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STATISTICAL ANALYSIS PLAN

Protocol Title:	A Double-Blind Phase 1b Study to Assess the Interaction Between ADX-629 and Ethanol While Exploring the Safety, Tolerability, and Activity of ADX-629 in Subjects With Elevated Ethanol Levels
Protocol Number:	ADX-629-ET-001
Protocol Version/Date:	V3.0/16 March 2022
Investigational Product:	ADX-629
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Avenue, Suite 320 Lexington, MA 02421 United States
SAP Version/Date:	V2.0/19 May 2022

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
[redacted]	

VERSION HISTORY

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
BAC	Blood alcohol concentration
CI	Confidence interval
CRF	Case report form
CSR	Clinical Study Report
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
HNE	Hydroxynonenal
IL	Interleukin
ITT	Intent-to-Treat
LS	Least squares
MAA	Malondialdehyde-acetaldehyde adduct
MAD	Malondialdehyde
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
PD	Pharmacodynamics
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number ADX-629-ET-001, version 3.0. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to assess the interaction between ADX-629 and ethanol while exploring the safety, tolerability, and activity of ADX-629 in subjects with elevated ethanol levels.

2.2 Study Design

2.2.1 Overview

ADX-629-ET-001 is a Phase 1b, single-center, double-blind, placebo-controlled, randomized, crossover study to assess the interaction between ADX-629 and ethanol while exploring the safety, tolerability, and activity of ADX-629 in subjects with elevated ethanol levels. Approximately 30 subjects are expected to be enrolled in the study.

This study will utilize a 2-sequence, 2-period, 2-way crossover design. Subjects will be randomized to 1 of 2 treatment sequences (AB or BA) on Day 1 of Treatment Period 1.

- Treatment A: 3 oral doses of ADX-629 600 mg (2 × 300 mg) oral tablets; and
- Treatment B: 3 oral doses of matching placebo.

Study procedures will be completed during the following periods:

- A Screening Period (Day -28 to -2);
- Two 3-day inpatient periods (Treatment Periods 1 and 2) (from Check-In through completion of treatment period), each consisting of the following:
    - Check-In: Subjects will be admitted to the study site on the day prior to dosing in each treatment period. Baseline symptom and sign assessments (except for the Clinical Global Impression [CGI] Improvement Scale) will be completed, and subjects will then be housed overnight where they will be required to adhere to a standardized high-fat, high-sucrose diet;
    - Day 1: 1 dose of study drug will be administered at approximately 4:30pm followed by standardized ethanol consumption as outlined in the manual, and 1 dose of study drug will be administered at approximately 7 pm followed by continued standardized ethanol consumption to reach a target blood alcohol concentration (BAC) of 0.14 g/100 mL, measured via breathalyzer. For more details on the breathalyzer measurements, refer to the Study Procedures Manual. Symptom and sign assessments (with the exception of the CGI Improvement Scale) will be evaluated and should be completed as soon as practical after target BAC is reached. Study procedures will be reviewed for randomized subjects, and, based on the emerging data, the standardized ethanol solution and/or

BAC testing methods may be modified as needed to ensure target BAC is reached within a 4-hour window for the remaining subjects; and

- Day 2: 1 dose of study drug will be administered at approximately 8 am, and symptom and sign assessments (including the CGI-Improvement Scale) will be completed at approximately 7 am, 10 am, and 1 pm. Subjects will be discharged from the study site after completion of study procedures (approximately 12 hours after the last dose of study drug). Prior to discharge, vital signs will be measured. Subjects will have to achieve a BAC of 0.00 g/100 mL as measured by a breathalyzer before discharge.

- A follow-up telephone call will occur 3 days (±1 day) after completion of Treatment Period 2.

For subjects who are withdrawn from the study prior to completion, study procedures will be performed at an Early Termination Visit.

There will be a 14-day (±2 days) washout period between the last dose of study drug in Treatment Period 1 and the first dose of study drug in Treatment Period 2. Subjects will need to refrain from drinking alcohol during the washout period.

2.2.2 Randomization and Blinding

Subjects will be randomized to 1 of 2 treatment sequences (AB or BA) on Day 1 of Treatment Period 1.

- Treatment A: 3 oral doses of ADX-629 600 mg (2 × 300 mg) oral tablets; and
- Treatment B: 3 oral doses of matching placebo.

Subjects, Investigators, and study site personnel (including the Sponsor/designee) involved in the administration and assessment of the study drug will be blinded to the subject treatment assignments throughout the study.

2.2.3 Study Drug

All subjects will receive 3 doses of ADX-629 600 mg (2 × 300 mg) oral tablets and 3 doses of matching placebo. The study drug will be administered twice on Day 1, the first dose prior to the commencement of the standardized ethanol consumption, and once on the day following ethanol consumption (Day 2). No dose interruptions or reductions will be permitted.

2.2.4 Sample Size Determination

Approximately 30 subjects are expected to be enrolled in the study. The sample size is not based on statistical considerations and is not formally powered as all endpoints are exploratory in nature.

2.3 Study Endpoints

As this study is not formally powered and there are no adjustments for multiplicity, and since the interaction between ethanol and ADX-629 has not been previously assessed, all efficacy endpoints are exploratory.

2.3.1 Primary Exploratory Efficacy Endpoints

The primary exploratory efficacy endpoints include the following:

- Assessment of symptoms using the Global Impression Visual Analog Scale, Clinical Global Impression (CGI)-Impairment Severity Scale, CGI-Improvement Scale, and the Alcohol Toxicity Symptom Scale;
- Assessment of signs, determined by evaluation of the following:
  - Objective flushing and ocular redness scales (via digital photography); and
  - Proprioception tests (Romberg Test [time of up to 60 seconds], One Leg Stand Test [time of up to 60 seconds], Straight-Line Heel-to-Toe Test [up to 100 steps]).
- Assessment of ADX-629 pharmacodynamic activity, determined by evaluation of the following PD markers 1 hour after the target BAC is achieved and 1 hour after the last dose of study drug on Day 2 of each treatment period:
  - 4-hydroxynonenal (HNE), acetaldehyde, malondialdehyde-acetaldehyde adduct (MAA), and malondialdehyde (MDA) plasma concentrations; and
  - Plasma cytokine concentrations including, but not limited to, interferon gamma, IL-1b, IL-10, IL-12, and IL-17.

2.3.2 Safety Endpoints

The safety endpoints will include:

- AEs;
- Physical examinations;
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation);
- 12-lead electrocardiograms (ECGs);
- BAC;
- Clinical laboratory assessments (including chemistry, hematology, and urinalysis); and
- Lipid panel evaluations.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the CRF.

3.1.3 Definition of Baseline

Baseline for safety assessments is defined as the last measurement prior to the first dose of study drug.

Baseline for efficacy assessments is defined as the last measurement prior to the first dose of study drug for each study period.

3.1.4 Summary Statistics

In general, categorical variables will be summarized by the count and percentage of subjects. Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation, median, minimum, and maximum values.

3.1.5 Handling of Dropouts and Missing Data

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Dates for AEs and concomitant medications will be printed in a format of DDMMMYYYY. In cases of incomplete dates for AE and concomitant medications, no imputation of start/end dates or times will be performed. If the partial AE onset date information does not indicate that the event started prior to or after the treatment, the event will be classified as treatment-emergent.

If a medication date is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a concomitant medication.

3.2 Analysis Populations

3.2.1 Safety Population

The Safety Population is defined as all randomized subjects who receive at least 1 dose of study drug.

3.2.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population is defined as all subjects who have at least 1 dose of study drug and 1 efficacy measurement.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition and Analysis Populations

The number of subjects who are randomized and treated in the study and the number and percentage of subjects who complete the study will be presented. Counts and percentages of subjects who is withdrawn or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized based on all randomized subjects.

Counts and percentage of subjects in each analysis population will be tabulated by treatment sequence and in total. Reasons for exclusion from each analysis will also be summarized.

3.3.2 Protocol Deviations

Counts and percentages of subjects with protocol deviations by deviation category will be summarized by treatment sequence and in total based on the Safety Population.

3.3.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment sequence and in total based on the Safety Population.

3.3.4 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment sequence and in total based on the Safety Population.

3.3.5 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version Mar 2021G B3.

Prior medications are defined as those occurring prior to the date of first dose of study drug. Concomitant medications refer to those on or after first dose of study drug. Prior medications that are ongoing will qualify as concomitant. Medications that were started prior to the first dose of study drug and were ongoing as of the date of first dose of study drug will be considered both prior and concomitant.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment sequence and in total based on the Safety Population.

3.3.6 Study Drug Exposure and Compliance

Study drug exposure will be summarized by the total number of tablets taken based on the Safety Population. Compliance (%) will be calculated based on (the total number of tablets taken/expected number of tablets taken) *100 per dosing.

Subjects who take 100% of study drug per protocol in accordance with their treatment will be considered treatment-compliant.

3.4 Efficacy Assessment

Efficacy assessment will be summarized on the ITT Population.

The primary exploratory efficacy endpoints will include the following:

Assessment of symptoms

- Global Impression Visual Analog Scale
- Clinical Global Impression (CGI)-Impairment Severity Scale

- CGI-Improvement Scale
- Alcohol Toxicity Symptom Scale (thirsty or dehydrated, more tired than usual, headache, nausea, vomiting, weak, difficulty concentrating, sensitive to light and sound, sweating, anxious, depressed, trembling or shaking)

Assessment of signs

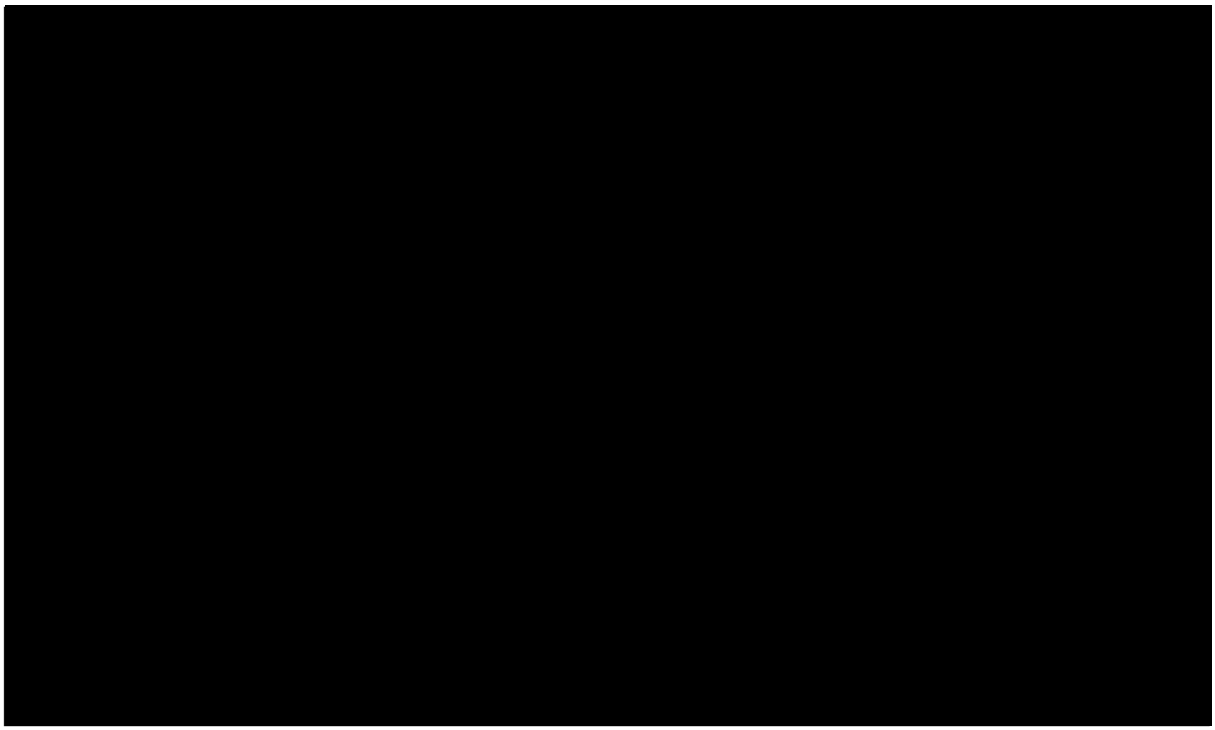
- Objective flushing and ocular redness scales (via digital photography)
- Proprioception tests (Romberg Test [time of up to 60 seconds], One Leg Stand Test [time of up to 60 seconds], Straight-Line Heel-to-Toe Test [up to 100 steps]).

Assessment of ADX-629 pharmacodynamic activity

- PD markers: HNE, acetaldehyde, malondialdehyde-acetaldehyde adduct (MAA), and MDA plasma concentrations;
- Plasma cytokine concentrations including, but not limited to, interferon gamma, IL-1b, IL-10, IL-12, and IL-17

Factors:

- Timepoint
- Baseline
- BAC
- Number of bodyweight-standardized drinks consumed
- Emesis volume
- Emesis 8-12 hours after first drink (binary)



3.5 Safety Assessment

Safety data will be summarized by treatment sequence and in total based on the Safety Population.

3.5.1 Adverse Events (AEs)

All AEs will be coded to system organ class and preferred term using MedDRA version 24.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any AEs
- Any AEs related to COVID-19
- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

Counts and percentages of subjects (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

3.5.2 Clinical Laboratory Tests

Clinical laboratory assessments will include clinical chemistry, hematology, and urinalysis.

Continuous laboratory variables will be summarized in terms of observed values and the change from Baseline at each visit. Categorical laboratory variables will be summarized at each visit with counts and percentages of subjects.

A blood sample for lipid panel evaluation will be collected after fasting at Screening and on Day 2 of both treatment periods. Observed values and change from Baseline at each scheduled visit will be summarized.

3.5.3 Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation.

Observed values and change from Baseline at each scheduled visit and timepoints will be summarized.

3.5.4 Blood Alcohol Concentration

Ethanol will be administered in a standardized oral solution to reach a target BAC of 0.14 g/100 mL following the first dose of study drug on Day 1.

A confirmatory blood ethanol test will be obtained on Day 1 of both treatment periods after the start of ethanol consumption but prior to the subject's final drink and associated 45-minute breathalyzer test.

All the data collected will be listed.

3.5.5 Electrocardiograms

Each continuous variable - heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), QTcF (msec), RR interval (msec) - will be summarized in terms of observed values and changes from Baseline at each visit.

Overall interpretation (normal/ abnormal and not clinically significant/ abnormal and clinically significant) will be summarized along with the proportion of subjects with abnormal QTcF intervals in the categories below will be provided.

- Absolute QTcF interval >450 msec
- Change from baseline QTcF interval increase >30 msec

All the data collected will be listed.

3.5.6 Physical Examinations

A complete physical examination will be performed at Screening (and the Early Termination Visit, if applicable) and will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.

Counts and percentages of subjects with physical examination abnormalities will be summarized at each visit.

All the data collected will be listed.

3.5.7 Other Safety Assessments

Drug and alcohol screen, SARS-CoV-2 RNA, FSH test, Peth blood test, pregnancy testing, fibroscan, AUDIT test and CAGE questionnaire will be listed.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned for the study.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The statistical analysis plan introduced the following modification to the analyses planned in the protocol:

1. PD Population is defined as all subjects who have at least 1 PD measurement in the protocol section 8.1. The ITT population will be defined as all subjects who have at least 1 dose of study drug and 1 efficacy measurement and will be used for the exploratory efficacy analyses.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: SAS SAMPLE CODE