CLINICAL STUDY PROTOCOL

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

Investigational Product: ADX-629

Protocol Number: ADX-629-ET-001

Sponsor:

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SIGNATURE PAGE

STUDY 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

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Aldeyra Therapeutics, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Aldeyra Therapeutics, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Aldeyra Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

INVESTIGATIONAL PRODUCT: ADX-629

PHASE: 1b

INDICATION: Elevated ethanol levels

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.

POPULATION:

Inclusion Criteria:

Subjects meeting all of the following criteria will be considered eligible for the study:

1. Male or female subjects between the ages of 21 and 65 years, inclusive, at Screening;
2. [redacted]
3. Subjects with the ability to obtain transportation to and from the study site;
4. Subjects with a history of alcohol-related symptoms or negative symptomatology following the consumption of ≤4 alcoholic beverages;

   Note: Alcohol-related symptoms may include any of the following: headache, flushing, fatigue, diarrhea, nausea, dizziness, confusion/disorientation, or nystagmus.
5. [redacted]
6. Subjects who agree to avoid use of prescription or over-the-counter medications, including topicals, herbal supplements, dietary supplements (excluding fish oil), or nutraceuticals within 14 days prior to Screening until the end of the study;

   Note: Subjects must avoid oral contraceptives from within 7 days prior to Screening until the end of the study and immunomodulators (eg, corticosteroids, cytokine inhibitors, and Janus kinase inhibitors) from within 60 days prior to Screening until the end of the study.
7. Subjects (all females of childbearing potential [FCBPs] and males with a female partner of childbearing potential) who agree to use an effective form of contraception (nonhormonal or barrier method) during the study and for 7 days after the last dose of study drug;

Note: An FCBP is defined as any female, regardless of sexual orientation, who has not undergone a hysterectomy, bilateral oophorectomy, salpingectomy, or bilateral tubal ligation or has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months) with a negative follicle-stimulating hormone (FSH) test. An FSH test will be performed at Screening in all naturally postmenopausal women to confirm menopausal status.

Note: Sperm donation is also prohibited during the study and for 90 days after the last dose of study drug.

8. Subjects who are willing to consume the standardized alcohol preparation;
9. [redacted]
10. Subjects who agree to abstain from consumption of non-study alcohol during the study.

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from the study:

1. [redacted]
2. Subjects with abnormal laboratory values of clinical significance, at the discretion of the Investigator, at Screening;

   Note: 1 repeat of laboratory assessments is allowed to confirm abnormal values.
3. [redacted]
4. Subjects with a history of or active:
   - Reactive airway disease;
   - Diabetes;
   - Kidney or bladder stones;
   - Kidney disease (including past or current dialysis requirement);
   - Liver disease;
   - Stomach ulcer;
   - Organ transplant;
   - Gastric bypass; or
   - Any other medical/surgical condition of clinical significance, at the discretion of the Investigator.
5. Subjects with nicotine product use within 14 days prior to Screening until the end of the study;

6. Subjects with any history of or current alcohol or other substance use disorder diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition;
7. Subjects with a positive urine drug screen or breath alcohol test at Screening or Check-In (both treatment periods);
8. [redacted]
9. Subjects who are currently pregnant or lactating or plan to become pregnant during the study;

   Note: A serum pregnancy test will be performed in all FCBPs at Screening and a urine pregnancy test will be performed at Check-In (both treatment periods).
10. Subjects who are positive for HIV antibody, hepatitis C virus antibody, hepatitis B virus surface antigen, or severe acute respiratory syndrome coronavirus-2 RNA;
11. Subjects who have participated in any other investigational study within the past 30 days or within 5 half-lives of the investigational therapy, whichever is longer, at Screening;
12. Subjects currently taking or who cannot abstain from corticosteroids, cytokine inhibitors, Janus kinase inhibitors, and/or nonsteroidal anti-inflammatory drugs; or
13. Subjects currently taking or who cannot abstain from medications that can cause a disulfiram-like reaction (eg, metronidazole) or who have taken such medications within the past 30 days at Screening.

STUDY DESIGN AND DURATION:

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;

    Note: Subjects will be reminded at the beginning of each treatment period that this study is placebo-controlled. The placebo-control reminder text will be read as follows: “You

are participating in a placebo-controlled study, which means that you will not know if you are taking a sugar pill or a drug pill. It is important that you try not to decide whether you have taken a sugar pill or a drug pill. Any questions that you answer about how you are feeling should not be influenced by whether or not you believe you have taken a sugar pill or a drug pill. Please answer questions about how you are feeling as if you had not taken any pill at all."

- Day 1: 1 dose of study drug will be administered at approximately 4:30 pm followed by standardized ethanol consumption as outlined in the manual, and then 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

  Note: Subjects will be observed for safety during the treatment periods by study site personnel who will be present to assist subjects at all times; there will be a minimum requirement of at least 2 study site personnel to assist subjects during their assessments. Safety measures will be in place to prevent falling.

  Note: Ethanol will be administered in a standardized oral solution. For more details on the consumption guidelines, refer to the Study Procedures Manual.

- 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 at least a 14-day 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.

An individual subject's participation in the study is estimated to be approximately 41 days.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Aldeyra Therapeutics, Inc. will supply sufficient quantities of study drug (ADX-629 and matching placebo) to allow for completion of the study. The lot numbers will be recorded in the final Clinical Study Report.

[redacted]

ENDPOINTS:

The study is not formally powered and all endpoints are exploratory in nature.

The primary exploratory efficacy endpoints include the following:

- Assessment of symptoms using the Global Impression Visual Analog Scale, 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 activity, determined by evaluation of the following pharmacodynamic (PD) markers, for both treatment periods, on Day 1 pre-dose, on Day 1 one hour after the target BAC is achieved, and on Day 2 one hour after the last dose of study drug:
  - 4-hydroxynonenal (HNE), acetaldehyde, malondialdehyde-acetaldehyde adduct (MAA), and malondialdehyde (MDA) plasma concentrations; and
  - Plasma cytokine concentrations including, but not limited to, interferon gamma, interleukin (IL)-1b, IL-10, IL-12, and IL-17.

The primary safety endpoint is the safety and tolerability of ADX-629, determined by evaluation of the following:

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

STATISTICAL ANALYSES:

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

The PD Population is defined as all subjects who have at least 1 PD measurement.

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.

In general, the comparison of change from baseline in endpoints over time between the 2 treatment sequences will be assessed by a mixed effect model for repeated measures. The model will include change from baseline as the dependent variable with sequence, period, timepoint, treatment, and the interaction of treatment by timepoint as fixed effects, and baseline as a covariate. [redacted]

Efficacy data will also be listed and summarized descriptively.

Demographic and baseline data will be listed and summarized descriptively.

Safety and tolerability assessments will be listed and summarized descriptively as the observations and, when appropriate, as the change from baseline, and shift tables will be produced.

The statistical analyses to be performed will be further outlined in the Statistical Analysis Plan (SAP). The SAP will supersede the protocol if there are any differences between the 2 documents in the plans for data analysis, and these differences will be noted in the SAP.

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.

SITES: 1 study site in the United States

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADH	Alcohol dehydrogenase
AE	Adverse event
ALDH	Aldehyde dehydrogenase
AUC	Area under the concentration-time curve
BAC	Blood alcohol concentration
BID	Twice daily
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HNE	Hydroxynonenal
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IRB	Institutional Review Board
MAA	Malondialdehyde-acetaldehyde adduct
MDA	Malondialdehyde
NAD^+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide + hydrogen
NASH	Nonalcoholic steatohepatitis
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
RASP	Reactive aldehyde species
RNA	Ribonucleic acid
ROS	Reactive oxygen species

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SUSAR	Suspected unexpected serious adverse reaction
Th	T-helper

1 INTRODUCTION AND BACKGROUND INFORMATION

Aldeyra Therapeutics, Inc. has developed ADX-629, a proprietary new chemical entity for the treatment of systemic immune-mediated and inflammatory diseases that are believed to be caused or exacerbated by elevated concentrations of reactive aldehyde species (RASP). ADX-629 is a small molecule formulated for oral administration that binds rapidly and irreversibly to RASP such as hydroxynonenal (HNE) and malondialdehyde (MDA), thereby preventing RASP-mediated inflammation and other toxicities.

1.1 Background

Ethanol, commonly referred to as alcohol, is a psychoactive substance with dependence-producing properties that has been widely used in many cultures for centuries.[1] The harmful use of alcohol causes large disease, social, and economic burdens in societies. Alcohol consumption is a causal factor in more than 200 disease and injury conditions.[1] Drinking alcohol is associated with a risk of developing health problems such as mental and behavioral disorders, including alcohol dependence; major noncommunicable diseases such as liver cirrhosis; some cancers; and cardiovascular diseases, as well as injuries resulting from violence and road clashes and collisions.[1]

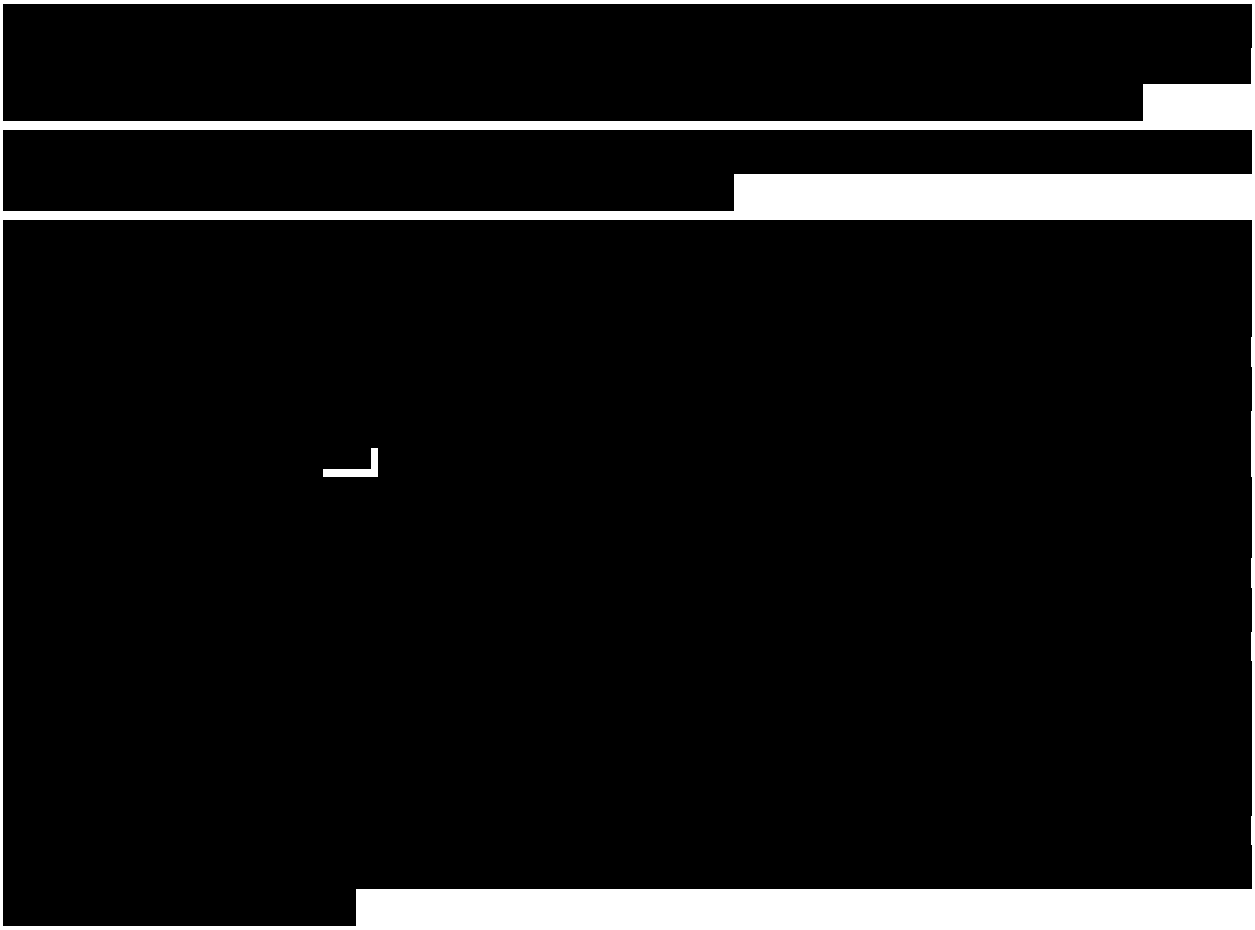
Furthermore, patients with nonalcoholic steatohepatitis (NASH) can have elevated levels of blood alcohol and proteobacteria, which produce alcohol. The understanding of the drug-alcohol interaction could help elucidate the mechanism of action of ADX-629 in NASH patients.

The major enzyme systems responsible for the oxidation of ethanol are the alcohol dehydrogenase (ADH), and to a lesser extent, the cytochrome P450-dependent ethanol-oxidizing systems.[2] These routes of ethanol metabolism result in the formation of acetaldehyde.[2,3] Ethanol is metabolized in the liver by ADH to produce acetaldehyde, which is then further converted to acetate by aldehyde dehydrogenase (ALDH).[2,3] The ADH and ALDH reactions lead to an accumulation of nicotinamide adenine dinucleotide + hydrogen (NADH), and the consequent reduction of the nicotinamide adenine dinucleotide (NAD^+)/NADH ratio has a significant effect on important biochemical pathways, such as glycolysis, the citric acid cycle, fatty acid oxidation, and gluconeogenesis.[3] NADH is mainly reoxidized to NAD^+ by the mitochondrial electron transfer chain.[4,5] During this electron transfer to oxygen, reactive oxygen species (ROS) are formed.[4] A small portion of these ROS can generate toxic effects through lipid peroxidation, enzyme inactivation, DNA mutations, and destruction of cell membranes.[6,7,8] Lipid peroxidation is the most important reaction involved in certain types of alcohol-induced damage, such as liver damage through the formation of RASP.[9,10]

Through covalent binding to amino and thiol groups on receptors and kinases, RASP, such as HNE and MDA, potentiate upstream pro-inflammatory signaling cascades that involve the nuclear factor kappa-light-chain-enhancer of activated B cells, inflammasomes, scavenger receptor A, and other mediators.[11,12,13,14] Elevations in RASP concentrations, particularly HNE and MDA, have been described in a variety of inflammatory diseases.

ADX-629 acts as a RASP-sequestering agent by irreversibly binding to aldehydes and thereby preventing RASP-mediated inflammation and other toxicities. ADX-629 forms these adducts with RASP on a 1:1 stoichiometric basis. Thus, target concentrations of ADX-629 approximate levels of MDA.

1.1.1 Nonclinical Studies of ADX-629



1.1.2 Clinical Studies of ADX-629

The potential benefit of RASP inhibition in immune-mediated and inflammatory diseases has been demonstrated by the first-in-class RASP inhibitor reproxalap (ADX-102), a structural homolog of ADX-629, which has shown to be beneficial in treating ocular inflammation, including dry eye disease and allergic conjunctivitis, across numerous Phase 2 and Phase 3 clinical trials, and is currently in Phase 3 clinical testing.

In addition to nonclinical safety studies, clinical development of ADX-629 in inflammatory disease is supported by safety testing in healthy human volunteers in single and multiple ascending dose (10-day), placebo-controlled Phase 1 trials. Overall, ADX-629 was found to be safe and tolerable at the doses explored, including the maximum dose of 600 mg twice daily (BID). The adverse event (AE) profile of ADX-629 was favorable compared to placebo. A total of 6 (9.4%) subjects who received ADX-629 had treatment-emergent AEs compared to 4 (19.1%) subjects who received placebo. None of the subjects required interruption or discontinuation of study drug.

Although pharmacokinetic (PK) variability was observed, a linear correlation was evident in maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) as dose increased. The half-life was consistent across cohorts and days, with mean values in multiple day exposures ranging between 3.49 to 6.83 hours. Little to no accumulation of the drug was observed

across cohorts. At the top dose (600 mg BID), a C_{max} of 1750 ng/mL (approximately 8.7 μM) and an AUC from time 0 to 12 hours of 6.260 h*ng/mL averaged at Day 1 and Day 10 were consistent with an adequate molar ratio to achieve stoichiometric efficacy against elevated RASP. A decrease in free MDA levels was observed in the plasma of healthy volunteers over 10 days of dosing with ADX-629 600 mg BID that was statistically greater than that of subjects treated with placebo. Following ingestion of a high-fat meal on Day 10 of dosing with 600 mg BID or placebo, levels of free fatty acids were statistically lower and levels of high-density lipoproteins were statistically higher in ADX-629-treated subjects than in placebo-treated subjects, potentially representing additional anti-inflammatory activity of ADX-629.

Additionally, ADX-629 is currently being evaluated in a Phase 2a clinical trial for the treatment of inflammation associated with coronavirus disease 2019 (COVID-19), asthma, and psoriasis.

1.2 Rationale

This Phase 1b, randomized, double-blind study will assess the interaction between ADX-629 and ethanol while exploring the safety, tolerability, and activity of ADX-629 in subjects with elevated ethanol levels.

Scientific evidence suggests that administration of ADX-629 may mitigate the effects of acetaldehyde and other toxic metabolites of ethanol in subjects with acute ethanol toxicity. ADX-629 may mitigate the inflammatory response sufficiently to lower levels of RASP and potentially improve outcomes of subjects.

1.3 Risk/Benefit

The ADX-629-ET-001 study will assess the interaction between ADX-629 and ethanol while exploring the safety, tolerability, and activity of ADX-629 in subjects with elevated ethanol levels.

The safety of the clinical dosing regimen in this study is supported by a Phase 1 study in healthy volunteers and a number of nonclinical toxicology and PK studies in which no serious safety concerns or treatment-related AEs were noted at the proposed dose after 10 days of BID administration.

Refer to the Investigator's Brochure for additional information.

2 STUDY OBJECTIVE

2.1 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.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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;

      Note: Subjects will be reminded at the beginning of each treatment period that this study is placebo-controlled. The placebo-control reminder text will be read as follows: “You are participating in a placebo-controlled study, which means that you will not know if you are taking a sugar pill or a drug pill. It is important that you try not to decide whether you have taken a sugar pill or a drug pill. Any questions that you answer about how you are feeling should not be influenced by whether or not you believe you have taken a sugar pill or a drug pill. Please answer questions about how you are feeling as if you had not taken any pill at all.”
    - Day 1: 1 dose of study drug will be administered at approximately 4:30 pm followed by standardized ethanol consumption as outlined in the manual, and then 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

      Note: Subjects will be observed for safety during the treatment periods by study site personnel who will be present to assist subjects at all times; there will be a minimum

requirement of at least 2 study site personnel to assist subjects during their assessments. Safety measures will be in place to prevent falling.

Note: Ethanol will be administered in a standardized oral solution. For more details on the consumption guidelines, refer to the Study Procedures Manual.

- 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 at least a 14-day 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.

An individual subject's participation in the study is estimated to be approximately 41 days.

3.2 Study Indication

This Phase 1b study will assess the interaction between ADX-629 and ethanol while exploring the safety, tolerability, and activity of ADX-629 in subjects with elevated ethanol levels.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects meeting all of the following criteria will be considered eligible for the study:

1. Male or female subjects between the ages of 21 and 65 years, inclusive, at Screening;
2. [redacted]
3. Subjects with the ability to obtain transportation to and from the study site;
4. Subjects with a history of alcohol-related symptoms or negative symptomatology following the consumption of ≤4 alcoholic beverages;

   Note: Alcohol-related symptoms may include any of the following: headache, flushing, fatigue, diarrhea, nausea, dizziness, confusion/disorientation, or nystagmus.
5. [redacted]
6. Subjects who agree to avoid use of prescription or over-the-counter medications, including topicals, herbal supplements, dietary supplements (excluding fish oil), or nutraceuticals within 14 days prior to Screening until the end of the study;

   Note: Subjects must avoid oral contraceptives from within 7 days prior to Screening until the end of the study and immunomodulators (eg, corticosteroids, cytokine inhibitors, and Janus kinase inhibitors) from within 60 days prior to Screening until the end of the study.
7. Subjects (all females of childbearing potential [FCBPs] and males with a female partner of childbearing potential) who agree to use an effective form of contraception (nonhormonal or barrier method) during the study and for 7 days after the last dose of study drug;

   Note: An FCBP is defined as any female, regardless of sexual orientation, who has not undergone a hysterectomy, bilateral oophorectomy, salpingectomy, or bilateral tubal ligation or has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months) with a negative follicle-stimulating hormone (FSH) test. An FSH test will be performed at Screening in all naturally postmenopausal women to confirm menopausal status.

   Note: Sperm donation is also prohibited during the study and for 90 days after the last dose of study drug.
8. Subjects who are willing to consume the standardized alcohol preparation;
9. [redacted]
10. Subjects who agree to abstain from consumption of non-study alcohol during the study.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. [redacted]
2. Subjects with abnormal laboratory values of clinical significance, at the discretion of the Investigator, at Screening;

   Note: 1 repeat of laboratory assessments is allowed to confirm abnormal values.
3. [redacted]
4. Subjects with a history of or active:
   - Reactive airway disease;
   - Diabetes;
   - Kidney or bladder stones;
   - Kidney disease (including past or current dialysis requirement);
   - Liver disease;
   - Stomach ulcer;
   - Organ transplant;
   - Gastric bypass; or
   - Any other medical/surgical condition of clinical significance, at the discretion of the Investigator.
5. Subjects with nicotine product use within 14 days prior to Screening until the end of the study;
6. Subjects with any history of or current alcohol or other substance use disorder diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition;
7. Subjects with a positive urine drug screen or breath alcohol test at Screening or Check-In (both treatment periods);
8. [redacted]
9. Subjects who are currently pregnant or lactating or plan to become pregnant during the study;

   Note: A serum pregnancy test will be performed in all FCBPs at Screening and a urine pregnancy test will be performed at Check-In (both treatment periods).
10. Subjects who are positive for HIV antibody, hepatitis C virus antibody, hepatitis B virus surface antigen, or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA;

11. Subjects who have participated in any other investigational study within the past 30 days or within 5 half-lives of the investigational therapy, whichever is longer, at Screening;
12. Subjects currently taking or who cannot abstain from corticosteroids, cytokine inhibitors, Janus kinase inhibitors, and/or nonsteroidal anti-inflammatory drugs; or
13. Subjects currently taking or who cannot abstain from medications that can cause a disulfiram-like reaction (eg, metronidazole) or who have taken such medications within the past 30 days at Screening.

4.3 Withdrawal Criteria

Participation of a subject in this study may be discontinued for any of the following reasons:

- Sponsor decision;
- The subject withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
- Any serious AE (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Subject requirement of prohibited concomitant medication;
- Subject failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

Unless a subject withdraws consent for further follow-up, subjects who discontinue study drug (ADX-629 or placebo) will continue in the study for acquisition of safety assessments through the follow-up telephone call. If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

Withdrawn subjects may be replaced at the discretion of the Sponsor.

Additional subjects will be screened as reserve subjects. Reserve subjects who are eligible for enrollment will also be admitted to the study site to ensure enough eligible subjects are available to fill the treatment sequence. Subjects who fulfill the eligibility criteria but are not randomized may either remain at the study site for participation on a subsequent dosing date or they may be discharged and return for a future dosing date. It is not required that the Screening procedures be repeated provided, the subject remains within the screening window. Check-In procedures do not need to be repeated if the subject remains confined to the study site and protocol restrictions are monitored and followed. If the subject is discharged and returns, Check-In procedures will be repeated. Reserve subjects who remain eligible but fall outside of the screening window will be allowed to rescreen.

4.4 Rescreening

Subjects who have met the eligibility criteria, but are out of the screening window before admission to the study site, are allowed to rescreen for the study.

Subjects who have screen failed for any reason are permitted to rescreen once, following consultation with the Medical Monitor.

5 STUDY TREATMENTS

5.1 Treatment Groups

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).

5.2 Rationale for Dosing

[redacted]

5.3 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.

5.4 Breaking the Blind

The Investigator is responsible for the medical care of subjects during the study. In an emergency, when knowledge of the subject's treatment assignment is essential for the clinical management or welfare of the subject, the Investigator can unblind the treatment assignment. It is encouraged that the Investigator contact the Medical Monitor (or designee) before proceeding with the unblinding process. Unblinding should only occur for the subject in question if it is critical for treatment decision making by the Investigator for the well-being of the subject.

Prior to unblinding the subject's treatment assignment, the Investigator should assess the relationship of the AE to study drug (yes or no). If unblinding is warranted, the Investigator must then follow the appropriate procedures to unblind an individual subject's treatment assignment.

Generally, the blind should only be broken for events that are considered to be serious, unexpected, and causally related to the study treatments, or as requested by local regulatory authorities.

If the study blind is broken, the Investigator must detail the date and reason for unblinding in the subject's records. The Investigator must also notify the Sponsor (and Institutional Review Board (IRB) if applicable), if this has not already been done, that the study blind has been broken. If the blind is broken due to an AE, the AE form must be completed and reported to the Sponsor (see Section 8.6).

5.5 Drug Supplies

5.5.1 Formulation and Packaging

Aldeyra Therapeutics, Inc. will supply sufficient quantities of study drug (ADX-629 and matching placebo) to allow for completion of the study. The lot numbers will be recorded in the final Clinical Study Report.

ADX-629 and matching placebo will each be available as tablets for oral administration. Study drug will be packaged in a kit with 2 bottles, each bottle containing thirty 300 mg tablets.

5.5.2 Study Drug Preparation and Dispensing

[redacted]

5.5.3 Study Drug Administration

For both treatment periods, ADX-629 600 mg (2 × 300 mg) oral tablets and matching placebo tablets 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).

Each subject will receive 3 doses of ADX-629. No dose interruptions or reductions will be permitted.

5.5.4 Treatment Compliance

To ensure treatment compliance, all doses will be administered under the supervision of study site personnel. A mouth and hand check will be carried out to ensure the tablets are swallowed.

The Investigator is responsible for maintaining specific subject records to document all study drug dispensed and administered.

5.5.5 Storage and Accountability

The pharmacist (or designee) will acknowledge receipt of all shipments of study drug and maintain an inventory. Study drug must be kept in a locked area with restricted access and stored and handled in accordance with the manufacturer's instructions. The pharmacist (or designee) will also keep accurate records of the quantities of study drug dispensed and used by each subject. The Clinical Research Associate (CRA) will periodically check the supply of study drug held by the pharmacist in a blinded fashion to verify accountability of all study drug used.

At the conclusion of the study, all unused study drug will be returned to the Sponsor unless other arrangements have been approved by the Sponsor. The Sponsor will verify that a final report of study drug accountability to the unit dose level is prepared and maintained in the Investigator clinical study file.

[redacted]

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications

[redacted]

5.6.2 Documentation of Prior and Concomitant Medication Use

Any medications administered 30 days prior to the first dose of study drug through Day 2 of Treatment Period 2 must be recorded.

6 STUDY PROCEDURES

Study staff will always be present to assist and ensure subject safety. There will be a minimum of 2 staff members to assist subjects during assessments, and a security officer will be in the unit supervising subjects while intoxicated. If a subject becomes a danger to themselves or others, they will be isolated and may be physically restrained using soft hospital-approved restraints.

During the study, subjects will stay in private rooms and not be sharing rooms. Some procedures (ie, digital photography) will occur outside their room, and subjects will be accompanied by staff throughout the protocol assessments. Throughout the study, subjects will be instructed to remain in their personal space and continuously supervised by multiple staff.

Staff will always be present to monitor, assist, and ensure subject safety. There will be a minimum of 2 staff members to assist subjects during assessments. Subjects will be sequestered to their private rooms while intoxicated. Staff will be available to escort subjects to the restroom. Each restroom is equipped with an alarm. Arrangements could also be made for a bedside commode and urinals as needed.

Study procedures will follow the Schedule of Procedures (Appendix A).

7 ENDPOINTS

The study is not formally powered as all endpoints are exploratory in nature.

The primary exploratory efficacy endpoints include the following:

- Assessment of symptoms using the Global Impression Visual Analog Scale, 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 activity, determined by evaluation of the following PD markers, for both treatment periods, on Day 1 pre-dose, on Day 1 one hour after the target BAC is achieved, and on Day 2 one hour after the last dose of study drug:
  - HNE, acetaldehyde, malondialdehyde-acetaldehyde adduct (MAA), and MDA plasma concentrations; and
  - Plasma cytokine concentrations including, but not limited to, interferon gamma, IL-1b, IL-10, IL-12, and IL-17.

7.1 Symptom Assessments

7.1.1 Global Impression Visual Analog Scale

For both treatment periods, subjects will be asked to assess the extent of their symptoms at the timepoints indicated in the Schedule of Procedures (Appendix A) utilizing the Global Impression Visual Analog Scale (Appendix C). The extent of symptoms will be assessed on a 100-point scale from no symptoms to maximal symptoms.

7.1.2 Clinical Global Impression-Impairment Severity and -Improvement Scales

For both treatment periods, subjects will be asked to rate their overall severity of impairment and improvement in symptoms at the timepoints indicated in the Schedule of Procedures (Appendix A) utilizing the CGI-Impairment Severity and CGI-Improvement Scales (Appendix C).

Overall severity of impairment will be assessed on a 7-point scale from no impairment to very severe impairment.

For both treatment periods on Day 2, overall improvement of symptoms (relative to symptoms upon waking on Day 2) will be assessed on a 7-point scale from very much worse to very much improved. The CGI-Improvement Scale will only be administered on Day 2 at approximately 7 am, 10 am, and 1 pm.

7.1.3 Alcohol Toxicity Symptom Scale

The subjects will be asked to score their symptoms at the timepoints indicated in the Schedule of Procedures (Appendix A) utilizing the Alcohol Toxicity Symptom Scale (Appendix C). This scale will include assessment of hydration status, fatigue, headache, and nausea including inquiries about vomiting, muscle weakness, ability to concentrate, light and sound sensitivity, sweating,

trembling/shaking, and mood such as anxiety and/or depression. For the 0 to 10 scale in the Alcohol Toxicity score, subjects will be instructed that a "10" implies that the subject would have to call off from work and/or be unable to perform normal activities until recovered, due to that specific symptom. A "5" implies that the subject could perform normal activities, such as work, but with a decreased performance level. A "0" implies that there would be no impact on normal activities at all. For the thirst/dehydration and sweating category, subjects will rank their symptom on a scale of 0 to 10 based on prior, subjective experience.

The vomiting category within the Alcohol Toxicity Symptom Scale is meant to measure the secondary effects of ethanol toxicity (ie, from acetaldehyde) as opposed to effects related to euphoria or central nervous system depression. Vomiting will be evaluated separately with individual AEs. A positive vomiting score will be documented if vomiting has occurred 8 to 12 hours after BAC is met. Vomiting observed 0 to 8 hours after BAC is met will not be included in the toxicity reporting.

7.2 Sign Assessments

7.2.1 Objective Flushing and Ocular Redness

Subjects will be evaluated for signs of objective flushing and ocular redness via digital photography at the timepoints indicated in the Schedule of Procedures (Appendix A).

7.2.2 Proprioception Tests

Subjects will be evaluated for proprioception using the Romberg Test, One Leg Stand Test, and Straight-Line Heel-to-Toe Test at the timepoints indicated in the Schedule of Procedures (Appendix A).

The Romberg Test will be conducted in a standing position with the subject's feet together, arms by the side, and eyes closed. Subjects will be evaluated to determine how long they can stand without movement, (eg, any part of body movement, including eyes opening). Slight swaying is allowed. The length of time the subject is able to stand without movement will be recorded.

The One Leg Stand Test will be conducted in a standing position with one of the subject's legs raised slightly off the ground. The length of time the subject is able to stand in this position will be recorded.

The Straight-Line Heel-to-Toe Test will be conducted with the subject walking heel-to-toe on a demarcated floor that will include a walking line and an "out-of-bounds" area marked 3 to 6 inches outside of the walking line. The number of steps the subject is able to take without stepping "out-of-bounds" will be recorded.

7.3 Pharmacodynamic Assessments

Blood samples for PD markers, such as plasma HNE, plasma acetaldehyde, plasma MAA, plasma MDA, and plasma cytokine concentrations (including, but not limited to, interferon gamma, IL-1b, IL-10, IL-12, and IL-17) will be collected for both treatment periods on Day 1 pre-dose, on Day 1 one hour after the target BAC is achieved, and on Day 2 one hour after the last dose of study drug.

8 SAFETY ASSESSMENTS

The primary safety endpoint is the safety and tolerability of ADX-629, determined by evaluation of the following:

- 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.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. SAEs occurring from the time of informed consent until 30 days following the last administration of study drug will be monitored and documented. Subjects should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at Screening, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring

during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of severity:

The severity of all AEs should be graded according to the latest version of Common Terminology Criteria for Adverse Events (CTCAE). For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; and
- CTCAE Grade 5: Death related to the AE.

Causality assessment:

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration;

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases;

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug;

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug;

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses; and

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug;

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

There are no AEs of special interest defined for this study.

8.1.5 Study Stopping Rules

[redacted]

8.1.6 Special Safety Considerations

Study staff will always be present to assist and ensure subject safety. There will be a minimum of 2 staff members to assist subjects during assessments, and a security officer will be in the unit supervising subjects while intoxicated. If a subject becomes a danger to themselves or others, they will be isolated and may be physically restrained using soft hospital-approved restraints.

During the study, subjects will stay in private rooms and not be sharing rooms. Some procedures (ie, digital photography) will occur outside their room, and subjects will be accompanied by staff throughout the protocol assessments. Throughout the study, subjects will be instructed to remain in their personal space and continuously supervised by multiple staff.

Staff will always be present to monitor, assist, and ensure subject safety. There will be a minimum of 2 staff members to assist subjects during assessments. Subjects will be sequestered to their private rooms while intoxicated. Staff will be available to escort subjects to the restroom. Each restroom is equipped with an alarm. Arrangements could also be made for a bedside commode and urinals as needed.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports:

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug will be monitored and documented and must be reported to [redacted] Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to [redacted] Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted]. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports:

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to [redacted] Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a subject becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug immediately and the subject should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] Clinical Safety within 24 hours of knowledge of the event. [redacted] Clinical Safety will then

provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted] Clinical Safety.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify [redacted] Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to [redacted] Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to study drug.

8.6 Special Situation Reports

Special Situation Reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- Overdose: Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).
- Misuse: Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- Abuse: Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

- Medication error: Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of subjects missing doses of investigational product are not considered reportable as medication errors.
- Product complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situation Report form and faxed/emailed to [redacted] Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation Reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

[redacted]

8.7 Clinical Laboratory Evaluations

Clinical laboratory assessments will include clinical chemistry, hematology, and urinalysis. See Appendix B for a list of clinical laboratory analytes.

Subjects will be tested for HIV antibody, hepatitis C virus antibody, and hepatitis B virus surface antigen at Screening to determine eligibility.

Subjects will present to the study site to have a SARS-CoV-2 RNA test administered on Day -2 (both treatment periods).

A serum pregnancy test will be performed in all FCBPs at Screening and a urine pregnancy test will be performed at Check-In (both treatment periods).

An FSH test will be performed at Screening in all naturally postmenopausal women to confirm menopausal status.

A blood sample for lipid panel evaluation will be collected after fasting (ie, before first meal of the day) at Screening and on Day 2 of both treatment periods.

A phosphatidyl ethanol blood test will be evaluated at Screening to determine eligibility.

BAC will be measured via breathalyzer at the timepoints specified in the Schedule of Procedures (Appendix A). For more details on the breathalyzer measurements, refer to the Study Procedures Manual.

8.8 Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation. Vital signs will be measured after a minimum 5-minute rest on Day 1 before each study drug administration, and blood pressure, heart rate, and oxygen saturation will be measured approximately every 30 minutes after consumption of alcohol until the subject's BAC returns to 0.11 g/100 mL. Vital signs may be measured in the seated or supine position. If there is a clinically important change in blood pressure or body temperature from the previous recording with values outside the normal range, measurements will be repeated to confirm the change.

Prior to discharge on Day 2, vital signs will be measured (both treatment periods).

8.9 Electrocardiograms

All 12-lead ECGs will be performed after the subject has been resting in the supine position for at least 10 minutes prior to each study drug administration on Days 1 and 2 and prior to discharge on Day 2. Repeat ECGs are permitted at the discretion of the Investigator.

8.10 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. Additional body systems may be assessed, per Investigator discretion.

A limited physical examination will be performed at Check-In (both treatment periods) and will consist of a minimum of general appearance, skin, heart, lungs, and abdomen. A symptom-based physical examination will be performed on Day 1 (pre-dose and post-dose of each study drug administration) and Day 2 (pre-dose and post-dose). Additional body systems may be assessed, per Investigator discretion.

Additional physical examinations may be performed, per Investigator discretion.

Height will be collected at Screening only. Body weight will be collected at Screening and Check-In (both treatment periods). Body weight and height will be used to calculate body mass index at Screening and Check-In (body mass index is calculated in Treatment Period 1 only).

9 STATISTICS

9.1 Analysis Populations

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

The PD Population is defined as all subjects who have at least 1 PD measurement.

9.2 Statistical Methods

The statistical analyses to be performed will be further outlined in the Statistical Analysis Plan (SAP). The SAP will supersede the protocol if there are any differences between the 2 documents in the plans for data analysis, and these differences will be noted in the SAP.

The study is not formally powered and all endpoints are exploratory in nature.

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.

9.2.1 Analysis of Efficacy

[redacted]

Efficacy data will also be listed and summarized descriptively.

9.2.2 Analysis of Demographic and Baseline Characteristics

Demographic and baseline data will be listed and summarized descriptively.

9.2.3 Analysis of Safety

Safety and tolerability assessments will be listed and summarized descriptively as the observations and, when appropriate, as the change from baseline, and shift tables will be produced.

9.2.4 Interim Analysis

No interim analysis is planned for the study.

9.2.5 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.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure,

eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

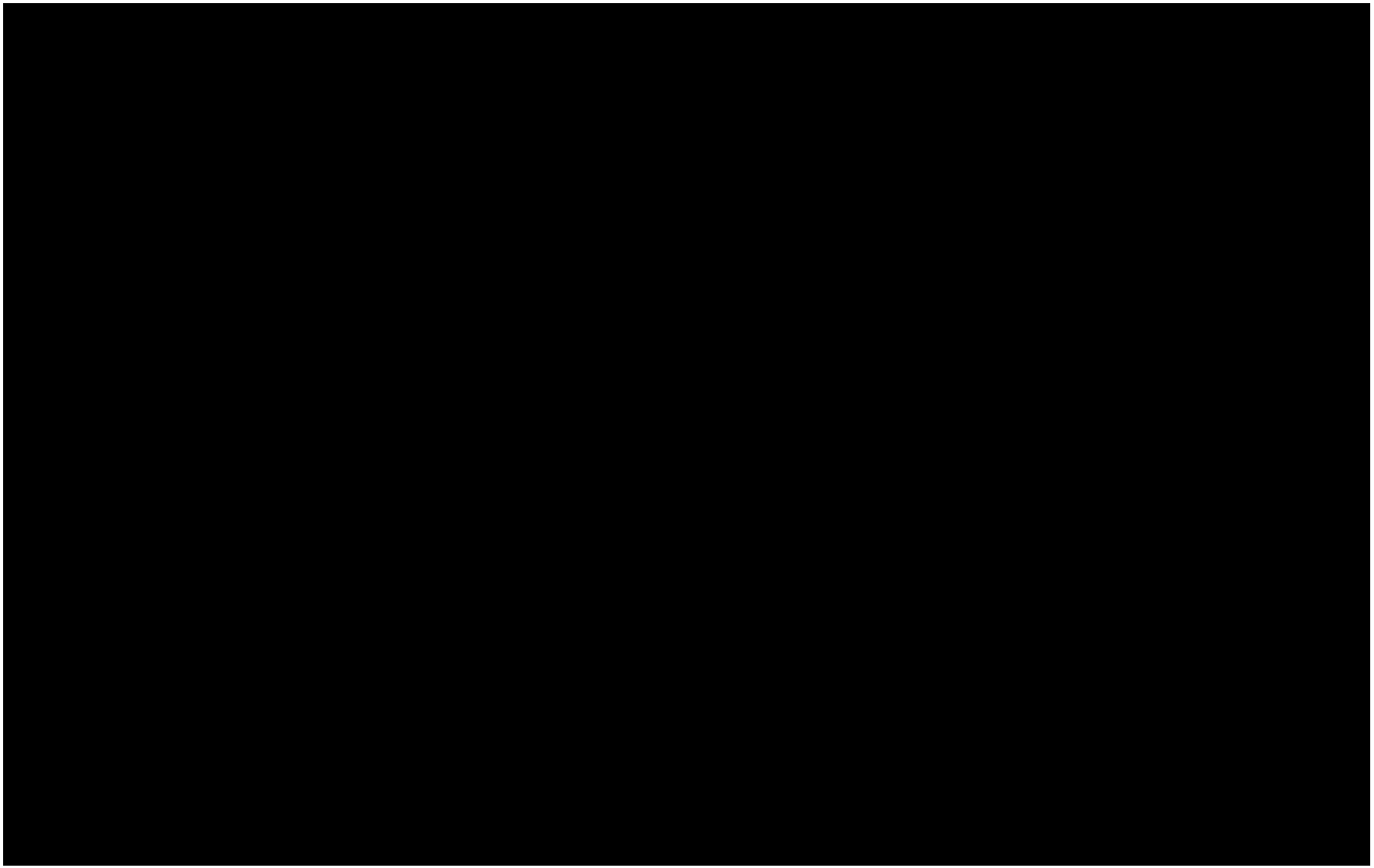
12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

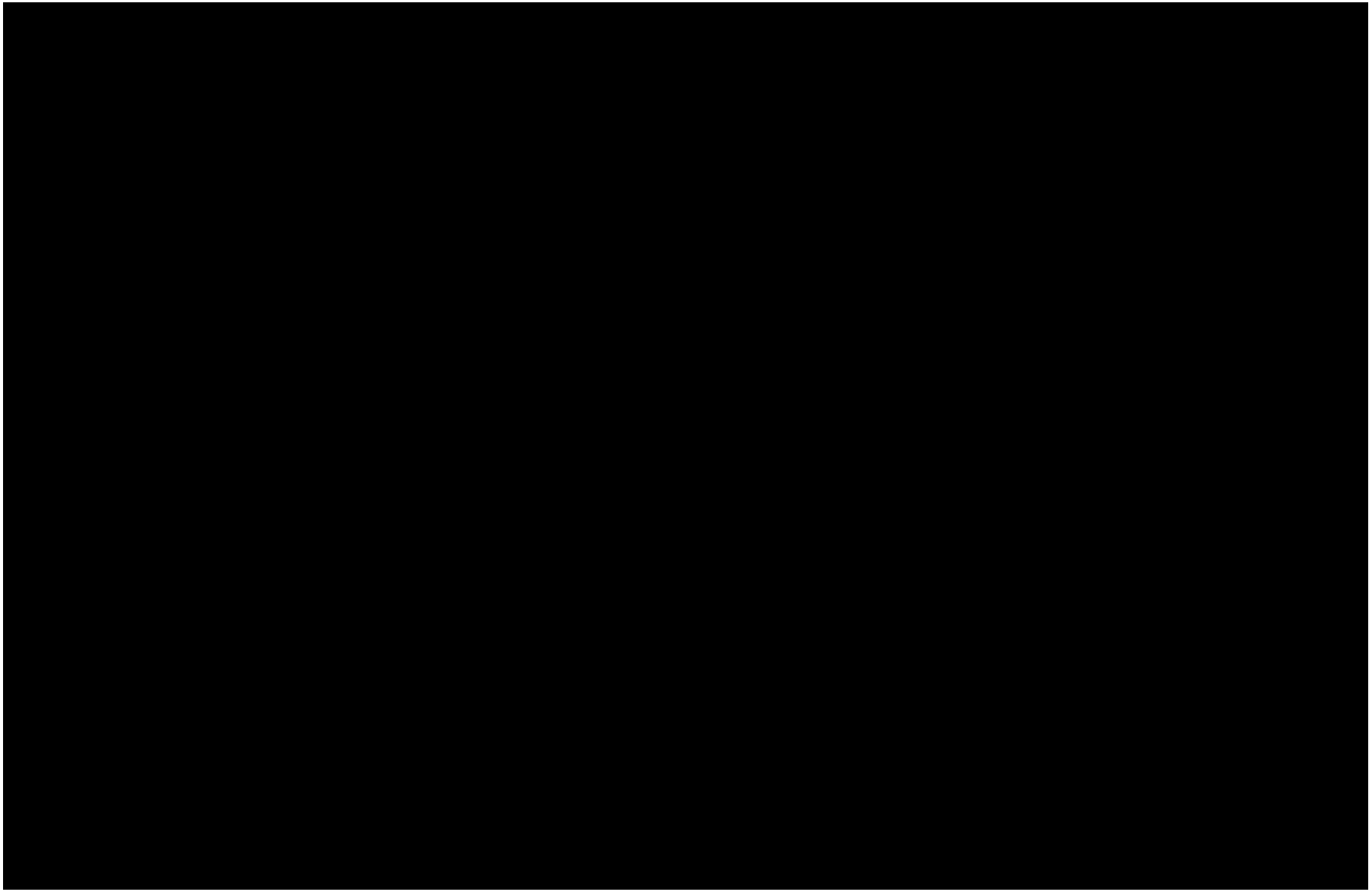
Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13 REFERENCES

APPENDIX A: SCHEDULE OF PROCEDURES



Appendix A: SCHEDULE OF PROCEDURES (Continued)



APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Direct bilirubin
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Indirect bilirubin
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

Endocrinology

Follicle-stimulating hormone (FSH) [1]

1. An FSH test will be performed at Screening in all naturally postmenopausal women to confirm menopausal status.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity

Urobilinogen

1. Microscopy is performed only as needed based on positive dipstick test results.

Pregnancy Tests

Serum human chorionic gonadotropin [1]	Urine human chorionic gonadotropin [2]

1. A serum pregnancy test will be performed in all females of childbearing potential at Screening.
2. A urine pregnancy test will be performed in all females of childbearing potential at Check-In (both treatment periods).

Viral Serology

Hepatitis B virus surface antigen	Hepatitis C virus antibody
Human immunodeficiency virus antibody	Severe acute respiratory syndrome coronavirus-2 RNA

Urine Drug Screen

3,4-methylenedioxy-methamphetamine	Amphetamines
Barbiturates	Benzodiazepines
Cannabinoids	Cocaine
Cotinine	Methadone
Methamphetamine	Opioids
Oxycodone	Phencyclidine
Tricyclic antidepressants	

Lipid Panel

High-density lipoprotein cholesterol	Low-density lipoprotein cholesterol
Total cholesterol	Triglycerides

Other Tests

Blood phosphatidyl ethanol
Blood ethanol

APPENDIX C: SYMPTOM ASSESSMENT SCALES

Alcohol Toxicity Symptom Scale