Safety and Tolerability of Initiating Aripiprazole Lauroxil in Subjects with Schizophrenia who are Inadequately Treated with Paliperidone Palmitate or Risperidone Long Acting Injection

Unique Protocol ID:	ALK9072-A401
NCT Number:	NCT02634320
Date of Statistical Analysis Plan:	18 July 2017

STATISTICAL ANALYSIS PLAN

PHASE 4

ALK9072-A401

Study Title:	Safety and Tolerability of Initiating Aripiprazole Lauroxil in Subjects with Schizophrenia who are Inadequately Treated with Paliperidone Palmitate or Risperidone Long Acting Injection
Document Status:	Final
Version:	1.0
Document Date:	July 18, 2017
Based on:	Study Protocol Amendment 1 (dated 07 September 2016)
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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ABBREVIATIONS

The following abbreviations are used in this statistical analysis plan.

Table 1: List of Abbreviations

Abbreviation or term	Explanation
AE	adverse event
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
BAS	Burden Assessment Scale
BIS	Birchwood Insight Scale
BPRS	Brief Psychiatric Rating Scale
CarerQOL-7D	Caregiver Quality of Life – Burden Dimensions
CGI-S	Clinical Global Impressions-Severity
CPK	creatine phosphokinase
CSA	Clinical Study Agreement
CSFQ-14	Changes in Sexual Functioning Questionnaire Short Form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ESRS-A	Extrapyramidal Symptom Rating Scale - Abbreviated
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGP	gamma-glutamyl transferase
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation or term	Explanation
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
ISR	injection site reaction
LAI	long acting injectable antipsychotic
LDH	lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
M.I.N.I.	Mini International Neuropsychiatric Interview
MSQ	Medication Satisfaction Questionnaire
NSA-16	Negative Symptom Assessment-16
NY-AACENT	New York Assessment of Adverse Cognitive Effects of Neuropsychiatric Treatment
PK	pharmacokinetics
PSP	Personal and Social Performance
QLS	Quality of Life Scale
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TSR-6	Sixth edition of the Treatment Services Review
UKU	Udvalg for Kliniske Undersøgelser
ULN	upper limit of normal
VAS	Visual Analog Scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data presentation to be used for analyzing and reporting safety, tolerability, and efficacy data for study ALK9072-A401. This document has been prepared based on Alkermes ALK9072-A401 Study Protocol Amendment 1 (dated 07 September 2016) [1].

1.1. Study Objectives

1.1.1. Primary Objectives

To evaluate the safety, tolerability, and efficacy of aripiprazole lauroxil in subjects with schizophrenia who are inadequately treated with paliperidone palmitate or risperidone long acting injection (LAI).

1.1.2. Secondary Objectives

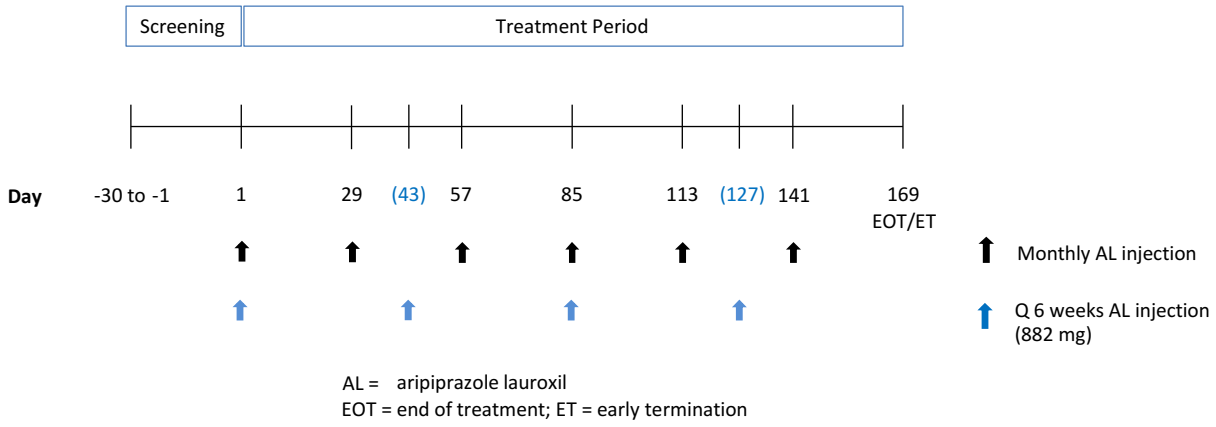
To evaluate quality of life, including daily and social functioning, after treatment with aripiprazole lauroxil.

To characterize the caregiver and healthcare burden.

1.2. Summary of the Study Design and Schedule of Assessments

ALK9072-A401 is a Phase 4, multicenter, open-label study in approximately 50 subjects who are transitioned to aripiprazole lauroxil from long acting injectable risperidone or paliperidone palmitate. In total, subjects will participate for approximately 7 months, including a screening period of up to 30 days, and will be administered 4 to 6 doses of IM aripiprazole lauroxil (Figure 1). Dosing may occur in monthly (441 mg, 662 mg, or 882 mg) or 6-week (882 mg only) intervals. The dose and frequency of dosing will be at the discretion of the investigator, based on the subject's history, dose selected, and on dosing instructions.

Figure 1: Study Design (ALK9072-A401)



Potential subjects will be evaluated for eligibility according to the inclusion and exclusion criteria at a screening visit and again pre-dose on Day 1. The first dose of aripiprazole lauroxil will be administered on Day 1. Subjects will receive their first dose of aripiprazole lauroxil no

earlier than one week and not later than six weeks following their previous injection of paliperidone palmitate or risperidone. The cross-tapering from risperidone or paliperidone to aripiprazole lauroxil is facilitated by the gradual disappearance of plasma risperidone/paliperidone while aripiprazole is concomitantly released from the initial IM aripiprazole lauroxil injection.

For subjects who have never taken aripiprazole, two test doses of oral aripiprazole 5 mg will be administered during the screening period. Only subjects who exhibit tolerability to oral aripiprazole (either following test doses or by past experience) are eligible to enroll in the study.

On Day 1, qualified subjects will be administered a single IM injection of aripiprazole lauroxil into the gluteal (441, 662 or 882 mg) or deltoid (441mg) muscle , according to the dosing instructions. Following the first injection, subjects will return to the study site monthly or every 6 weeks (882 mgonly) for IM aripiprazole lauroxil administration and outpatient assessments. Additional outpatient assessments may be scheduled at the discretion of the investigator.

Efficacy will be evaluated based on Clinical Global Impressions-Severity (CGI-S) and Brief Psychiatric Rating Scale (BPRS) responses.

Safety and tolerability will be evaluated based on adverse events (AEs), injection site reactions (ISRs), clinical laboratory data, vital sign data, Columbia Suicide Severity Rating Scale (C-SSRS) responses, and Abbreviated Extrapyramidal Symptom Rating Scale (ESRS-A) scores.

Potential changes in informant-rated cognition, insight, treatment satisfaction, quality of life, daily and social functioning, caregiver and healthcare burden, and psychosocial care needs following a transition to aripiprazole lauroxil will be examined.

The sixth edition of the Treatment Services Review (TSR-6)-Modified for Mental Health survey will also be listed.

2. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

No formal sample size calculations have been performed. The sample size is based on clinical considerations.

3. DATA ANALYSIS

3.1. General Statistical Methodology

Descriptive statistics for continuous variables include n, mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical variables include subject counts and percentages. All data summarized will have a corresponding listing created as well. All data listings, summaries, and statistical analyses will be generated using SAS® version 9.3 or higher.

Baseline is defined as the last non-missing value before study drug administration.

Study days will be numbered relative to the first day of study drug administration. The start of treatment (Day 1) is defined as the date on which a patient takes study drug. Days will be numbered relative to study start (i.e., ..., -2, -1, 1, 2, ...; with day 1 being the start of study drug and day -1 being the day before the start of study drug).

By visit summarization will be tabulated nominally at the visit information was collected. Treatment groups will be categorized into the following 3 groups based on the primary switch reasons:

1. Due to tolerability or metabolic effect
2. Due to suboptimal efficacy in negative symptoms
3. Due to suboptimal efficacy in positive symptoms

3.2. Study Population

3.2.1. Definitions of Analysis Populations (Analysis Sets)

3.2.1.1. Safety Population

The safety population will include all subjects who received at least one aripiprazole lauroxil injection. All analyses will be carried out using the safety population.

3.2.2. Disposition

The number and percentage of subjects enrolled, subjects in the safety population, subjects who completed the study, and subjects who were prematurely terminated from the study will be summarized by treatment group and overall. For subjects who discontinued from the study, the reasons for discontinuation as recorded in the disposition page will also be presented. Percentage will be calculated based on safety population.

3.2.3. Protocol Deviations

All major protocol deviations will be summarized and listed.

3.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height, body mass index [BMI]), will be summarized by treatment group and overall. Categories for missing data will be provided as necessary. Prior antipsychotic medications (risperidone LAI or paliperidone palmitate) and its associated dose level or frequency count at last dose, primary and secondary transition reasons, aripiprazole lauroxil dose at initial injection and last injection, caregiver paid or non-paid will also be summarized by overall subjects.

Medical and psychiatric history will be summarized and listed by treatment group and overall.

3.4. Treatment Adherence Rate and Extent of Exposure

All dosing and exposure information will be included in supportive listings. Cumulative number of injection by treatment group and overall for the safety population will be summarized. The categories of dose change will be also summarized.

3.5. Efficacy Analyses

3.5.1. Clinical Global Impressions-Severity (CGI-S)

The Clinical Global Impressions – Severity (CGI-S) and the change from baseline at each visit will be summarized by treatment group and overall using descriptive statistics. A plot of mean (SE) of CGI-S score over time will be displayed for all subjects. The one-sample T test at the end of treatment period will be conducted to see if the change from baseline is different from zero. The T-test will be only applied to all subjects.

3.5.2. Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (BPRS) total score and the change from baseline at each visit will be summarized by treatment group and overall using descriptive statistics. A plot of mean (SE) of BPRS total score over time will be displayed for all subjects. The one-sample T test at the end of treatment period will be conducted to see if the change from baseline is different from zero. The T-test will be only applied to all subjects. The score of unreported item will be imputed with the average of all other items at the same visit.

3.6. Quality of Life Analyses

3.6.1. Personal and Social Performance Scale (PSP)

Observed values and changes of PSP total score and subscale from baseline values will be summarized by treatment group and overall at each visit using descriptive statistics.

3.6.2. Negative Symptom Assessment-16 (NSA-16)

Global rating and total score of Negative Symptom Assessment-16 (NSA-16) and the changes from baseline will be summarized by treatment group and overall using descriptive statistics.

3.6.3. Quality of Life Scale (QLS)

Each 6 subscale of Quality of Life Scale (QLS), total score of 21-items, and the changes from baseline will be summarized by treatment group and overall using descriptive statistics. The score of unreported item will be imputed with the average of all other items at the same visit.

3.7. Safety and other Analysis

3.7.1. Adverse Events

Summaries will be presented by treatment group and overall.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Treatment-emergent AEs (TEAEs) are defined as AEs that are newly occurring or worsening from the time of the first dose of study drug.

An overview table, including number of subjects with any TEAEs, serious adverse events (SAEs), study drug related TEAEs, TEAE by severity, and AE leading to discontinuation will be summarized.

In addition, the TEAEs will be summarized for the following:

- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by SOC, PT, and severity
- Drug Related TEAEs by System Organ Class and Preferred Term
- SAEs by System Organ Class and Preferred Term
- AEs leading to discontinuation by System Organ Class and Preferred Term

A subject having the same AE (as determined by the coded MedDRA preferred term) more than once will be counted only once in the number and percentage of subjects' calculation for that AE. Similarly, if a subject had more than one AE in a System Organ Class, the subject will be counted only once in the number of subjects with an AE for that System Organ Class. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) recorded for the event will be presented in the AEs by severity table. Treatment-related AEs are defined as those events with a 'Relationship to Study Treatment' recorded on CRF as 'Definitely Related', 'Probably Related' or 'Possibly Related', others will be not related AEs.

Listings for all AEs, SAEs, and AEs leading to discontinuation will be presented.

3.7.2. Prior and Concomitant Medications

Prior medications are defined as medications that started and stopped prior to the first dose of study drug. Concomitant mediations are defined as medications that started after or were ongoing at the time of the first dose of study drug. All medications will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Drug dictionary version March 2016 of medical codes (WHO Drug). All prior and concomitant medications will be summarized and listed.

3.7.3. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional (CN) units. Only scheduled lab parameters will be included in the laboratory results summaries.

Observed values and change from baseline will be summarized by treatment group and overall at each visit for chemistry and hematology parameters. Additionally, the number and percentage of subjects with potentially clinically significant (PCS) results will be presented (and by sex for prolactin). Only subjects with non-PCS values at baseline and PCS at any post-baseline visit will be included in the summary table. All PCS values (including baseline) will be included in supportive listings. For urinalysis, rate of abnormalities will be summarized.

Criteria for PCS are listed in Table 2:

Table 2: Clinical Laboratory Parameters - PCS Criteria

Lab Parameters	Criteria (Conventional units)
Chemistry	
Albumin	< 2.5 g/dL
Alkaline phosphatase(ALK-P)	≥ 3 x ULN
Alanine aminotransferase	≥ 3 x ULN

Lab Parameters	Criteria (Conventional units)
ALT	
Aspartate aminotransferase AST	≥ 3 x ULN
Bilirubin, Total	≥ 2.0 mg/dL
Blood Urea Nitrogen (BUN)	> 30mg/dL
Creatinine Kinase (CK)	> 3 x ULN
Creatinine	≥ 2.0 mg/dL
Creatine phosphokinase (CPK), Total	≥ 3 x ULN
Cholesterol, Total, fasting	≥ 240 mg/dL
Cholesterol, HDL, fasting	≤ 30 mg/dL
Cholesterol, LDL, fasting	≥ 160 mg/dL
Glucose	< 50mg/dL or ≥ 200 mg/dL
Lactic Dehydrogenase (LDH)	> 3 x ULN
Potassium	< 3 mEq/L or > 5.5 mEq/L
Prolactin by gender	> 1 x ULN > 2 x ULN > 3 x ULN
Sodium	< 130 mEq/L or > 150 mEq/L
Triglycerides, fasting	Female ≥120 mg/dL Male ≥ 160 mg/dL
Hematology	
Eosinophils	> 1 x 10^3 /µL
Hematocrit	Female ≤ 32% and 3 point decrease from baseline Male ≤ 37% and 3 point decrease from baseline
WBC	≤ 2.8 x 10^3 /µL or ≥ 16.0 x 10^3 /µL
Neutrophils, absolute	< 1.5 x 10^3 /µL
Platelet count	< 75,100 cells/µL or ≥ 700,000 cells/µL

3.7.4. Vital Signs

Observed values and changes from baseline values will be summarized by treatment group and overall and assessment time point for each vital sign parameter. Additionally, the number and percentage of subjects with potentially clinically significant (PCS) results will be presented.

Criteria for PCS are listed in Table 3.

Table 3: Vital Signs - Clinical Laboratory Parameters - PCS Criteria

Parameter	PCS Criteria
Supine Systolic blood pressure	Low: ≤ 90mm Hg and decrease ≥ 20 mm Hg
	High: ≥180 mm Hg and increase ≥ 20 mm Hg
Supine Diastolic blood pressure	Low: ≤ 50mm Hg and decrease ≥ 15 mm Hg
	High: ≥105 mm Hg and increase ≥ 15 mm Hg
Supine Pulse	Low: ≤ 50 bpm and decrease ≥ 15 bpm
	High: ≥120 bpm and increase ≥ 15 bpm

3.7.5. Body Weight, Waist Circumferences, and Body Mass Index (BMI)

Body weight (kg) and waist circumferences (baseline and change from baseline) will be summarized by treatment group and overall. The number and percentage of subjects with PCS values (≥7% increase or ≥7% decrease at any post-baseline visit will be summarized by treatment group and overall. The PCS increase in weight will also be summarized by baseline BMI category (Underweight [<18.5 kg/m^2], Normal [≥18.5 to <25 kg/m^2], Overweight [≥25 to <30 kg/m^2], and Obese [≥30 kg/m^2]).

3.7.6. Injection Site Reactions

All injection site reactions will be reported as AEs. Injection site reaction AE preferred terms (injection site pain, injection site erythema, injection site swelling, etc.) will be summarized by treatment group and overall.

3.7.7. Columbia Suicide Severity Rating Scale (C-SSRS)

The number and percentage of subjects with suicidal ideation and/or behavior (overall and for each subcategory) as assessed by the C-SSRS scale during the overall treatment period will be summarized by treatment group and overall using descriptive statistics.

3.7.8. Extrapyramidal Symptom Rating Scale – Abbreviated (ESRS-A)

Each subcategory (Parkinsonism, Dystonia, Dyskinesia, Akathisia), and total score of the Abbreviated Extrapyramidal Symptom Rating Scale (ESRS-A) will be summarized by treatment group and overall using descriptive statistics.

3.7.9. Modified Medication Satisfaction Questionnaire (Modified –MSQ)

The proportion of subjects for each category for each question at each visit will be summarized by treatment group and overall .

3.7.10. Sexual Functioning Subscale from UKU Side Effect Rating Scale and CSFQ-14

Observed values and changes of each CSFQ subscale and total score from baseline values will be summarized by gender and overall using descriptive statistics.

The proportion of subjects with each UKU side effect will be summarized by treatment group and overall using descriptive statistics.

3.7.11. Burden Assessment Scale (BAS)

Observed values and changes of BAS total score from baseline values will be summarized by treatment group and overall using descriptive statistics. In addition, the BAS will also be summarized by paid or non-paid caregivers.

3.7.12. Birchwood Insight Scale (BIS)

Observed values and changes of each BIS subscale and total score from baseline values will be summarized by treatment group and overall using descriptive statistics.

3.7.13. Mini International Neuropsychiatric Interview (M.I.N.I.) Module I & J

The proportion of subjects with Mini International Neuropsychiatric Interview (M.I.N.I.) Module I (alcohol use disorder) and Module J (substance use disorder) will be summarized by treatment group and overall.

3.7.14. Other Assessments

Caregiver Quality of Life – Burden Dimensions (CarerQOL–7D) and VAS happiness score, and the changes from baseline will be summarized using descriptive statistics as appropriate by treatment group, as well as by paid or non-paid caregivers.

New York Assessment of Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT) subscales clinician will be summarized for at least one occurrence, each domain. For each domain, the severity, drug related, or functional/role impairment will be summarized. Data from patients and caregiver will be listed only.

Treatment Services Review (TSR-6)-Modified for Mental Health will be listed.

4. INTERIM ANALYSES

Not applicable

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Not applicable

6. DEFINITIONS AND CONVENTIONS FOR HANDLING OF THE DATA

Dataset specifications will be provided in a separate document.

6.1. Analysis Visit Windows

For all analyses for this study, the scheduled visit and/or time point from the CRF (ie, CRF visit) will be used as the analysis visit and/or time point. There would be one valid value of assessment kept for each scheduled analysis visit in summary/analysis statistics.

Unless specified otherwise, measurements collected from unscheduled visits, will not be included in the summary tables, except for PCS analysis, and will be included in the subject listings.

6.2. Safety Data Handling

All efforts should be made to obtain the missing information from the investigator.

6.3. Handling of Partial Dates of Concomitant Medication

Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, medication will be assumed to be ongoing.

7. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

8. MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

Mock-up tables and listings will be provided in a separate document.

9. REFERENCES

1. Alkermes ALK9072-A401 Study Protocol Amendment 1 (dated 07 September 2016)