissue overlaying the injection site muscle. CDRH found the proposed labeling to be acceptable, and recommended approval of the device constituent parts of the drug administration kit.

4.7. Consumer Study Reviews

No consumer study reviews were conducted in the course of this application.

5. Sources of Clinical Data and Review Strategy

5.1. Clinical Studies

This NDA application is supported by three pharmacokinetic studies designed to establish the optimal dose for Aristada Initio and to demonstrate that the drug exposures provided by the optimal dose are comparable to the exposures provided by the administration of 21 days of oral aripiprazole. These three studies also provide data on the safety and tolerability of Aristada Initio.

5.2. Review Strategy

No new efficacy data is presented in this review. Efficacy for the (b) (4) intramuscular dose of Aristada Initio combined with a single oral dose of aripiprazole 30 mg is established through pharmacokinetic bridging to 21 days of oral aripiprazole 15 mg.

This review will focus on the safety of the 662 mg dose of Aristada Initio used in the pharmacokinetic studies. The rationale for proposing a dose of 675 mg for commercial use, (b) (4) will be discussed.

The safety review is limited by the reliance on pharmacokinetic studies, in that the three studies were all open-label studies with no blinding or control group. A high-level comparison between the observed safety profile of Aristada Initio and the known safety profile of the previously-approved doses will be conducted. Safety data will be discussed in Chapter 8, Review of Safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study ALK9072-B101 (short name: B101)

6.1.1. Study Design

Overview and Objective

Study Title: "A Phase 1, Placebo-controlled, Single Ascending-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072N in Adults with Schizophrenia"

Primary objective: To determine the safety, tolerability, and pharmacokinetics of three formulations of ALKS 9072N over a range of dose levels in adults with schizophrenia.

B101 was a single ascending-dose study designed to evaluate three formulations of Aristada Initio (A, B, and C) differing in particle size distributions. Five doses were tested for each formulation: 110 mg, 221 mg, 441 mg, 662 mg, and 882 mg.

Trial Design

This was a Phase 1, placebo-controlled, single ascending-dose study to evaluate three ALKS 9072N formulations (A, B, and C) at ascending doses.

A sentinel cohort of two subjects received ALKS 9072N Formulation B 110 mg. After a review of available safety and PK data at two weeks, additional subjects were randomized in a 3:1 ratio to receive a single injection of either Aristada Initio or placebo (phosphate-buffered saline). In addition to the sentinel cohort, the design included a total of 15 cohorts across four ALKS 9072N dose groups, with up to three sub-cohorts (for the three formulations) per ALKS 9072N dose group. Each subject could participate in only one cohort. PK data were reviewed prior to escalation to ensure that aripiprazole concentrations did not exceed the upper limit of the maximum concentration (C_{max}) associated with a 30 mg oral dose. Table 2 provides escalation details and reflects the planned doses and formulations to be evaluated.

Table 2. Dose Escalation Details for Study B101

Cohorts	ALKS 9072N Dose	Subjects per Cohort
S1B	110 mg	2
1A, 1B, 1C	221 mg	4
2A, 2B, 2C	441 mg	8
3A, 3B, 3C	441 mg	8
4A, 4B, 4C	662 mg	16
5A, 5B, 5C	882 mg	16

Source: ALK9072-B101 Clinical Study Report, page 3.

Trial Location: The study was conducted in 13 study centers in the United States.

Diagnostic Criteria: Eligible subjects were required to have a diagnosis of chronic schizophrenia or schizoaffective disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).

Key Inclusion Criteria:

- Between 18 and 65 years of age, inclusive, at screening.
- Documented history of tolerated use of aripiprazole, or demonstrated tolerability to test doses of oral aripiprazole during screening.
- Diagnosis of either chronic schizophrenia or schizoaffective disorder.
- Clinically stable as evidenced by meeting both of the following criteria:
    - Had no hospitalizations for acute psychiatric exacerbations within the three months prior to screening or upon admission;
    - Had a CGI-S score of ≤ 3 (mild) at screening and upon admission.
- Had been on a stable antipsychotic medication regimen for at least two months prior to screening and had no antipsychotic medication regimen change (medication or dose level, unless the dose level change was due to tolerability) between screening and admission.
- Agreed to remain on current antipsychotic regiment for the duration of the study unless a change was medically indicated.
- Body mass index between 18.0 and 40.0 kg/m2, inclusive, at screening and upon admission.
- Agreed to use an acceptable method of contraception for the duration of the study unless surgically sterile or postmenopausal.

Key Exclusion Criteria:

- Pregnant, planning to become pregnant, or currently breastfeeding at screening or upon admission.
- Met any of the following exclusionary medication criteria:
    - Had received aripiprazole within 28 days before randomization.
    - Had taken any other extended-release injectable antipsychotic within three months prior to admission.
    - Had received any antipsychotic medication via IM injection within the two months prior to admission
- Participation in a clinical trial involving any investigational product within the past six months.
- History of psychopathology other than schizophrenia or schizoaffective disorder.
- Elevated risk of harm to self or to others, based on either the investigator's opinion or the patient's responses on the C-SSRS.
- History or current evidence of a clinically significant condition, laboratory test result, or ECG finding that could preclude safe participation in the study or that could confound protocol assessments.
- History of neuroleptic malignant syndrome or clinically significant tardive dyskinesia.
- QTcF > 450 msec for men or > 470 msec for women at screening or upon admission.
- Had used potent cytochrome CYP3A4 inducers or inhibitors or CYP2D6 inhibitors within the 30 days prior to admission
- Was a CYP2D6 poor metabolizer based on pharmacogenetic testing at screening.
- Positive urine drug test for drugs of abuse at screening or upon admission.

Dose Selection: Planned ALKS 9072N doses for the study cohorts ranged from 110 mg to 882 mg, with the dose of each subsequent cohort determined based on review of available safety and PK data from the preceding completed cohort.

Study Treatments: The following cohorts and dose levels were planned for the study:

- ALKS 9072N Formulation A: 221, 441, 662, and 882 mg (the 662-mg and 882-mg doses were not used
- ALKS 9072N Formulation B: 110, 221, 441, 662, and 882 mg
- ALKS 9072N Formulation C: 221, 441, 662, and 882 mg (the 882-mg dose was not used)

All formulations were administered as an intramuscular injection into the gluteal muscle. Each subject assigned to ALKS 9072N received a single injection. Placebo was phosphate-buffered saline with a volume equivalent to the 662 mg dose level of ALKS 9072N. Placebo was administered using the same method as described for ALKS 9072N.

Study Endpoints: Pharmacokinetic Measures

The following pharmacokinetic parameters were assessed:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the concentration-time curve (AUC) from time zero to the last quantifiable time interval (AUC_{last})
- AUC from time zero to infinity ($AUC\infty$)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution during the terminal phase (Vz/F)
- AUC calculated using the trapezoidal method normalized to the dose (AUC/D)
- C_{max} normalized to the dose (C_{max}/D)

Statistical Analysis Plan

The enrolled population included all subjects who signed inform consent and were enrolled to a treatment cohort including the sentinel cohort, regardless of whether they received study drug or not. The safety population included all subjects who received study drug. The PK population included all subjects who received study drug and had at least one measurable concentration.

Protocol Amendments

The original protocol was finalized on October 20, 2014. There was one amendment.

Amendment 1, finalized on January 23, 2015, made the following changes to the protocol:

1. Clarified the plan to consider available safety and PK data in the decision to initiate the next cohort.
2. One exclusion criterion, regarding the history or current evidence of a clinically significant condition or lab test result that could have precluded safe participation in the study, was clarified.
3. Addressed the intent to collect plasma samples in the event of an SAE.

Changes in Planned Analyses:

1. One of the protocol-specified PK parameters, AUC calculated using the trapezoidal method from time 0 to 28 days, was not derived. After finalization of the Statistical

Analysis Plan, the study team decided that this analysis was not necessary to support the overall objectives of the study. It was not included in the final analyses and summary tables.

2. An analysis for potentially clinically significant (PCS) weight values (≥ 7% increase or decrease from baseline) was added post hoc to align this study with others in this clinical program.

6.1.2. Study Results

Compliance with Good Clinical Practices

The cover page of the ALK9072-B101 Clinical Study Report states: "This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation Harmonised Tripartite Guideline."

Financial Disclosure

No disclosable financial interests or arrangements reported for Study B101.

Patient Disposition

The study enrolled 114 subjects. Two sentinel subjects received open-label ALKS 9072N. One sentinel subject completed the study, and one was discontinued. The last assessment for the discontinued subject was done 82 days after dosing. A total of 112 subjects were randomized to either placebo (29 subjects) or ALKS 9072N (83 subjects). Of the randomized subjects, 22 receiving placebo and 70 receiving ALKS 9072N completed the study. Disposition of patients in Study B101 assigned to ALKS 9072N Formulation B or to placebo is presented in Table 3.

Table 3. Disposition of Subjects in Study B101 Assigned to ALKS 9072N or Placebo

Analysis Group	Treatment Group					
	Placebo n (%)	ALKS 9072N 221 mg n (%)	ALKS 9072N 441 mg n (%)	ALKS 9072N 662 mg n (%)	ALKS 9072N 882 mg n (%)	Total n (%)
Enrolled Population	14	4	13	12	12	41
Safety Population	14 (100)	4 (100)	13 (100)	12 (100)	12 (100)	41 (100)
PK Population	0	4 (100)	13 (100)	12 (100)	12 (100)	41 (100)
Completed Study	11 (78.6)	3 (75.0)	11 (84.6)	10 (83.3)	8 (66.7)	32 (78.0
Discontinued Study	3 (21.4)	1 (25.0)	2 (15.4)	2 (16.7)	4 (33.3)	9 (22.2)
Adverse Event	1 (7.1)	0	0	0	0	0
Withdrawal by Subject	1 (7.1)	0	2 (15.4)	1 (8.3)	2 (16.7)	5 (12.2)

Lost to Follow-up	1 (7.1)	0	0	1 (8.3)	1 (8.3)	2 (4.9)
Physician Decision	0	1 (25.0)	0	0	0	1 (2.4)
Protocol Deviation	0	0	0	0	1 (8.3)	1 (2.4)

Source: NDA 209830 Summary of Clinical Safety, Table 4, page 22.

Protocol Violations/Deviations

All subjects met all the inclusion criteria, and none of the exclusion criteria. The most common deviation was exceeding the screening window of < 30 days. In these cases, safety labs, vitals, and ECG readings were performed as an unscheduled visit. Other common deviations were missed or incomplete clinic visits or routine safety assessments.

- *Reviewer Comment:* Overall, it does not appear that the deviations that did occur would have a significant impact on the analysis of the study data.

Demographic Characteristics

The majority of subjects were male. The most common race was Black or African American. Mean ages (by dose) ranged from 42.3 to 49.3 years (minimum-maximum: 20 to 63 years). Mean body mass index (by dose) ranged from 26.85 to 30.71 kg/m^2 (minimum-maximum: 18.4 - 39.7 kg/m^2). Detailed demographics of the Safety Population are presented in Chapter 8, Table 11.

Pharmacokinetic Results

The Sponsor presents the following pharmacokinetic results from the study:

- Exposure to aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole increased with increasing dose of IM ALKS 9072N over the 221 to 882 mg dose range tested for these three formulations. There were no meaningful differences among the three formulations for these analytes.
- Formulation B was selected for continued development on the basis of drug product stability, and process and manufacturing capabilities at the time of the study.
- Aripiprazole lauroxil was generally not measurable following IM administration of ALKS 9072N at doses up to 882 mg.
- Plasma aripiprazole concentrations following ALKS 9072N administration increased steadily (median t_{max} 16-31 days), then gradually declined through Day 115. There was no evidence of early release of aripiprazole following IM administration of ALKS 9072N.
- The mean $t_{½}$ of aripiprazole following ALKS 9072N administration was independent of dose and ranged from 14 to 15 days for Formulation A, 16 to 20 days for Formulation B, and 11 to 16 days for Formulation C.

- Aripiprazole exposure (C_{max}, AUC) was dose-proportional for Formulation B across the dose range of 441 mg to 882 mg.
- Dehydro-aripiprazole concentrations increased slowly following IM administration of ALKS 9072N (median t_{max} Day 21 to 35 days), and then declined through Day 115.
- The metabolite-to-parent ratios (dehydro-aripiprazole/ aripiprazole) were 35% to 49% over the 221- to 882-mg dose range for the three formulations combined.
- Total N-hydroxymethyl aripiprazole exposure (AUC_{last}) was, on average, approximately 5% to 10% of that for aripiprazole exposure across all dose levels and formulations.
- Overall variability in aripiprazole, N-hydroxymethyl aripiprazole, and dehydro-aripiprazole PK following IM ALKS 9072N administration was consistent, and generally not greater, as compared to previously reported variability for Aristada.

The conclusions from Study B101 are as follows:

- For all single doses, the average aripiprazole concentrations increased gradually through Day 20, then declined through Day 115.
- There was no evidence of early release of aripiprazole (dose dumping).
- The three formulations showed no meaningful difference in the aripiprazole concentration-time curve.

Formulation B was selected on the basis of drug product stability and manufacturing capabilities.

6.2. Study ALK9072-B102 (short name: B102)

6.2.1. Study Design

Overview and Objective

Study Title: "A Phase 1 Study of an ALKS 9072N Initiation Regimen in Adults with Schizophrenia"

Primary Objective: To compare the pharmacokinetics of the ALKS 9072N initiation regimen and the current oral initiation regimen.

Secondary Objective: To compare the safety and tolerability of the ALKS 9072N initiation regimen and the current oral initiation regimen.

Study B102 was designed to identify a treatment regimen that would provide therapeutic concentrations of aripiprazole within four days, which would be similar to the therapeutic concentrations provided by the existing oral initiation treatment regimen. PK simulation using results from Study B101 predicted that the combination of ALKS 9072N 662 mg and a single dose of oral aripiprazole 30 mg would result in therapeutic aripiprazole concentrations within four days when coadministered with Aristada.

Trial Design

This was a Phase 1, double-blind, placebo-controlled study to assess the PK, safety, and tolerability of two initiation regimens administered concurrently with either a 441 or 882 mg intramuscular (IM) dose of aripiprazole lauroxil (AL):

- *ALKS 9072N initiation regimen,* consisting of a single 662 mg IM dose of ALKS 9072N coadministered with a single 30 mg oral dose of aripiprazole;
- *Oral initiation regimen,* consisting of 21 days of 15 mg oral aripiprazole.

Prospective subjects were evaluated during a 30-day Screening Period prior to enrollment in the study. For subjects who had never taken aripiprazole, 5 mg test doses of oral aripiprazole were administered on Day -30 and Day -29. Only subjects who exhibited tolerability to oral aripiprazole (either following test doses or from past reported experience) were eligible to enroll in the study. For eligible subjects who received oral aripiprazole during Screening, 28 days elapsed between the last dose of oral aripiprazole and the IM injection of study drug on Day 1. Subjects remained on their regular oral antipsychotic regimens, excluding oral aripiprazole, for the duration of the study.

All subjects were admitted to an inpatient study facility the day prior to scheduled dosing (Day -1). Upon admission, subjects were re-evaluated for eligibility and safety assessments were conducted. Subjects were randomly assigned in a 1:1:1:1 fashion to one of four treatment groups: Group 1 and Group 2 receiving the ALKS 9072N initiation regimen, and Group 3 and Group 4 receiving the oral initiation regimen. Group 1 and Group 3 received 441 mg AL on Day 1, while Group 2 and Group 4 received 882 mg AL on Day 1.

Subjects were discharged from the inpatient study facility following assessments on Day 15, unless the Investigator decided that additional assessments were medically indicated. Following discharge, subjects returned to the study site for outpatient follow-up assessments until Day 141.

Trial Location: The trial was conducted at 13 study centers in the United States.

Diagnostic Criteria: Eligible subjects were required to have a diagnosis of chronic schizophrenia or schizoaffective disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Key Inclusion Criteria:

- Between 18 and 65 years of age, inclusive, at screening.
- Documented history of tolerated use of aripiprazole, or demonstrated tolerability to test doses of oral aripiprazole during screening.
- Diagnosis of either chronic schizophrenia or schizoaffective disorder.
- Clinically stable as evidenced by meeting both of the following criteria:
    - Had no hospitalizations for acute psychiatric exacerbations within the three months prior to screening or upon admission;
    - Had a CGI-S score of ≤ 3 (mild) at screening and upon admission.
- Had been on a stable antipsychotic medication regimen for at least two months prior to screening and had no antipsychotic medication regimen change (medication or dose level, unless the dose level change was due to tolerability) between screening and admission.
- Agreed to remain on current antipsychotic regiment for the duration of the study unless a change was medically indicated.
- Body mass index between 18.0 and 40.0 kg/m2, inclusive, at screening and upon admission.
- Agreed to use an acceptable method of contraception for the duration of the study unless surgically sterile or postmenopausal.

Key Exclusion Criteria:

- Pregnant, planning to become pregnant, or currently breastfeeding at screening or upon admission.
- Met any of the following exclusionary medication criteria:
    - Had received aripiprazole within 28 days before randomization.
    - Had received AL or IM depot aripiprazole within six months prior to admission.
    - Had taken any other extended release injectable antipsychotic within three months prior to admission.
    - Was currently being treated with clozapine.
- Participation in a clinical trial involving any investigational product within the past three months.
- History of psychopathology other than schizophrenia or schizoaffective disorder.
- Elevated risk of harm to self or to others, based on either the investigator's opinion or the patient's responses on the C-SSRS.
- History or current evidence of a clinically significant condition, laboratory test result, or ECG finding that could preclude safe participation in the study or that could confound protocol assessments.

- History of neuroleptic malignant syndrome or clinically significant tardive dyskinesia.
- QTcF > 450 msec for men or > 470 msec for women at screening or upon admission.
- Had used potent cytochrome CYP3A4 inducers or inhibitors or CYP2D6 inhibitors within the 30 days prior to admission
- Was a CYP2D6 poor metabolizer based on pharmacogenetic testing at screening.
- Positive urine drug test for drugs of abuse at screening or upon admission.

Study Treatments: The study compared four treatment initiation regimens, two using ALKS 9072N and two using oral initiation. The treatment initiation regimens are described in Table 4.

Table 4. Treatment Initiation Regimens Compared in Study B102

Group	Type of Initiation	AL Dose (IM), Day 1	ALKS 9072N Dose (IM), Day 1	Oral Aripiprazole Dose, Day 1	Oral Aripiprazole Dose, Days 2-21
1	ALKS 9072N	441 mg	662 mg	30 mg	oral placebo daily
2	ALKS 9072N	882 mg	662 mg	30 mg	oral placebo daily
3	Oral	441 mg	IM placebo	15 mg	15 mg daily
4	Oral	882 mg	IM placebo	15 mg	15 mg daily

Source: ALK9072-B102 Clinical Study Report, Table 3, page 16.

For all study groups, the order of treatment administration on Day 1 was fixed as follows:

1. Oral aripiprazole;
2. IM injection of ALKS 9072N or placebo, no more than 15 minutes after oral aripiprazole;
3. IM injection of AL, no more than 30 minutes after IM injection of ALKS 9072N or placebo.

Aripiprazole lauroxil, ALKS 9072N, and ALKS 9072N placebo were all provided to study sites in prefilled syringes. AL was administered as an IM injection into the deltoid (441 mg) or gluteal (882 mg) muscle. ALKS 9072N and ALKS 9072N placebo were each administered as an IM injection into the gluteal muscle. When AL and ALKS 9072N/placebo were to be injected into the same muscle type, doses were injected into collateral muscles.

Assignment to Treatment: Subjects were randomly assigned to one of four treatment groups.

Blinding: Blinding was accomplished by administering 20 days of oral placebo (to simulate a total of 21 days of oral medication) to subjects in Group 1 and Group 2, and a placebo injection (to simulate an injection of ALKS 9072) in Group 3 and Group 4.

Schedule for Pharmacokinetic Sampling: Blood samples were collected within 1 hour predose and 1, 2, 3, 4, 5, 6, and 8 hours (±15 minutes) postdose on Day 1. On Days 2 to 15, a single sample was collected prior to oral aripiprazole (or oral placebo) administration and after the ECG assessment. On Days 16 to 21, a single sample was collected prior to oral aripiprazole (or oral placebo) administration. Following collection of the predose sample on Day 21, additional samples were collected at 1, 2, 3, 4, 5, 6, and 8 hours (±15 minutes) postdose. For Days 23 to 85, a single sample was collected within ±2 hours of the Day 1 oral dosing time or as close to that timeframe as possible. A single PK sample was collected on Day 113 and Day 141.

Study Endpoints: Pharmacokinetic Measures

Concentrations of AL, N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole (the primary metabolite of aripiprazole) were quantified in plasma samples for the computation of the following PK parameters:

- Maximum observed concentration (C_{max})
- Time to the Cmax (t_{max})
- Area under the concentration-vs-time curve from time zero to the time of the last quantifiable concentration, using the linear trapezoidal rule (AUC_{last})
- Area under the concentration-vs-time curve from time zero to 28 days postdose, using the linear trapezoidal rule (AUC_{0-28})
- Time of last measurable concentration (T_{last})

Statistical Analysis Plan

Concentration data were summarized according to nominal (protocol-specified) sampling times. Pharmacokinetic parameters were calculated for four analytes: AL, N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole, using noncompartmental analysis. Actual elapsed time from dosing was used to estimate individual plasma PK parameters. Given the limited number of quantifiable samples for AL, no PK parameters were computed for this analyte. On days where intensive PK samples were collected following oral aripiprazole administration (Day 1 and Day 21), only the trough plasma concentrations were used in the PK parameter calculations.

Pharmacokinetic parameters for N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole in plasma were listed separately and summarized by treatment group. Descriptive

statistics of PK parameters consisted of number of subjects (n), arithmetic mean, geometric mean, SD, standard error, percent coefficient of variation, median, minimum, and maximum. A by-subject listing of individual PK parameters for each treatment group was provided.

Protocol Amendments

The original protocol was finalized on July 14, 2015. There were two amendments.

Amendment 1, finalized on August 21, 2015, made the following changes to the protocol:

1. Inclusion/exclusion criteria were revised to prohibit use of clozapine.
2. The schedule of assessments was revised to include ECGs on Days 3 to 7 and Days 9 to 14 for increased safety monitoring.

Amendment 2, finalized on September 25, 2015, made the following changes to the protocol:

1. Study objectives were revised to increase clarity.
2. Treatment Groups 3 and 4 were added, in which 40 subjects each were to receive 15 mg oral aripiprazole (in contrast to 30 mg oral aripiprazole in Treatment Groups 1 and 2). Accordingly, the number of subjects planned to be enrolled in Groups 1 and 2 was decreased from 44 to 40 each. Thus, the overall number of subjects planned to be enrolled in the study was increased from 88 to 160.
3. Study methodology and procedures were clarified to align with the revised study objectives.

Changes in planned analyses: During the conduct of the PK analysis, a total of 18/161 subjects were identified as having quantifiable predose aripiprazole concentrations on Day 1. Of these, six subjects had predose concentrations > 10 ng/mL, i.e. > 10-fold higher than the lower limit of quantitation. To evaluate whether these levels might impact the outcome of the study, additional PK analyses were conducted following removal of these subjects.

Data Quality and Integrity

The study database was initially locked on August 18, 2016. Thereafter, discrepancies for injection location (deltoid vs gluteal) or study drug injected (AL vs ALKS 9072N) were identified in the injection site reaction dataset for six subjects. Accordingly, the database was unlocked on November 28, 2016. The discrepancies were corrected, and the database was relocked on November 30, 2016.

Subsequent to the database relock, three subjects were identified in the exposure dataset as having incorrect injection site locations. The data for these three subjects were corrected

programmatically in the dataset. Protocol violations pertaining to injection site location for these three subjects were recorded.

The data were considered final on December 16, 2016.

6.2.2. Study Results

Compliance with Good Clinical Practices

Page 13 of the ALK9072-B102 Clinical Study Report includes this statement: "The study was conducted in accordance with the principles of Good Clinical Practice (GCP) as outlined in or derived from the Declaration of Helsinki and its amendments and in accordance with local regulations and the International Conference on Harmonisation (ICH) guidelines."

Financial Disclosure

(b) (6) was a sub-investigator on Study B102, at Clinical Study Site (b) (6) consulted and spoke on behalf of Alkermes in regards to the approved product Aristada, concomitantly with his duties as a sub-investigator on Study B102. In addition, (b) (6) consulted for Alkermes regarding a Phase III program for the ALKS 3831 (oral samidorphan + olanzapine) program. The Financial Disclosure Statement submitted by the Sponsor indicates that the total income received by (b) (6) was likely greater than $25,000.

(b) (6) became an employee of Alkermes on June 1, 2016, after relinquishing his responsibilities at Site (b) (6) Study B102 ran from October 27, 2015 to July 26, 2016. The Sponsor states that potential bias resulting from (b) (6) participation in the studies was mitigated through study designs including randomization and blinding.

The disclosed financial information does not affect the approvability of the application.

Patient Disposition

A total of 161 subjects were enrolled, including 39 in Group 1 (ALKS 9072N initiation regimen/AL 441 mg); 41 in Group 2 (ALKS 9072N initiation regimen/AL 882 mg); 40 in Group 3 (Oral initiation regimen/AL 441 mg); and 41 in Group 4 (Oral initiation regimen/AL 882 mg). All 161 subjects were included in analyses of safety and PK data. Disposition of subjects in Study B102 is presented in Table 5.

Table 5. Disposition of Subjects in Study B102

Analysis Group	Treatment Group						All
	ALKS 9072N Initiation + AL 441 mg	ALKS 9072N Initiation + AL 882 mg	Total ALKS 9072N Initiation	Oral Initiation + AL 441 mg	Oral Initiation + AL 882 mg	Total Oral Initiation	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Enrolled Population	39	41	80	40	41	81	161
Safety Population	39 (100.0)	41 (100.0)	80 (100.0)	40 (100.0)	41 (100.0)	81 (100.0)	161 (100.0)
Pharmacokinetic Population	39 (100.0)	41 (100.0)	80 (100.0)	40 (100.0)	41 (100.0)	81 (100.0)	161 (100.0)
Completed Treatment	31 (79.5)	37 (90.2)	68 (85.0)	36 (90.0)	36 (87.8)	72 (88.9)	140 (87.0)
Completed Study	31 (79.5)	36 (87.8)	67 (83.8)	32 (80.0)	34 (82.9)	66 (81.5)	133 (82.6)
Discontinued Study	8 (20.5)	5 (12.2)	13 (16.3)	8 (20.0)	7 (17.1)	15 (18.5)	28 (17.4)
Withdrawal by Subject	1 (2.6)	3 (7.3)	4 (5.0)	3 (7.5)	3 (7.3)	6 (7.4)	10 (6.2)
Lost to Follow-up	2 (5.1)	2 (4.9)	4 (5.0)	4 (10.0)	2 (4.9)	6 (7.4)	10 (6.2)
Adverse Event	3 (7.7)	0	3 (3.8)	1 (2.5)	1 (2.4)	2 (2.5)	5 (3.1)
Protocol Deviation	1 (2.6)	0	1 (1.3)	0	1 (2.4)	1 (1.2)	2 (1.2)
Other	1 (2.6)	0	1 (1.3)	0	0	0	1 (0.6)

Source: NDA 209830 Summary of Clinical Safety, Table 5, page 24.

Protocol Violations/Deviations

In this study, 17 protocol violations occurred. Nine were related to informed consent, four to dosing, three to the PK sampling schedule, and one to the enrollment criteria. The nine informed consent violations were related to consents obtained at screening using an outdated informed consent form. All subjects were reconsented using the current informed consent form. The rest of the protocol deviations are presented in Table 6.

- *Reviewer Comment:* The most significant deviations were the three pre-dose PK samples that were drawn post-dose. These all occurred in subjects in the AL 882 mg + oral initiation group. The number of affected subjects (n = 3) was small in relation to the number of subjects in this group who completed the study (n = 34). Overall, it does not appear that the deviations that did occur would have a significant impact on the analysis of the study data.

Table 6. Protocol Deviations in Study B102: Enrollment Criteria, Dosing, and PK Sampling[a]

Treatment Group	Subject ID	Deviation Category	Deviation Description
AL 441 mg + ALKS 9072N	(b) (6)	Enrollment Criteria	Subject is taking an exclusionary medication, an SSRI (Celexa). Subject reported this to nursing staff during admission to the inpatient portion of the study. This was not reported to the PI and site study staff.
AL 882 mg + ALKS 9072N		Dosing	Subject was dosed with AL 882 mg in the deltoid instead of gluteal muscle.
AL 882 mg + ALKS 9072N		Dosing	Subject was dosed with two 30 mg capsules of aripiprazole.
AL 441 mg + oral initiation		Dosing	Placebo was injected into the deltoid muscle instead of the gluteal muscle, and AL 441 mg was injected into the gluteal muscle instead of the deltoid muscle.
AL 882 mg + oral initiation		Dosing	Subject was dosed with AL 882 mg in the deltoid instead of gluteal muscle.
AL 882 mg + oral initiation		PK Sampling Schedule	On Day 19, the pre-dose PK was drawn post-dose.
AL 882 mg + oral initiation		PK Sampling Schedule	On Day 8, the pre-dose PK was drawn post-dose.
AL 882 mg + oral initiation		PK Sampling Schedule	On Day 14, the pre-dose PK was drawn post-dose.

[a]*The nine informed consent protocol violations are not presented in the table.*

Source: reviewer-generated table.

Demographic Characteristics

The majority of subjects were male (73.3%). The most common race was Black or African American (77.6%). Mean ages (by initiation regimen) ranged from 42.3 to 45.0 years (minimum-maximum: 18 to 64 years). Mean body mass index (by initiation regimen) ranged from 28.06 to 30.30 kg/m^2 (minimum-maximum: 19.1 – 41.4 kg/m^2). Detailed demographics of the Safety Population are presented in Chapter 8, Table 12.

Pharmacokinetic Results

The results of Study ALK9072-B102 are as follows:

- A rapid increase in mean plasma aripiprazole concentrations was seen in each ALKS 9072N initiation regimen group, which was comparable to each corresponding oral initiation regimen group.

- Higher aripiprazole concentrations were observed during the first 24 hours upon initiation with the ALKS 9072N initiation regimen as compared to the oral initiation regimen. This was anticipated due to the administration of 30 mg oral aripiprazole on Day 1 in the ALKS 9072N initiation regimen versus 15 mg oral aripiprazole on Day 1 in the oral initiation regimen.
- Mean plasma aripiprazole concentrations over time overlapped across each of the initiation regimens through Day 21.
- After Day 21, plasma aripiprazole concentrations persisted in each ALKS 9072N initiation regimen group, whereas plasma aripiprazole concentrations began to decline in each oral initiation regimen group. Mean aripiprazole concentrations in the ALKS 9072N initiation regimen began to decline after Day 30, at an apparently less rapid rate as compared to the decline following the end of the oral initiation regimen.
- The ALKS 9072N initiation regimen was designed to achieve therapeutic aripiprazole concentrations (ie, > 102 ng/mL) within four days after treatment initiation. A larger proportion of subjects in each ALKS 9072N initiation regimen group had plasma concentrations > 102 ng/mL as compared to each corresponding oral initiation regimen group by Day 4.
- There were no meaningful differences among treatment regimens with respect to exposure to aripiprazole. Although Tmax was longer in each ALKS 9072N initiation regimen group compared to the corresponding oral initiation regimen group, mean $AUC_{0\text{-}28}$ and AUC_{last} values were relatively similar between the ALKS 9072N initiation regimen groups and the corresponding oral initiation regimen groups. Overall, the ALKS 9072N initiation regimen resulted in total exposure of aripiprazole that was at or above the total exposure achieved with the 21-day oral aripiprazole initiation regimen.

Key pharmacokinetic parameters are presented in Table 7.

Table 7. Key Pharmacokinetic Parameters from Study B102

PK Parameter	**ALKS 9072N Initiation / AL 441 mg (N=39)**	**ALKS 9072N Initiation / AL 882 mg (N=41)**	**Oral Initiation / AL 441 mg (N=40)**	**Oral Initiation / AL 882 mg (N=41)**
C_{max} (ng/mL), Mean (SD)	268.15 (127.97)	217.53 (102.66)	191.69 (64.10)	220.64 (82.55)
T_{max} (day), median	21.0	27.0	16.5	18.0
$AUC_{0\text{-}28}$	4256.4	3570.7	3371.6	3911.9

(day*ng/mL, Mean (SD)	(1703.6)	(1935.2)	(1110.5)	(1661.6)
AUC_{last} (day*ng/mL), Mean (SD)	9794.6 (3826.4)	11627.2 (5921.8)	6104.9 (2017.9)	9365.5 (5172.7)

Source: ALK9072-B102 Clinical Study Report, Table 17, page 57.

The Sponsor concluded that the combination of Aristada Initio and 30 mg oral aripiprazole resulted in plasma aripiprazole concentrations either at or above those achieved by initiation of treatment with 21 days of oral aripiprazole.

6.3. Study ALK9072-B103 (short name: B103)

6.3.1. Study Design

Overview and Objective

Study Title: "A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072N Following Administration to the Deltoid or Gluteal Muscle in Adults with Schizophrenia or Schizoaffective Disorder"

Primary Objective: To determine the safety, tolerability and pharmacokinetics (PK) of ALKS 9072N 662 mg, administered as a single intra-muscular (IM) injection in the deltoid or gluteal muscle in adults with schizophrenia or schizoaffective disorder.

Secondary Objective: To evaluate the relative bioavailability of ALKS 9072N 662 mg following a single IM injection in the deltoid muscle compared to exposure following administration to the gluteal muscle in adults with schizophrenia or schizoaffective disorder.

Study B103 was designed to compare deltoid versus gluteal administration of ALKS 9072N on safety, tolerability, and pharmacokinetics.

Trial Design

This was a multicenter, randomized, open-label, single-dose study of ALKS 9072N 662 mg following IM injection to the deltoid or gluteal muscle in subjects with schizophrenia or schizoaffective disorder.

Subjects who met eligibility criteria were admitted to an inpatient study facility on Day -1, the day prior to dosing. For eligible subjects who received oral aripiprazole during screening, 28

days elapsed between the last dose of oral aripiprazole and the IM injection of study drug on Day 1. Subjects remained on their regular oral antipsychotic regimens, not including oral aripiprazole, for the duration of the study.

On Day 1, subjects were randomized in a 1:1 ratio to receive a single 662 mg IM dose of ALKS 9072N in either the deltoid muscle (Group 1) or gluteal muscle (Group 2). Subjects remained in the inpatient unit for eight days. Subjects returned to the study center for outpatient study visits between discharge on Day 8 and Day 85.

Trial Location: The study was conducted in 13 study centers in the United States.

Diagnostic Criteria: Eligible subjects were required to have a diagnosis of chronic schizophrenia or schizoaffective disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Key Inclusion Criteria:

- Between 18 and 65 years of age, inclusive, at screening.
- Documented history of tolerated use of aripiprazole, or demonstrated tolerability to test doses of oral aripiprazole during screening.
- Diagnosis of either chronic schizophrenia or schizoaffective disorder.
- Clinically stable as evidenced by meeting both of the following criteria:
    - Had no hospitalizations for acute psychiatric exacerbations within the three months prior to screening or upon admission;
    - Had a CGI-S score of ≤ 3 (mild) at screening and upon admission.
- Had been on a stable antipsychotic medication regimen for at least two months prior to screening and had no antipsychotic medication regimen change (medication or dose level, unless the dose level change was due to tolerability) between screening and admission.
- Agreed to remain on current antipsychotic regiment for the duration of the study unless a change was medically indicated.
- Body mass index between 18.0 and 40.0 kg/m^2, inclusive, at screening and upon admission.
- Agreed to use an acceptable method of contraception for the duration of the study unless surgically sterile or postmenopausal.

Key Exclusion Criteria:

- Pregnant, planning to become pregnant, or currently breastfeeding at screening or upon admission.
- Met any of the following exclusionary medication criteria:
    - Had received aripiprazole within 28 days before randomization.
    - Had received AL or IM depot aripiprazole within six months prior to admission.

  - Had taken any other extended release injectable antipsychotic within three months prior to admission.
  - Was currently being treated with clozapine.
- Participation in a clinical trial involving any investigational product within the past three months.
- History of psychopathology other than schizophrenia or schizoaffective disorder.
- Elevated risk of harm to self or to others, based on either the investigator's opinion or the patient's responses on the C-SSRS.
- History or current evidence of a clinically significant condition, laboratory test result, or ECG finding that could preclude safe participation in the study or that could confound protocol assessments.
- History of neuroleptic malignant syndrome or clinically significant tardive dyskinesia.
- QTcF > 450 msec for men or > 470 msec for women at screening or upon admission.
- Had used potent cytochrome CYP3A4 inducers or inhibitors or CYP2D6 inhibitors within the 30 days prior to admission
- Was a CYP2D6 poor metabolizer based on pharmacogenetic testing at screening.
- Positive urine drug test for drugs of abuse at screening or upon admission.

Pharmacokinetic Sampling: Serial blood samples were collected beginning on Day 1, and continued through Day 85 to measure plasma concentrations and evaluate the PK of ALKS 9072N and its metabolites. The total duration of the study was approximately four months, including up to 30 days for screening.

Study Endpoints: Pharmacokinetic Measures

The following parameters were calculated for each analyte using noncompartmental analysis methods:

- Maximum observed concentration (C_{max})
- Time to the Cmax (t_{max})
- Area under the concentration-vs-time curve from time zero to the time of the last quantifiable concentration, using the linear trapezoidal rule (AUC_{last})
- Area under the concentration-vs-time curve from time zero to infinity ($AUC\infty$)
- Terminal elimination half-life ($t_{1/2}$)

In addition, the relative bioavailability of ALKS 9072N administered as a deltoid versus a gluteal IM injection was evaluated based on aripiprazole exposure.

Statistical Analysis Plan

Summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) were provided for all evaluated variables. Concentration data were summarized according to protocol-specified nominal sampling times. PK parameters were calculated using noncompartmental techniques, and actual elapsed time from dosing was used to estimate individual plasma PK parameters. Individual subject concentrations and calculated PK parameters were presented in by-subject data listings.

The relative bioavailability of ALKS 9072N administered as an IM injection in the deltoid muscle versus in the gluteal muscle was assessed via evaluation of the ratio of deltoid:gluteal for PK parameters of exposure.

Protocol Amendments

The original protocol was finalized on August 20, 2015. There was one amendment.

Amendment 1, finalized on October 15, 2015, made the following change to the protocol:

- Inclusion/exclusion criteria were revised to prohibit use of clozapine.

There were no changes made to the planned analyses.

6.3.2. Study Results

Compliance with Good Clinical Practices

Page 13 of the ALK9072-B103 Clinical Study Report includes the following statement: "The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (1964), the Good Clinical Practice (GCP) Guidelines issued by the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, Federal Code of Regulations Title 21 (21 CFR), and other applicable international and local laws and regulations."

Financial Disclosure

No disclosable financial interests or arrangements reported for Study B103.

Patient Disposition

A total of 47 subjects were enrolled in the study. Twenty-three were randomized to the deltoid group and 24 to the gluteal group. All of these subjects received one dose of study drug and 45

(95.7%) completed the study: 23 (100.0%) in the deltoid group and 22 (91.7%) in the gluteal group. Disposition of subjects in Study B103 is presented in Table 8.

Table 8. Disposition of Subjects in Study B103

Analysis Group, n (%)	ALKS 9072N Treatment Group		
	662 mg Deltoid	662 mg Gluteal	Total
Enrolled population	23	24	47
Safety Population	23 (100.0)	24 (100.0)	47 (100.0)
Pharmacokinetic Population	23 (100.0)	24 (100.0)	47 (100.0)
Completed Study	23 (100.0)	22 (91.7)	45 (95.7)
Discontinued Study	0	2 (8.3)	2 (4.3)
Reason for Discontinuation			
Lost to Follow-up	0	1 (4.2)	1 (2.1)
Withdrawal by Subject	0	1 (4.2)	1 (2.1)

Source: NDA 209830 Summary of Clinical Safety, Table 6, page 25.

Protocol Violations/Deviations

All subjects met all the inclusion criteria, and none of the exclusion criteria. The most common deviations were visits outside the visit window, PK assessments outside of the time window, and missed or incomplete routine safety assessments.

- *Reviewer Comment:* Overall, it does not appear that the deviations that did occur would have a significant impact on the analysis of the study data.

Demographic Characteristics

The majority of subjects were male (72.3%). The most common race was Black or African American (78.7%). Mean age was 48.6 years (minimum-maximum: 26 to 64 years). Mean body mass index was 28.8 kg/m^2 (minimum-maximum: 18.5 – 39.6 kg/m^2). Detailed demographics of the Safety Population are presented in Chapter 8, Table 13.

Pharmacokinetic Results

The PK conclusions of the study were as follows:

- Plasma profiles of aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl-aripiprazole after a single IM injection of ALKS 9072N 662 mg were comparable between deltoid and gluteal administration.

- The relative bioavailability of aripiprazole following deltoid administration of ALKS 9072N 662 mg IM was similar to gluteal administration, suggesting that the two injection sites can be used interchangeably.

The safety results for the study will be discussed in Chapter 8, Review of Safety.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The efficacy of Aristada Initio 662 mg single intramuscular injection combined with a single oral dose of aripiprazole 30 mg for the initiation of treatment of adults with schizophrenia was established through pharmacokinetic bridging to 21 days of oral aripiprazole 15 mg. The pharmacokinetic studies demonstrated that the Aristada Initio treatment initiation regimen resulted in plasma aripiprazole concentrations that are similar to the plasma concentrations provided by the oral initiation regimen. An overview of the results of the three pharmacokinetic studies submitted with the NDA application was presented in Chapter 6, Review of Relevant Individual Trials Used to Support Efficacy.

No new efficacy data was submitted with this supplement.

8. Review of Safety

In general, the safety data submitted with this supplemental NDA are consistent with the known safety profile of aripiprazole and the previously-approved aripiprazole lauroxil doses. This review revealed no safety findings that would preclude approval of this supplement.

8.1. Safety Review Approach

The Safety Review is based on review of the Development Safety Update Report submitted to IND 121179 for the reporting period November 25, 2016 to November 24, 2017; the safety data submitted for the three pharmacokinetic studies ALK9072-B101, ALK9072-B102, and ALK9072-B103; and the Summary of Clinical Safety submitted with the NDA application. The development international birth date (DIBD) for Aristada Initio is November 25, 2014.

During the reporting period, one nonclinical study was completed, and no nonclinical studies are ongoing. One Phase 1 clinical study, ALK9072-B102, was completed. One Phase 3b clinical study, ALK9072-A306, is ongoing, with two subjects having received blinded study treatment.

This study is a comparison of the safety and effectiveness of Aristada using the Aristada Initio initiation strategy to the safety and effectiveness of paliperidone palmitate in the treatment of patients with schizophrenia hospitalized for an acute exacerbation of symptoms. No deaths occurred during the reporting period. There were no new or unexpected findings related to safety during this reporting period.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

As of November 24, 2017, 212 subjects have been exposed to Aristada Initio in the development program. This includes 85 subjects in Study ALK9072-B101, 80 subjects in ALK9072-B102, and 47 subjects in ALK9072-B103.

Across the three Phase 1 studies, a total of 170 subjects received the ALKS 9072N formulation intended for commercialization (Formulation B), and 95 subjects received corresponding placebo. The ALKS 9072N Formulation B dose received across the three studies was 110 mg for two subjects, 221 mg for four subjects, 441 mg for 13 subjects, 662 mg for 139 subjects, and 882 mg for 12 subjects. The two subjects in Study B101 who received the 110 mg dose were sentinel subjects who received sub-therapeutic, open-label doses of ALKS 9072N before other subjects were randomized. These two subjects are not included in the Safety Population.
110 subjects received a single IM injection of placebo, including 29 subjects in Study B101 and 81 subjects in Study B102.

A total of 139 subjects received ALKS 9072N Formulation B at a dose of 662 mg. This is the formulation and dose strength that is planned for commercialization.

A summary of the overall exposure to ALKS 9072N is presented in Table 9. Key subsets of the safety population are depicted in Table 10.

Table 9. Overall Exposure to ALKS 9072N

Injection Site:	Gluteal						Deltoid
Dose Strength:	Formulation	110 mg	221 mg	441 mg	662 mg	882 mg	662 mg
B101	A	-	3	12	-	-	-
	C	-	3	12	12	-	-
	B	2	4	13	12	12	
B102	B	-	-	-	80	-	-
B103	B	-	-	-	24	-	23
Total		2	10	37	128	12	23

Source: NDA 209830 Summary of Clinical Safety, Table 7, page 25.

Table 10. Key Subsets of the Safety Population

Subset	N
Any ALKS 9072N formulation	212
ALKS 9072N Formulation B	170
ALKS 9072N Formulation B, excepting sentinel subjects in B101	168
ALKS 9072N Formulation B, 662 mg dose	139

Source: NDA 209830 Summary of Clinical Safety, Table 7, page 25.

8.2.2. Relevant characteristics of the safety population:

The Safety Population is defined as all subjects who received at least one injection of ALKS 9072N or placebo, with the exception of two sentinel subjects from Study ALK9072-B101. Across the three Phase 1 studies, the majority of subjects were male (73.4%) and Black or African American (79.1%). Subject ages ranged from 18 to 64 years. Subject demographics for the three studies are presented in Table 11, Table 12, and Table 13.

Table 11. Demographics for Study B101

	221 mg		441 mg		662 mg		882 mg	
	Placebo (N = 3)	ALKS 9072N (N = 10)	Placebo (N = 13)	ALKS 9072N (N = 37)	Placebo (N = 9)	ALKS 9072N (N = 24)	Placebo (N = 4)	ALKS 9072N (N = 12)
Age, years								
Mean (SD)	45.7 (11.37)	43.1 (6.72)	44.0 (12.29)	48.4 (9.11)	46.0 (5.34)	45.3 (12.16)	49.3 (4.11)	42.3 (9.64)
Min – Max	33 – 55	35 – 55	25 – 61	29 – 61	36 – 54	20 – 63	44 – 54	24 – 57
Gender, n (%)								
Male	3 (100.0)	7 (70.0)	11 (84.6)	26 (70.3)	6 (66.7)	22 (91.7)	2 (50.0)	9 (75.0)
Female	0	3 (30.0)	2 (15.4)	11 (29.7)	3 (33.3)	2 (8.3)	2 (50.0)	3 (25.0)
Race, n (%)								
Asian	0	0	0	1 (2.7)	0	0	0	0
Black or African American	3 (100.0)	8 (80.0)	10 (76.9)	30 (81.1)	8 (88.9)	18 (75.0)	4 (100.0)	10 (83.3)
White	0	2 (20.0)	3 (23.1)	6 (16.2)	1 (11.1)	6 (25.0)	0	2 (16.7)
Ethnicity, n (%)								
Not Hispanic or Latino	3 (100.0)	10 (100.0)	11 (84.6)	32 (86.5)	9 (100.0)	22 (91.7)	4 (100.0)	11 (91.7)
Hispanic or Latino	0	0	2 (15.4)	5 (13.5)	0	2 (8.3)	0	1 (8.3)

BMI, kg/m^2								
Mean (SD)	31.57 (6.266)	28.88 (5.602)	30.16 (5.908)	30.68 (5.533)	30.71 (5.272)	28.44 (5.190)	26.85 (5.587)	28.05 (4.750)
Min – Max	27.8 – 38.8	19.9 – 37.5	20.9 – 38.1	18.5 – 39.7	21.4 – 37.1	18.4 – 38.9	21.4 – 32.7	21.5 – 38.2

Source: ALK9072-B101 Clinical Study Report, Table 7, page 52.

Table 12. Demographics for Study B102

	Treatment Group				**Total (N = 161)**
	ALKS 9072N Initiation + AL 441 mg (N = 39)	**ALKS 9072N Initiation + AL 883 mg (N = 41)**	**Oral Initiation + AL 441 mg (N = 40)**	**Oral Initiation + AL 882 mg (N = 41)**	
Age, years					
Mean (SD)	44.4 (10.03)	42.3 (12.39)	44.2 (9.67)	45.0 (10.19)	44.0 (10.59)
Min – Max	25 – 61	20 - 61	18 - 59	22 - 64	18 - 64
Gender, n (%)					
Male	30 (76.9)	29 (70.7)	27 (67.5)	32 (78.0)	118 (73.3)
Female	9 (23.1)	12 (29.3)	13 (32.5)	9 (22.0)	43 (26.7)
Ethnicity, n (%)					
Not Hispanic or Latino	39 (100.0)	38 (92.7)	38 (95.0)	40 (97.6)	155 (96.3)
Hispanic or Latino	0	3 (7.3)	2 (5.0)	1 (2.4)	6 (3.7)
Race, n (%)					
Black or African American	31 (79.5)	33 (80.5)	26 (65.0)	35 (85.4)	125 (77.6)
White	8 (20.5)	8 (19.5)	14 (35.0)	5 (12.2)	35 (21.7)
Asian	0	0	0	1 (2.4)	1 (0.6)
BMI, kg/m^2					
Mean (SD)	28.06 (5.46)	29.79 (4.66)	30.30 (5.29)	29.71 (5.88)	29.48 (5.35)
Min – Max	19.1 - 38.9	20.8 - 39.5	22.3 - 41.4	19.7 - 39.4	19.1 - 41.4

Source: ALK9072-B102 Clinical Study Report, Table 11, page 47.

Table 13. Demographics for Study B103

	ALKS 9072N Treatment Group		Total (N = 47)
	662 mg Deltoid (N = 23)	662 mg Gluteal (N = 24)	
Age, years			
Mean (SD)	47.2 (9.87)	50.0 (9.86)	48.6 (9.87)
Min – Max	28 - 62	26 - 64	26 - 64
Gender, n (%)			
Male	18 (78.3)	16 (66.7)	34 (72.3)
Female	5 (21.7)	8 (33.3)	13 (27.7)
Race, n (%)			
Black or African American	18 (78.3)	19 (79.2)	37 (78.7)
White	5 (21.7)	4 (16.7)	9 (19.1)
Asian	0	1 (4.2)	1 (2.1)
Ethnicity, n (%)			
Not Hispanic or Latino	22 (95.7)	23 (95.8)	45 (95.7)
Hispanic or Latino	1 (4.3)	1 (4.2)	2 (4.3)
BMI, kg/m^2			
Mean (SD)	27.8 (5.29)	29.8 (4.82)	28.8 (5.11)
Min – Max	18.5-39.6	21.9-38.7	18.5-39.6

Source: ALK9072-B103 Clinical Study Report, Table 5, page 39.

8.2.3. Adequacy of the safety database:

The safety database is limited by the small size of the three pharmacokinetic studies. However, the previous clinical studies of aripiprazole lauroxil and the postmarketing pharmacovigilance of Aristada provide a more robust body of safety information for aripiprazole lauroxil. The three PK studies submitted with this NDA application did not reveal any new safety signal that was not identified in the previous clinical studies and postmarketing pharmacovigilance of aripiprazole lauroxil.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant provided original Case Report Forms (CRFs) for all deaths, SAEs, and AEs leading

to discontinuation. On review of the AE data files, it appears that the AEs were coded appropriately.

8.3.2. Categorization of Adverse Events

For Studies B101, B102, and B013, an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. A treatment-emergent adverse event (TEAE) was defined as an AE that is newly occurring or worsening from the time of the first dose of study drug. A serious adverse event (SAE) was defined as an AE that meets at least one of the following conditions:

- Results in death.
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in disability or incapacity; for example, a substantial disruption of a person's ability to conduct normal life functions.

All AEs were coded by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA Version 17.0 was used for coding AEs for Study B101 and B103. MedDRA Version 18.0 was used for coding AEs for Study B102.

8.3.3. Routine Clinical Tests

Laboratory measurements were provided by subject. Normal ranges were presented in the listings, and values outside of normal ranges were flagged. Subjects who met PCS criteria laboratory tests were presented.

8.4. Safety Results

8.4.1. Deaths

To date, one death has been reported during the clinical development program. Subject (b) (6) in Study ALK9072-B102 died in a road traffic accident. The incident occurred approximately four months after the last dose of study drug. The subject's vehicle was hit after he changed lanes on the freeway. The vehicle came to rest on the side of the road. The subject exited his vehicle, and ran across the freeway to confront the other driver. The subject then ran back across the freeway and was struck by multiple vehicles. The cause of death was reported as multiple blunt force injuries due to accident. The Investigator noted that there was no evidence of any suicidal ideation throughout the subject's involvement in the study. The SAE

does not appear to have been related to the study drug.

8.4.2. Serious Adverse Events

Fifteen SAEs have been reported in six of the 212 subjects exposed to Aristada Initio in the development program. Eight of the 15 SAEs were associated with the System Organ Class (SOC) of psychiatric disorders, including schizoaffective disorder (five cases), schizophrenia (one case), and psychotic disorder (one case). These could be attributable to the subjects' underlying psychiatric illness. There was one incident of suicidal ideation. There were no completed suicides, and no attempted suicides. There have been no SAEs related to study drug (SADRs). The SAEs are summarized by organ class in Table 14.

Table 14. Cumulative Summary of Serious Adverse Events Reported in the ALKS 9072N Clinical Development Program

System Organ Class Preferred Term	ALKS 9072N	Aristada and Placebo	Total
Any SAEs (number of events)	9	6	15
Endocrine disorders			1
Hypothyroidism	1		
Gastrointestinal disorders			1
Upper gastrointestinal hemorrhage		1	
Infections and infestations			1
Cellulitis		1	
Injury, poisoning, and procedural complications			3
Road traffic accident	1	1	
Accidental overdose		1	
Nervous system disorders			1
Status epilepticus	1		
Psychiatric disorders			8
Psychotic disorder	1		
Schizophrenia	1		
Schizoaffective disorder	3	2	
Suicidal ideation	1		

Source: IND 121179 Development Safety Update Report, Table 11, page 44.

The only suspected unexpected serious adverse reaction (SUSAR) during the Aristada Initio development program is an incident of status epilepticus during Study ALK9072-B102.

The subject, (b) (6), is a Caucasian male, age 59 years at the time of the incident. On Day 1 (b) (6) the subject received a single dose of 30 mg oral aripiprazole, followed by a single IM dose of 662 mg Aristada Initio in the gluteal muscle, followed by a single IM dose of Aristada 441 mg in the deltoid muscle. The subject continued to receive daily oral placebo beginning on Day 2. On (b) (6), the subject was transported to the emergency department for a possible seizure. The subject was given antiepileptic medications but did not improve. The subject was intubated and admitted to the ICU. The subject was placed initially on levetiracetam, and later on valproic acid, but continued to have seizures. On (b) (6), the subject was placed on lacosamide. On (b) (6), the subject was discharged to a rehabilitation facility due to significant debility. The event of status epilepticus was considered to be resolved. The subject was discharged on lacosamide 100 mg orally twice daily. The Principal Investigator assessed the SAE as moderate in intensity and possibly related to the study drug. The Sponsor assessed the event as unexpected and possibly related to the study drug.

The subject had no known prior history of seizures. An electroencephalogram (EEG) on (b) (6) showed isolated infrequent generalized sharp activity, possibly of epileptogenic potential, and isolated infrequent sharp activity over the left temporal region, possibly associated with partial onset seizures.

The subject's only concomitant medication was asenapine 5 mg daily by mouth, prescribed since 2013. It is known that antipsychotic medications, including the atypical antipsychotic medications can lower the seizure threshold. At the time of the incident, the subject was taking two antipsychotic medications. It is possible that the combination of antipsychotic medications lowered the seizure threshold enough to precipitate a seizure in this patient, who had no previous seizures but had EEG findings suggestive of a latent seizure focus.

There have been no other incidents of status epilepticus in either the Aristada development program or the Aristada Initio development program. A single SAE of seizure occurred in study ALK9072-003EXT in the Aristada development program. The subject, a 55-year-old female, had a concurrent SAE of squamous cell carcinoma. In that case, the seizure was assessed by the Principal Investigator as unrelated to the study drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Three (1.8%) of 168 ALKS 9072N-treated patients and 2 (2.1%) of 95 placebo-treated patients, all of whom participated in Study B102, discontinued from a study because of a TEAE. TEAEs leading to discontinuation among ALKS 9072N-treated patients were road traffic accident, extrapyramidal symptoms, and status epilepticus, each occurring in one subject only, with the

latter two events considered by the Investigator to be study drug-related. The incident of status epilepticus was discussed in Section 8.4.2, Serious Adverse Events.

8.4.4. Significant Adverse Events

Injection site reactions across studies B101, B102, and B103 are summarized in Table 15. The majority of these cases were injection site pain, assessed as mild to moderate in severity and resolving within one week. There were no study discontinuations as a result of injection site reactions.

Table 15. Cumulative Summary of Injection Site Reactions Reported in the ALKS 9072N Clinical Development Program

	Injection Site						
	Gluteal						Deltoid
	110 mg	221 mg	441 mg	662 mg	882 mg	Placebo	662 mg
Study	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
B101	0	0	2/13 (15.4)	3/12 (25)	3/12 (25)	0	NA
B102	NA	NA	NA	14/80 (17.5)	NA	5/81 (6.2)	NA
B103	NA	NA	NA	5/24 (20.8)	NA	NA	7/23 (30.4)
Total	0	0	2/13 (15.4)	22/116 (19.0)	3/12 (25)	5/95 (5.26)	7/23 (30.4)

Source: IND 121179 Development Safety Update Report, Table 1, page 11.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAEs: Study B101

The incidence of TEAEs in Study B101 was similar among subjects who received ALKS 9072N (58.5%) and those who received placebo (57.1%). TEAEs occurring at an incidence ≥ 5% among ALKS 9072N-treated subjects included injection site pain (17.1%), headache (9.8%), nasopharyngitis (9.8%), and akathisia (7.3%). There did not appear to be any relationship between overall frequency of TEAEs and ALKS 9072N dose, but the incidence of injection site pain increased with increasing ALKS 9072N dose. No subject treated with ALKS 9072N experienced a severe TEAE.

The study drug-related TEAEs reported for >1 ALKS 9072N-treated patient were injection site pain (17.1%), akathisia (7.3%), and headache (4.9%).

TEAEs with incidence ≥ 5% are listed in Table 16.

Table 16. TEAEs with Incidence ≥ 5% in Study B101

MedDRA Preferred Term	Placebo (N=14) n (%)	ALKS 9072N Treatment Group				
		221 mg (N=4) n (%)	441 mg (N=13) n (%)	662 mg (N=12) n (%)	882 mg (N=12) n (%)	Total ALKS 9072N (N=41) n (%)
Subjects with at least one TEAE	8 (57.1)	3 (75.0)	8 (61.5)	7 (58.3)	6 (50.0)	24 (58.5)
Injection site pain	0	0	2 (15.4)	2 (16.7)	3 (25.0)	7 (17.1)
Headache	1 (7.1)	0	1 (7.7)	2 (16.7)	1 (8.3)	4 (9.8)
Nasopharyngitis	0	1 (25.0)	2 (15.4)	1 (8.3)	0	4 (9.8)
Akathisia	0	0	1 (7.7)	1 (8.3)	1 (8.3)	3 (7.3)

Source: NDA-209830 Summary of Clinical Safety, page 34, Table 11.

TEAEs: Study B102

The overall incidence of TEAEs was similar among subjects in the ALKS 9072N initiation group (67.5%) and those in the oral initiation group (64.2%). TEAEs with a reported incidence ≥ 5% included injection site pain (21.3%), weight increased (11.3%), headache (7.5%), anxiety (7.5%), dyspepsia (6.3%), injection site induration (5.0%), insomnia (5.0%), and akathisia (5.0%). TEAEs reported at a higher incidence in the ALKS 9072N initiation group than in the oral initiation group were weight increased (11.3% vs 3.7%) and anxiety (7.5% vs 2.5%). Interestingly, the incidence of injection site pain was higher in the oral initiation group (24.7%) than in the ALKS 9072N initiation group (21.3%).

The ALKS 9072N initiation regimen was associated with a higher incidence of study-drug related TEAEs (47.5%) than the oral initiation regimen (39.5%). The most common study drug-related TEAEs overall were injection site pain (23.0%) and weight increased (5.6%).

The only severe TEAE reported for more than one subject was road traffic accident, reported for two subjects. One accident was fatal, and was discussed in Section 8.4.1, Deaths. Severe TEAEs in the ALKS 9072N initiation group included arthralgia, psychotic disorder, and schizoaffective disorder, each reported for one subject. Severe TEAEs in the oral initiation group

included accidental overdose, cellulitis, and upper gastrointestinal hemorrhage, each reported for one subject.

The SAE of psychotic disorder occurred in a subject whose treatment initiation regimen was AL 441 mg IM + ALKS 9072N 662 mg IM + oral aripiprazole 30 mg. On Day 100, the subject requested voluntary hospitalization due to thoughts of harming others. The subject improved, was discharged after two days, and continued in the study.

- *Reviewer Comment:* no other details are provided in the narrative for this SAE.

The SAE of accidental overdose occurred in a subject whose treatment initiation regimen was AL 882 mg IM + placebo IM + oral aripiprazole 15 mg. On Day 39, the subject had an unintentional overdose of quetiapine and trazodone because she could not remember whether she had already taken her medications. The subject denied any suicidal ideation. The SAE of upper gastrointestinal hemorrhage also occurred on Day 39 for this subject, due to GI ulceration following gastric lavage performed to treat the overdose. The subject was hospitalized for four days, and was discharged once the GI bleeding resolved. Neither SAE was assessed by the Investigator as related to the study drug.

The incident of cellulitis of the right hand developed after the subject crushed his right hand with metal. The cellulitis resolved after a hospital admission for IV vancomycin. The subject's treatment initiation regimen was AL 441 mg IM + placebo IM + oral aripiprazole 15 mg. The cellulitis was not related to the site of injection of either AL 441 mg IM or placebo IM.

Only the case of schizoaffective disorder was considered possibly related to study drug. The subject had two hospitalizations for exacerbation of schizoaffective disorder during the study. The subject had a previous diagnosis of schizoaffective disorder. The subject's treatment initiation regimen was AL 441 mg IM + ALKS 9072N 662 mg IM + oral aripiprazole 30 mg. Concurrent medications included valproic acid, quetiapine, haloperidol decanoate, and gabapentin. On Day 24, the TEAE of exacerbation of schizoaffective disorder was recorded. On Day 26, the subject's symptoms had worsened, with irritability, aggressive behavior, poor sleep, and disorganized thought process. He was hospitalized, and the TEAE was upgraded to serious. He was reported to have been non-compliant with medications for three weeks prior to the SAE. The dose of quetiapine was increased. The subject improved, was discharged from the hospital on Day 32, and continued in the study. The Investigator considered the study drug to be possibly related to the SAE. The subject had a second hospitalization on Day 44, also for an SAE of exacerbation of schizoaffective disorder, presenting with grandiosity, paranoid ideation, disorganized thinking, and aggressive behavior. Adjustments were made to the patient's concurrent medications, and he showed improvement. The subject was hospitalized for 27 days. The Investigator considered the SAE to be possibly related to the study drug. This subject also suffered a SAE of road traffic accident on Day 37 when his vehicle was struck by a truck on the passenger side. The SAE was considered to be unrelated to the study drug.

- *Reviewer Comment:* It is difficult to assess whether the two SAEs of exacerbation of schizoaffective disorder were due to the study drug, due to the use of multiple concurrent psychotropic medications, the subject's history of poor treatment compliance, and the natural course of the illness, which includes periods of exacerbation of symptoms.

The SAE of arthralgia occurred in two subjects, one receiving the treatment initiation regimen of AL 441 mg IM + ALKS 9072n 662 mg IM + oral aripiprazole 30 mg, the other receiving the treatment initiation regimen of AL 882 mg IM + ALKS 9072n 662 mg IM + oral aripiprazole 30 mg.

- *Reviewer Comment:* The B102 Study Report does not include narratives for these two SAEs.

TEAEs with incidence ≥ 5% are listed in Table 17.

Table 17. TEAEs with Incidence ≥ 5% in Study B102

	Initiation Regimen + AL Dose					
MedDRA Preferred Term	**ALKS 9072N Initiation + AL 441 mg (N=39) n (%)**	**ALKS 9072N Initiation + AL 882 mg (N=41) n (%)**	**Total ALKS 9072N Initiation (N=80) n (%)**	**Oral Initiation + AL 441 mg (N=40) n (%)**	**Oral Initiation + AL 882 mg (N=41) n (%)**	**Total Oral Initiation (N=81) n (%)**
Subjects with at least one TEAE	26 (66.7)	28 (68.3)	54 (67.5)	24 (60.0)	28 (68.3)	52 (64.2)
Injection site pain	9 (23.1)	8 (19.5)	17 (21.3)	11 (27.5)	9 (22.0)	20 (24.7)
Weight increased	5 (12.8)	4 (9.8)	9 (11.3)	2 (5.0)	1 (2.4)	3 (3.7)
Headache	3 (7.7)	3 (7.3)	6 (7.5)	5 (12.5)	5 (12.2)	10 (12.3)
Anxiety	2 (5.1)	4 (9.8)	6 (7.5)	2 (5.0)	0	2 (2.5)
Dyspepsia	3 (7.7)	2 (4.9)	5 (6.3)	1 (2.5)	3 (7.3)	4 (4.9)
Injection site induration	2 (5.1)	2 (4.9)	4 (5.0)	2 (5.0)	1 (2.4)	3 (3.7)
Insomnia	2 (5.1)	2 (4.9)	4 (5.0)	3 (7.5)	3 (7.3)	6 (7.4)
Akathisia	1 (2.6)	3 (7.3)	4 (5.0)	0	2 (4.9)	2 (2.5)

Source: NDA-209830 Summary of Clinical Safety, page 35, Table 12.

TEAEs: Study B103

In Study B103, the overall incidence of TEAEs was higher in the gluteal group (79.2%) than in the deltoid group (65.2%). TEAEs with a reported incidence ≥ 5% included injection site pain

(25.5%), nasopharyngitis (10.6%), constipation (8.5%), headache (8.5%), and toothache (8.5%). Injection site pain was reported at a higher incidence in the deltoid group (30.4%) than in the gluteal group (20.8%).

One subject in the deltoid administration group had a SAE of suicidal ideation on Day 44, resulting in hospitalization, with resolution by Day 49. The subject reported depressed mood, loss of interest in usual activities, poor sleep, and low energy for several weeks. However, the subject was negative for suicidal ideation and suicidal behavior on the C-SSRS at all study timepoints, including at visits preceding the SAE (Day 27) and following the SAE (Day 58). The SAE was assessed by the Investigator as not related to the study drug.

Two subjects, both in the gluteal group, had severe TEAEs, including cyst on back and right leg injury secondary to fall. Neither of these was assessed by the Investigator as being related to study drug.

The incidence of study drug-related TEAEs was similar in the deltoid group (43.5%) and the gluteal group (45.8%). The most common study drug-related TEAE, injection site pain, was higher in the deltoid group (30.4%) than in the gluteal group (20.8%).

TEAEs with incidence $\geq$ 5% are listed in Table 18.

Table 18. TEAEs with Incidence ≥ 5% in Study B103

MedDRA Preferred Term	ALKS 9072N Treatment Group		
	662 mg Deltoid (N=23) n (%)	662 mg Gluteal (N=24) n (%)	Total (N=47) n (%)
Subjects with at least one TEAE	15 (65.2)	19 (79.2)	34 (72.3)
Injection site pain	7 (30.4)	5 (20.8)	12 (25.5)
Nasopharyngitis	2 (8.7)	3 (12.5)	5 (10.6)
Constipation	1 (4.3)	3 (12.5)	4 (8.5)
Headache	0	4 (16.7)	4 (8.5)
Toothache	2 (8.7)	2 (8.3)	4 (8.5)

Source: NDA-209830 Summary of Clinical Safety, page 36, Table 13.

8.4.6. Laboratory Findings

Across the 168 subjects treated with ALKS 9072N at doses of 221 mg to 882 mg in the three Phase 1 pharmacokinetic studies, there was no evidence of hepatic injury or clinically

meaningful changes in metabolic, renal, electrolyte, or hematology parameters.

Liver Function Tests

Liver function tests (LFTs) measured during the Phase 1 studies included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, lactate dehydrogenase (LDH), and gamma-glutamyl transferase (GGT).

Study B101: There was no apparent dose relationship across the range of ALKS 9072N doses from 221 mg to 882 mg, and no notable differences from placebo in changes from baseline in LFTs. No potentially clinically significant (PCS) values were noted for LFTs among ALKS 9072N-treated subjects, and no LFT abnormalities were reported as TEAEs.

Study B102: There was no notable difference between the ALKS 9072N initiation regimen and the oral initiation regimen in changes from baseline in LFTs. PCS values for ALT were observed for similar proportions of subjects who received the ALKS 9072N initiation regimen (2.6%) and the oral initiation regimen (2.5%). For one subject who received the ALKS 9072N initiation regimen, the ALT elevation was $\geq$ 5 x ULN. For this subject, the maximum ALT value was 254 U/L, which is 5.8 x ULN of 44 U/L. This event was reported as a TEAE, and was assessed as mild in severity and study drug-related. One subject who received the oral initiation regimen also had PCS values for AST. No subject who received the ALKS 9072N initiation regimen had PCS values for AST. No PCS values were seen in ALP, bilirubin, LDH, or GGT.

Study B103: There was no notable difference between IM injection of ALKS 9072N in the gluteal vs deltoid muscle in change from baseline in LFTs. One subject in the deltoid group had PCS elevated ALT and AST. One subject in the gluteal group had PCS elevated ALT.

No subject had LFT abnormalities meeting the criteria for Hy's Law. There were no study discontinuations due to LFT TEAEs.

Metabolic Parameters

Metabolic parameters measured during the Phase 1 studies included glucose, hemoglobin A1c, total cholesterol (fasting), high-density lipoprotein (HDL) cholesterol (fasting), low-density lipoprotein (LDL) cholesterol (fasting), and triglycerides (fasting). No ALKS 9072N-treated subject had an abnormal metabolic parameter reported as a TEAE.

Study B101: No clinically meaningful trends in metabolic parameters were noted within or across dose groups. No PCS values were noted for metabolic parameters among ALKS 9072N-treated subjects. No metabolic abnormalities were reported as TEAEs.

Study B102: No clinically meaningful trends in metabolic parameters were noted within or across treatment groups. PCS elevated glucose values (≥ 200 mg/dL) were seen in 1.3% of subjects who received the ALKS 9072N initiation regimen, and in 2.5% of subjects who received the oral initiation regimen. 1.3% of subjects who received the oral initiation regimen had a PCS decreased glucose value (< 50 mg/dL). One subject who received the oral initiation regimen had moderate hyperlipidemia reported as a TEAE. The event was deemed non-serious and unrelated to study drug.

Study B103: No clinically meaningful trends in metabolic parameters were seen within or across treatment groups. One subject in the gluteal group had an isolated, transient PCS decreased glucose value (< 50 mg/dL). No subject had an abnormal metabolic parameter reported as a TEAE.

Creatine Kinase

No ALKS 9072N-treated subject had a creatine kinase (CK) abnormality reported as a TEAE.

Study B101: No clinically meaningful trends were noted within or across dose groups. 14.6% of subjects in any ALKS 9072N dose group and 15.4% of placebo-treated subjects had at least one PCS CK elevation (> 3 x ULN). Across ALKS 9072N dose groups, the incidence of PCS CK elevations was 25.0% for the 221 mg dose group, 8.3% for the 441 mg dose group, 9.1% for the 662 mg dose group, and 25.0% for the 882 mg dose group. There was no apparent dose-related trend, as the incidence of PCS CK elevations was the same for the lowest and highest dose groups.

Study B102: No clinically meaningful trends were noted within or across treatment groups. PCS values for CK were noted for 9.3% of subjects who received the ALKS 9072N initiation regimen and for 6.5% of subjects who received the oral initiation regimen. These PCS values were all isolated and transient. One subject who received the oral initiation regimen had a mild increase in CK reported as a TEAE. The event was considered non-serious and unrelated to study treatment.

Study B103: No clinically meaningful trends were seen within or across treatment groups. PCS CK elevations (> 3 x ULN) were noted in 17.4% of subjects in the deltoid group, and in 4.3% of subjects in the gluteal group. These PCS values were all isolated and transient, with none reported as a TEAE.

Renal Parameters

Renal parameters assessed in the Phase 1 studies included creatinine and blood urea nitrogen (BUN). No ALKS 9072N-treated subject had a renal parameter abnormality reported as a TEAE.

Study B101: No clinically meaningful trends were noted within or across dose groups. No PCS creatinine or BUN values were seen. No subject had an abnormal renal parameter reported as a TEAE.

Study B102: No clinically meaningful trends were noted within or across treatment groups. One subject who received the oral initiation regimen had a PCS BUN value (> 30 mg/dL) at the final study visit. No subject in the study had a PCS creatinine value (> 3 x ULN). No subject had an abnormal renal parameter reported as a TEAE.

Study B103: No clinically meaningful trends were noted within or across treatment groups. No subject had PCS abnormalities in renal parameters, and no subject had an abnormal renal parameter reported as a TEAE.

Electrolytes

Electrolytes measured in the Phase 1 studies included potassium and sodium.

Study B101: No clinically meaningful trends in electrolytes were seen within or across dose groups. One subject in the ALKS 9072N 441 mg dose group had an isolated, transient PCS potassium value (> 5.5 mEq/L). The event was assessed by the Investigator as not related to study drug.

Study B102: No clinically meaningful trends in electrolytes were seen within or across treatment groups. PCS elevated potassium values were seen for 1.3% of subjects who received the ALKS 9072N initiation regimen and 2.5% of subjects who received the oral initiation regimen. A PCS elevated sodium value (> 150 mEq/L) was seen for one subject who received the ALKS 9072N initiation regimen. Mild kyperkalemia was reported as a TEAE for one subject who received the ALKS 9072N initiation regimen. The event was deemed non-serious and unrelated to study drug.

Study B103: No clinically meaningful trends in electrolytes were seen within or across treatment groups. One subject in the gluteal group had an isolated, transient PCS elevated potassium value (> 5.5 mEq/L). No PCS sodium values were reported. No abnormal electrolyte values were reported as TEAEs.

Hematology

Hematology parameters measured in the Phase 1 studies included hematocrit, hemoglobin, platelets, red blood cell count, total white blood cell count, and differential white blood cell count.

Study B101: No clinically meaningful trends in hematologic parameters were seen within or across dose groups. One ALKS 9072N subject each had a PCS decreased hematocrit value (≤ 37% and a three-point decrease from baseline) and a PCS increased leukocyte value (≥ 16.0 x $10^3/\mu/L$). Neither event was reported as a TEAE.

Study B102: There were no clinically meaningful trends observed for hematology parameters within or across treatment groups. The percentages of subjects with PCS hematology parameters were < 1% for eosinophils, 4.7% for hematocrit (females), 2.6% for hematocrit (males), 1.3% for neutrophils, and 1.9% for leukocytes, with 2.6% of subjects receiving ALKS 9072N initiation and 1.3% of subjects receiving oral initiation demonstrating elevated leukocyte counts. The only hematology-related TEAEs were for anemia, which occurred in one subject receiving the ALKS 9072N initiation regimen and one subject receiving the oral initiation regimen. Anemia was considered study drug related for the ALKS 9072N-treated subject, but did not result in study discontinuation.

Study B103: There were no clinically meaningful trends observed for hematology parameters. Three subjects, all in the gluteal group, had post-baseline PCS hematology values, including decreased hematocrit in one subject and decreased neutrophils in two subjects. One subject had decreased neutrophil count reported as a TEAE. The event was assessed as moderate in severity and study drug related.

Prolactin

Study B101: No clinically meaningful trends in prolactin were seen within or across dose groups. 9.7% (3/31) of ALKS 9072N-treated subjects and 25.0% (3/12) of placebo-treated subjects had a PCS prolactin value (> ULN). No dose relationship was apparent across dose groups. No subject had a PCS prolactin value reported as a TEAE.

Study B102: There were no clinically meaningful trends for prolactin values. PCS prolactin levels were noted in 3.3% of subjects receiving the ALKS 9072N initiation regimen and in 1.5% of subjects who received the oral initiation regimen. No TEAEs related to prolactin levels were reported.

Study B103: There were no clinically meaningful trends for prolactin values. Three subjects had a PCS prolactin value recorded. No TEAEs related to prolactin levels were reported.

8.4.7. Vital Signs

Blood pressure and Heart Rate

Study B101: No clinically meaningful trends observed within or across dose groups. No subject had a PCS vital sign abnormality during the study. No ALKS 9072N-treated subject had a vital sign abnormality reported as a TEAE during the study.

Study B102: A low frequency of PCS vital sign values was seen during the study, as follows: decreased systolic blood pressure, 0.6%; increased systolic blood pressure, 1.9%; decreased diastolic blood pressure, 1.2%; increased diastolic blood pressure, 0.6%; decreased heart rate, 1.9%; increased heart rate, 1.2%. One case of PCS decreased diastolic blood pressure occurred in a subject receiving the oral initiation regimen. All other PCS vital sign values occurred in subjects receiving the ALKS 9072N initiation regimen. However, no clear trend is discernible, due to the low PCS event frequencies, small study size, and similar frequencies of both low and high PCS values. A TEAE of increased blood pressure was reported for one subject who received the ALKS 9072N initiation regimen and four subjects who received the oral initiation regimen. None of these TEAEs resulted in study discontinuation.

Study B103: There were no clinically meaningful trends observed for changes from baseline in vital sign parameters. Two subjects, both of whom had a history of hypertension, had a PCS elevated blood pressure at a single time point during the study.

Body Weight and Body Mass Index

Reviewer Comment: Weight increases were noted to different degrees in each of the Phase 1 studies. However, this does not indicate a new safety finding, as weight gain is a known adverse effect for all atypical antipsychotic medications.

Study B101: PCS weight increases were reported for 14.6% (6/41) of ALKS 9072N-treated patients at 7.1% (1/14) of placebo-treated subjects. One ALKS 9072N-treated patient had a PCS weight decrease. Three subjects at the 662 mg dose level and three subjects at the 882 mg dose level had PCS weight increases. Two ALKS 9072N-treated subjects, both at the 221 mg dose level and neither of whom had a PCS weight increase, had weight increase reported as a TEAE. The small study size and difference in size between the ALKS 9072N group and the placebo group prevents the discernment of any clinically meaningful patterns in weight changes for this study.

Study B102: The number of subjects with a weight increase $\geq$ 7% from baseline was comparable between the two initiation regimen groups: 26.9% in the group receiving the ALKS 9072N initiation regimen and 22.5% in the group receiving the oral initiation regimen. Six

subjects (7.5%) receiving the ALKS 9072N initiation regimen and two subjects (2.5%) receiving the oral initiation regimen experienced a PCS weight increase and had increased weight reported as a TEAE.

Study B103: A higher percentage of subjects in the deltoid group (30.4%) had PCS weight increases compared with the gluteal group (12.5%). One subject in each treatment group had PCS decreases in body weight from baseline, representing 4.3% of the deltoid group and 4.2% of the gluteal group. Body weight increase was reported as a TEAE in two subjects, both in the deltoid group. No subject had weight decrease reported as a TEAE. The small study size prevents the discernment of any clinically meaningful patterns in weight changes for this study.

8.4.8. Electrocardiograms (ECGs)

ECG parameters measured during the Phase 1 studies included QRS, PR, RR, QT, QTcB, and QTcF intervals. No clinically meaningful trends were observed for ECG parameters among the ALKS 9072N-treated subjects. No apparent dose relationship was noted across the range of ALKS 9072N doses from 221 mg to 882 mg. No meaningful difference from baseline in ECG parameters was noted between the ALKS 9072N initiation regimen and the oral initiation regimen, or between gluteal vs deltoid ALKS 9072N administration. QTcB and QTcF intervals will be discussed in Section 8.4.9, QT.

8.4.9. QT

Study B101: The proportions of ALKS 9072N-treated and placebo-treated subjects with PCS QTcF and QTcB values revealed no clear differences between drug treatment and placebo, and no dose relationship across the ALKS 9072N-treated groups. A TEAE of QT prolongation > 500 msec was reported for one subject and this event was assessed by the Investigator as study-drug related. Percentages of subjects with PCS QTc abnormalities are shown in Table 19.

Table 19. Subjects with Abnormal QTcF and QTcB Values: Study B101

Category	Placebo n/N (%)	ALKS 9072N Treatment Group			
		221 mg n/N (%)	441 mg n/N (%)	662 mg n/N (%)	882 mg n/N (%)
QTcF (msec)					
> 450 to ≤ 480	1/14 (7.1)	0/ 4 (0.0)	1/13 (7.7)	1/12 (8.3)	1/12 (8.3)
> 480 to ≤ 500	0/14 (0.0)	0/4 (0.0)	0/13 (0.0)	0/12 (0.0)	0/12 (0.0)
> 500	0/14 (0.0)	0/4 (0.0)	1/13 (7.7)	0/12 (0.0)	0/12 (0.0)
change from baseline > 30 to ≤ 60	3/14 (21.4)	0/4 (0.0)	4/13 (30.8)	0/12 (0.0)	0/12 (0.0)

change from baseline > 60	0/14 (0.0)	0/4 (0.0)	1/13 (7.7)	0/12 (0.0)	1/12 (8.3)
QTcB (msec)					
> 450 to ≤ 480	3/10 (30.0)	2/4 (50.0)	2/13 (15.4)	3/12 (25.0)	3/12 (25.0)
> 480 to ≤ 500	0/10 (0.0)	0/4 (0.0)	0/13 (0.0)	0/12 (0.0)	1/12 (8.3)
> 500	0/10 (0.0)	0/4 (0.0)	1/13 (7.7)	0/12 (0.0)	0/12 (0.0)
change from baseline > 30 to ≤ 60	2/10 (20.0)	0/4 (0.0)	1/13 (7.7)	4/12 (33.3)	3/12 (25.0)
change from baseline > 60	0/10 (0.0)	0/4 (0.0)	3/13 (23.1)	0/12 (0.0)	1/12 (8.3)

Source: NDA-209830 Summary of Clinical Safety, page 66-67, Table 29.

Study B102: The proportions of subjects with PCS ECG abnormalities showed no clear differences between subjects who received the ALKS 9072N initiation regimen and those who received the oral initiation regimen. No subject experiences QTc prolongation > 500 msec. Percentages of subjects with PCS QTc abnormalities are shown in Table 20.

Table 20. Subjects with Abnormal QTcF and QTcB Values: Study B102

	Treatment Group					
Category	**ALKS 9072N Initiation + AL 441 mg (N-39) n/N (%)**	**ALKS 9072N Initiation + AL 882 mg (N=41) n/N (%)**	**Total ALKS 9072N Initiation (N=80) n/N (%)**	**Oral Initiation + AL 441 mg (N=40) n/N (%)**	**Oral Initiation + AL 882 mg (N=41) n/N (%)**	**Total Oral Initiation (N=80) n/N (%)**
QTcF (msec)						
> 450 to ≤ 480	2/38 (5.3)	2/41 (4.9)	4/79 (5.1)	1/40 (2.5)	2/40 (5.0)	3/80 (3.8)
> 480 to ≤ 500	0/38	0/41	0/79	0/40	0/40	0/80
> 500	0/38	0/41	0/79	0/40	0/40	0/80
change from baseline > 30 to ≤ 60	5/38 (13.2)	5/41 (12.2)	10/79 (12.7)	7/40 (17.5)	2/40 (5.0)	9/80 (11.3)
change from baseline > 60	1/38 (2.6)	0/41	1/79 (1.3)	0/40	0/40	0/80

QTcB (msec)						
> 450 to ≤ 480	10/36 (27.8)	9/38 (23.7)	19/74 (25.7)	8/37 (21.6)	7/37 (18.9)	15/74 (20.3)
> 480 to ≤ 500	0/36	1/38 (2.6)	1/74 (1.4)	3/37 (8.1)	1/37 (2.7)	4/74 (5.4)
> 500	0/36	0/38	0/74	0/37	0/37	0/74
change from baseline > 30 to ≤ 60	9/36 (25.0)	9/38 (23.7)	18/74 (24.3)	12/37 (32.4)	11/37 (29.7)	23/74 (31.1)
change from baseline > 60	4/36 (11.1)	1/38 (2.6)	5/74 (6.8)	2/37 (5.4)	0/37	2/74 (2.7)

Source: NDA-209830 Summary of Clinical Safety, page 68, Table 30.

Study B103: No subjects had a QTcF > 500 msec or a change from baseline > 60 msec. One subject each in the gluteal group and the deltoid group had QTcF > 450 and ≤ 480 msec. Two subjects in the gluteal group had QTcF increased from baseline of > 30 to ≤ 60 msec. No ECG abnormalities were reported as TEAEs in this study.

8.4.10. Immunogenicity

Immunogenicity testing was not performed in the course of the three Phase 1 studies.

8.5. Analysis of Submission-Specific Safety Issues

The submission-specific safety issues reviewed were injection site reactions, assessment for abnormal movements, and assessment for suicidal ideation and behavior.

8.5.1. Injection Site Reactions

No clinically meaningful differences in injection site reactions were noted across ALKS 9072N doses, between ALKS 9072N and placebo-treated patients, or between deltoid vs gluteal drug administration.

Study B101: Injection site pain was the most common injection site reaction, reported for 17.1% of ALKS 9072N-treated patients and no placebo-treated patients. One injection site reaction for a subject in the 441 mg group was assessed by the Investigator as moderate in severity; all others were assessed as mild in severity.

Study B102: The most common injection site reaction was pain, reported for 15% of ALKS 9072N-treated patients and 4.9% of placebo-treated patients. 1.2% of ALKS 9072N-treated patients and 1.3% of placebo-treated patients experienced injection site erythema. Injection site pain was similar for the two AL dose groups, reported by 22.8% of patients receiving AL 441 mg (given via deltoid injection) and 18.3% of patients receiving AL 882 mg (given via gluteal injection)

Study B103: Injection site reactions were reported for seven subjects (30.4%) in the deltoid injection group vs. five subjects (20.8%) in the gluteal injection group. All injection site reactions were assessed by the Investigator as mild or moderate in severity.

8.5.2. Abnormal Movement Scales

Movement disorders were assessed during the Phase 1 studies using three clinician-administered scales: the BARS, SAS, and AIMS. Overall, the incident of treatment-emergent movement disorders was low and slightly higher for ALKS 9072N-treated subjects (4.2%) than for placebo-treated subjects (2.1%).

Study B101: No subject in the study had a treatment-emergent movement disorder. 7.3% of ALKS 9072N-treated subjects experienced akathisia, compared to 0% of placebo-treated subjects.

Study B102: The incidence of treatment-emergent extrapyramidal symptoms, as measured by the SAS, was 2.5% for subjects receiving the ALKS 9072N initiation regimen vs. 0% for subjects receiving the oral initiation regimen. The incidence of treatment-emergent akathisia, as measured by the BARS, was 3.8% for the ALKS 9072N initiation regimen and 1.2% for the oral initiation regimen. No subject experienced treatment-emergent symptoms of dyskinesia, as assessed using the AIMS.

Study B103: One subject in the gluteal group experienced treatment-emergent extrapyramidal symptoms, with a SAS total score > 3. No subject had treatment-emergent akathisia as assessed by the BARS, or treatment-emergent dyskinesia as assessed by the AIMS.

8.5.3. Columbia-Suicide Severity Rating Scale

No ALKS 9072N-treated subject had post-baseline suicidal ideation or behavior as assessed by the C-SSRS.

8.6. Safety Analyses by Demographic Subgroups

Safety analysis by demographic subgroups was not performed.

8.7. Specific Safety Studies/Clinical Trials

The application does not include data from safety studies or clinical trials other than the three Phase 1 studies B101, B102, and B103.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No new human carcinogenicity studies were submitted with this NDA.

8.8.2. Human Reproduction and Pregnancy

No new human reproduction/pregnancy data was submitted with this NDA.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled in studies conducted in association with this NDA. The Pediatric Research Equity Act (PREA) requirement for pediatric studies has been waived by the FDA for two reasons: [1] recruitment of a sufficient number of clinical trial subjects diagnosed with schizophrenia in the pediatric age group would be impractical; and [2] current treatment guidelines do not recommend the use of long-term injectable antipsychotic medication for treatment of schizophrenia in the pediatric age group.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No assessments related to these issues were submitted with this NDA.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

[1] Labeling Regarding Pathological Gambling

On May 03, 2016, the FDA submitted a Safety Labeling Change Notification to Alkermes. Review of the medical literature, review of reports in the FDA Adverse Event Reporting Systems (FAERS) database, and regulatory action taken by Health Canada in November 2015, together resulted in recognition of an association between aripiprazole and pathological gambling, as well as

other impulse-control problems. The letter requested the addition of statements in the Warnings and Precautions section and the Patient Counseling Information section to alert prescribers of this potential problem. Alkermes provided a response in NDA-207533 Supplement 003, dated May 23, 2016. The Applicant's response accepted the request for a labeling change. The Applicant has submitted draft labeling for Aristada Initio that includes a warning regarding pathological gambling.

[2] Labeling Regarding Falls

On November 10, 2016, the FDA submitted a Safety Labeling Change Notification to Alkermes, as well as to all companies marketing antipsychotic agents. New information from the research literature and the FAERS database suggests an association between the use of antipsychotics and an increased risk of falls. The letter requests inclusion of the new safety information in labeling for all antipsychotic medications. Alkermes provided a response in NDA-207533 Supplement 006, dated December 9, 2016. The Applicant's response accepted the request for a labeling change. The Applicant has submitted draft labeling for Aristada Initio that includes a warning regarding falls.

[3] Injection Clogging

Sixty-seven cases of needle clogging were reported to the FAERS database between October 5, 2015, and January 5, 2017, through weekly Medication Error Screen Reports related to the approved product Aristada. While the reports did not all give detailed descriptions of the needle clogging incidents, some clinicians noted that they had tapped and shaken the syringe as described in the medication administration guide. Some clinicians reported changing the needle and re-injecting into a different site, while some clinicians had repeat clogging after changing the needle. Although the raw number of needle clogging events was higher with increasing doses, this may reflect the higher utilization of the higher doses in the community. The percentage of needle clogging incidents was similar across doses after accounting for drug utilization.

The Applicant has taken two actions to help reduce the incidence of needle clogs for Aristada. The first is a revision to the Aristada package insert to emphasize the need to depress the needle plunger quickly using a rapid, continuous action. The second is the development of an instructional kit to be used by Alkermes representatives in the course of educating clinicians on the correct injection method. The revisions to the Aristada package insert have also been incorporated into the Aristada Initio package insert.

The Division anticipates that needle clogs may be less of an issue for Aristada Initio than for Aristada, because the particle size for Aristada Initio is smaller than the particle size for the lowest dose strength of Aristada. In addition, the number of injections to be given over a

patient's lifetime will be much lower for Aristada Initio than for Aristada, since Aristada Initio is given only at the time of initiation or re-initiation of treatment with Aristada. Postmarketing surveillance for Aristada Initio will include continued monitoring for the incidence of needle clogs.

8.9.2. Expectations on Safety in the Postmarket Setting

The Applicant will continue pharmacovigilance of needle clogging events. The Division of Pharmacovigilance will continue routine pharmacovigilance monitoring of needle clogging events for all formulations of long-acting injectable aripiprazole lauroxil, including Aristada and Aristada Initio.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues have been raised by other disciplines.

8.10. Integrated Assessment of Safety

The only new safety issue that has emerged since the initial approval of aripiprazole lauroxil is the occurrence of needle clogging events. Needle clogging events have occurred with all dose strengths of Aristada. No needle clogging events were recorded during the three Phase 1 studies of Aristada Initio. This issue will be addressed through continued routine pharmacovigilance.

Due to molecular structure that is identical to that of Aristada, it is anticipated that Aristada Initio will have a risk profile similar to that of Aristada. However, because Aristada Initio is administered only as a single dose during the initiation or re-initiation of treatment, Aristada Initio is unlikely bring the risks typically seen in the course of long-term administration of atypical antipsychotics, such as tardive dyskinesia and metabolic syndrome. This safety review has not identified any safety issues that would preclude the approval of this NDA application.

9. Advisory Committee Meeting and Other External Consultations

The evaluation of the safety data did not reveal particular safety issues that were unexpected for aripiprazole lauroxil. The design and results of the pharmacokinetic bridging study did not raise particular concerns. This application was not presented to an Advisory Committee.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Division has recommended the development of separate labeling for Aristada and Aristada Initio, with each label including only the administration instructions, warnings, and supporting data relevant to that product. At the time of completion of this review, the Division is still working with the Applicant on finalization of the labeling for the two products.

10.2. Nonprescription Drug Labeling

Not relevant to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS has not been implemented or proposed for Aristada Initio.

12. Postmarketing Requirements and Commitments

No post-marketing requirements or commitments have been initiated as a result of this review.

13. Appendices

13.1. References

No literature review was conducted for this NDA supplement review.

13.2. Financial Disclosure

(b) (6) was a sub-investigator on Study ALK9072-B102, at Clinical Study Site (b) (6) consulted and spoke on behalf of Alkermes in regards to the approved product Aristada, concomitantly with his duties as a sub-investigator on ALK9072-B102. In addition, (b) (6) consulted for Alkermes regarding a Phase III program for the ALKS 3831 (oral samidorphan + olanzapine) program. The Financial Disclosure Statement submitted by the Sponsor indicates that the total income received by (b) (6) was likely greater than $25,000.

(b) (6) became an employee of Alkermes on June 1, 2016, after relinquishing his responsibilities at Site (b) (6) ALK9072-B102 ran from October 27, 2015 to July 26, 2016. The Sponsor states that potential bias resulting from (b) (6) participation in the studies was mitigated through study designs including randomization and blinding.

The disclosed financial information does not affect the approvability of the application. Financial disclosures for (b) (6) are attached below

Covered Clinical Study (Name and/or Number): ALK9072-B102

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 195		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

DAVID H MILLIS
06/29/2018

JAVIER A MUNIZ
06/29/2018