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STATISTICAL ANALYSIS PLAN

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial to Evaluate the Safety, Tolerability, Efficacy, and Pharmacodynamics of ADX-629 Administered Orally for the Treatment of COVID-19
Protocol Number:	ADX-629-COVID-19-001
[redacted]	
Investigational Product:	ADX-629
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Avenue, Suite 320 Lexington, MA 02421 United States Telephone: 781-761-4904 Fax: 339-674-6495
SAP Version/Date:	1.0 / 18 August 2021

SIGNATURE PAGE

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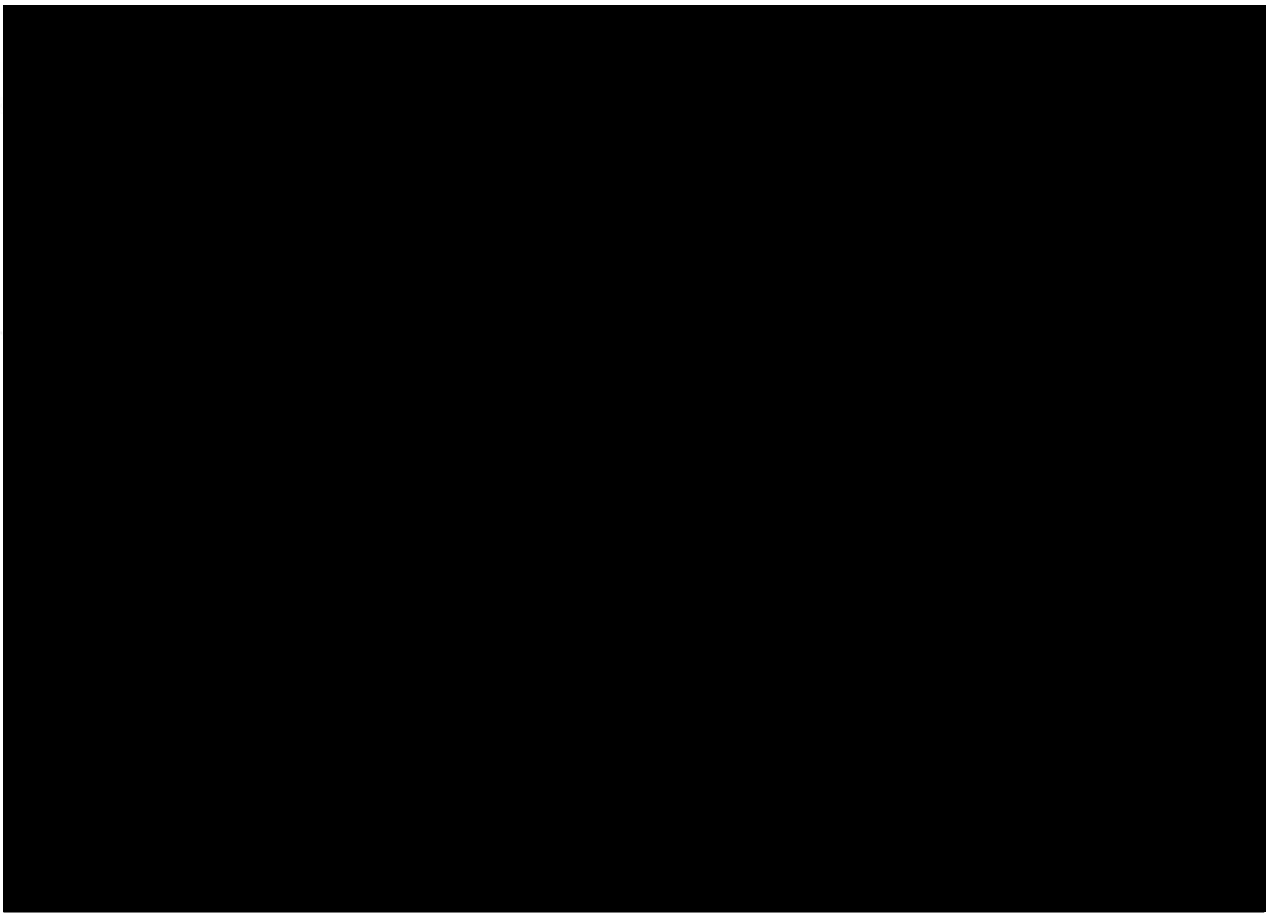
We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature **Date**



VERSION HISTORY

Version	Version Date	Description
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TABLE OF CONTENTS

1 Introduction 7
2 Study Overview 7
2.1 Study Objectives 7
2.1.1 Primary Objective 7
2.1.2 Secondary Objectives 7
2.2 Study Design 7
2.2.1 Overview 7
2.2.2 Randomization and Blinding 8
2.2.3 Study Drug 8
2.2.4 Sample Size Determination 8
3 Statistical Methodology 8
3.1 General Considerations 8
3.1.1 Analysis Day 8
3.1.2 Analysis Visits 8
3.1.3 Definition of Baseline 8
3.1.4 Summary Statistics 9
3.2 Analysis Populations 9
3.2.1 Intent-to-Treat (ITT) Population 9
3.2.2 Per-Protocol (PP) Population 9
3.2.3 Safety Population 9
3.2.4 Pharmacodynamic (PD) Population 9
3.3 Subject Data and Study Conduct 9
3.3.1 Subject Disposition 9
3.3.2 Protocol Deviations 9
3.3.3 Analysis Populations 10
3.3.4 Demographic and Baseline Characteristics 10
3.3.5 Medical History 10
3.3.6 Concomitant Medications and Procedures 10
3.3.7 Study Drug Exposure and Compliance 11
3.4 Efficacy Assessment 11
3.4.1 Key Efficacy Endpoint 11
3.4.2 Other Efficacy Endpoints 12
3.5 Pharmacodynamic (PD) Assessment 13
3.6 Safety Assessment 13
3.6.1 Adverse Events (AEs) 13

3.6.2 Clinical Laboratory Tests 14
3.6.3 Vital Signs 14
3.6.4 Physical Examinations 14
3.6.5 Electrocardiograms (ECG) 14
3.6.6 SARS-CoV-2 Testing 14
4 Data Safety Monitoring Board 15
5 Analysis Timing 15
5.1 Interim Analysis 15
5.2 Pre-Final Analysis 15
5.3 Final Analysis 15
6 Changes from Protocol-Specified Statistical Analyses 15
7 Programming Specifications 15
Appendix A: Schedule of Procedures 16
Appendix B: Clinical Laboratory Analytes 19

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* or twice daily
BMI	Body Mass Index
CRF	Case Report Form
CS	Compound Symmetry
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOT	End of Treatment
ePRO	Electronic Patient-Reported Outcomes
GEE	Generalized Estimating Equation
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model Repeated Measures
NIAID	National Institute of Allergy and Infectious Diseases
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred Term
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RASP	Reactive Aldehyde Species
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SOC	System Organ Class
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-COVID-19-001. 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 of this clinical trial is to evaluate the safety and tolerability of ADX-629, administered orally, in adult subjects with COVID-19 of moderate severity.

2.1.2 Secondary Objectives

The secondary objectives of this clinical trial are the following:

- To evaluate the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale for COVID-19 scores of adult subjects with COVID-19 of moderate severity who were administered ADX-629 orally; and
- To assess the pharmacodynamics (PD) by measuring plasma reactive aldehyde species (RASP) in adult subjects with COVID-19 of moderate severity who were administered ADX-629 orally.

2.2 Study Design

2.2.1 Overview

ADX-629-COVID-19-001 is a Phase 2a, randomized, double-blind, placebo-controlled, clinical trial to evaluate the safety, tolerability, efficacy, and PD of ADX-629, administered orally, in adult subjects with COVID-19 of moderate severity. Approximately 30 subjects will be randomized in a 2:1 ratio (ADX-629 to placebo) to receive either ADX-629 300 mg *bis in die* or twice daily (BID) or placebo BID for up to 28 days.

Treatment will begin on Day 1 following randomization. In addition to ADX-629 or placebo, all subjects will receive standard of care treatment for COVID-19. Treatment may commence whether a subject is hospitalized or is treated as an outpatient at Screening. During the Treatment Period (Days 1 to 28/End of Treatment [EOT]), all subjects will receive study drug (either ADX-629 or placebo) BID. The study drug will continue to be taken on an outpatient basis if a subject is discharged from the hospital prior to Day 28 for hospitalized subjects. If a subject is placed on mechanical ventilation and/or is otherwise unable to ingest an oral tablet, dosing will be stopped. However, the subject will continue to be monitored for efficacy and safety. Dosing of the study drug may resume once the subject is able to safely ingest an oral tablet.

All subjects will also have an assessment using the NIAID ordinal scale score daily on Days 1 to 28/EOT. The NIAID score will be evaluated directly for inpatient subjects and assessed via a subject diary for outpatient subjects through Day 28.

After treatment is completed, subjects will undergo a follow-up visit on Day 35 (±3 days) and a telephone follow-up on Day 60 (±3 days). The purpose of the telephone follow-up is to assess survival status and evaluate for COVID-19 relapse. A telephone follow-up visit may be performed in lieu of the Day 35 follow-up visit if the subject is unable to attend in person.

The schedule of study assessments is described in Appendix A.

2.2.2 Randomization and Blinding

Subjects will be randomized in a 2:1 ratio to receive an oral tablet of either ADX-629 300 mg BID or placebo BID for up to 28 days. Subjects, Investigators, and clinical trial 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 clinical trial.

2.2.3 Study Drug

ADX-629 and the corresponding placebo will each be available as a tablet for oral administration. The study drug will be packaged in a kit with 2 bottles, each bottle containing thirty (30) 300 mg tablets.

ADX-629 and the corresponding placebo will each be administered orally as a tablet, at the discretion of the Investigator, without food, defined as no food for at least 2 hours prior to dosing and at least 1 hour after dosing. Each subject will receive either ADX-629 300 mg BID or placebo BID for up to 28 days. If a subject is temporarily unable to tolerate dosing, a temporary dose interruption of up to 2 days may be permitted, after discussion with the Medical Monitor. No dose reductions will be permitted.

2.2.4 Sample Size Determination

Approximately 30 subjects will be randomized in a 2:1 ratio to 1 of 2 treatment groups: ADX-629 or placebo, both with standard of care treatment for COVID-19. This clinical trial is exploratory in nature and is not formally powered.

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

Nominal visits (i.e., study visits captured on the CRF) will be used for all efficacy and safety analyses.

3.1.3 Definition of Baseline

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

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population is defined as all randomized subjects. The ITT Population will be the primary population for analysis of secondary (efficacy) endpoints.

3.2.2 Per-Protocol (PP) Population

The PP Population is defined as all subjects in the ITT Population who completed the study with no major protocol deviations that may impact the key secondary endpoint. The PP Population will be a secondary population for analysis of the key secondary endpoint.

A list of subjects with major protocol deviations leading to exclusion from the PP Population will be finalized prior to unblinding the randomized treatment assignments.

3.2.3 Safety Population

The Safety Population is defined as all randomized subjects who received at least one dose of study drug. All safety data will be analyzed using the Safety Population. In the event that a subject takes the wrong study drug (i.e., did not take the randomized study drug), the actual treatment received will be used for analysis.

3.2.4 Pharmacodynamic (PD) Population

The PD Population is defined as all subjects who have at least 1 PD measurement after at least one dose of drug.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent), discontinued early during screening (screen failures), and reasons for failed screening will be summarized based on all screened subjects.

Counts and percentages of subjects who were randomized, discontinued early from the treatment, discontinued early from the study, completed the treatment and completed the study will be summarized by treatment and in total based on all randomized subjects. Reasons for early discontinuation will also be summarized.

3.3.2 Protocol Deviations

Medpace Protocol Deviation Plan contains details on the key description and classification of protocol deviations (PDs). CSR-reportable PDs by deviation category will be summarized by treatment group and in total based on all randomized subjects.

All CSR-reportable PDs and COVID-19 related non-reportable PDs will be listed.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Race
- Ethnicity
- Inpatient (yes/no)
- SARS-CoV-2 test result (positive/negative)
- COVID-19 severity categorization
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- SARS-CoV-2 Variant (if available)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for all randomized subjects and each defined analysis population.

3.3.5 Medical History

Medical history will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized subjects.

3.3.6 Concomitant Medications and Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using WHO Drug B3 Global, September 2020. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

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

Data listings will be provided for prior & concomitant medications and concomitant procedures / non-drug therapies.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <1 week (<7 days)
- 1 - <2 weeks (7 - 13 days)
- 2 - <3 weeks (14 – 20 days)
- 3- <4 weeks (21 – 27 days)
- ≥4 weeks (≥28 days)

Percent compliance to the study drug regimen will be calculated as 100 x number of actual tablets taken / number of expected tablets taken. The number of actual tablets taken will be calculated as (# of tablets dispensed - # of tablets returned). The number of tablets expected will be calculated as (date of last visit in Treatment Period [Day 28/EOT] – date of randomization + 1) x 2, i.e., the number of days study drug was expected to be taken x 2 tablets per day. Percent compliance to the study drug regimen will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <80%
- 80-120%
- >120%

All study drug accountability data and study drug administration (inpatient) data will be listed.

3.4 Efficacy Assessment

Efficacy data (i.e., secondary endpoints) will be analyzed by randomized treatment based on the ITT Population. The key efficacy endpoint will also be analyzed based on the PP Population. The trial is exploratory and not formally powered. All assessments will be deemed exploratory.

3.4.1 Key Efficacy Endpoint

The key efficacy endpoint is the NIAID ordinal scale score (Table 1) over Day 1 through Day 28.

Table 1. NIAID 8 Point Ordinal Scale for COVID 19

Numerical Score	Definition
1	Death

2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitation on activities
[redacted]	

NIAID scores change from baseline to Day 28 will be summarized by treatment group (ADX-629 or placebo) using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

[redacted]

All NIAID data will be listed.

3.4.2 Other Efficacy Endpoints

Additional efficacy endpoints include the following:

- Proportion of subjects alive and not mechanically ventilated over Day 1 through Day 28;
- Time to recovery (for hospitalized subjects at Screening), defined as the first day on which the subject has an NIAID score of 6 or larger;
- Time to recovery (for non-hospitalized subjects at Screening), defined as the second consecutive day on which the subject has an improvement in the NIAID ordinal scale by 1 point;
- Proportion of subjects alive and not in the intensive care unit over Day 1 through Day 28;
- Proportion of subjects alive and not in the hospital over Day 1 through Day 28;

- Proportion of subjects alive and not on supplemental oxygen over Day 1 through Day 28;
- Mortality; and
- Time to hospital discharge (for hospitalized subjects), defined as time from first hospital admission to first hospital discharge in the 28 day study period.

The proportions will be presented by treatment group (ADX-629 or placebo). The difference between treatment groups will be analyzed by a Generalized Estimating Equation (GEE) model similar to the MMRM model for the key efficacy endpoint if applicable. If the GEE model does not converge, then the Fisher's exact test will be used.

Time to recovery (censored at Day 28) from randomization and time to hospital discharge will be addressed by Kaplan-Meier analysis, including a comparison between the treatment groups by a log-rank test if applicable.

The mortality rate, calculated as the number of subjects who died by Day 28 divided by the number of subjects randomized, will be summarized by treatment group. The difference between treatment groups will be analyzed by Fisher's exact test if applicable.

3.5 Pharmacodynamic (PD) Assessment

The PD endpoints include the following:

- RASP plasma concentrations; and
- Plasma exploratory biomarker concentrations (e.g., interleukin [IL]-1β, IL-6, IL-10, and tumor necrosis factor alpha).

For each PD parameter, descriptive statistics (n, mean, standard deviation, median, minimum, maximum) will be summarized by treatment group for the PD Population at pre-dose and post-dose of each scheduled visit.

A MMRM analysis similar to that of the key efficacy endpoints will be used for the analysis of PD endpoints as appropriate.

3.6 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Population.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 23.1.
Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of the first dose date.

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

- Any TEAEs (overall and by maximum severity)

- Any study drug related TEAEs
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESEAEs)
- Any TEAEs leading to discontinuation of study drug
- 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.

Listings will be presented for all AEs and hospitalization data.

3.6.2 Clinical Laboratory Tests

All standard blood tests will be analyzed by the local laboratory as specified in the Schedule of Procedures (Appendix A). A list of laboratory tests to be performed is included in Appendix B.

The incidence of abnormalities (as defined by normal ranges) after the first dose of study drug will be summarized with counts and percentages of subjects for each treatment group.

Post-baseline clinically significant lab results will also be summarized with counts and percentages of subjects for each treatment group.

All abnormal lab data will be listed.

3.6.3 Vital Signs

Vital signs will be measured as specified in the Schedule of Procedures (Appendix A). Vital signs will be collected BID, both times prior to dosing with study drug. On Day 1, vital signs will also be collected at 2, 4, 6, and 8 hours post the morning dose. The BID measurements prior to dosing will be averaged prior to summarization.

Vital signs parameters (heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation) will be listed and summarized using descriptive statistics for each treatment group by visit and timepoint. Change from baseline to each scheduled post-dose time point will also be summarized.

3.6.4 Physical Examinations

Physical examination will be performed as specified in the Schedule of Procedures (Appendix A). All physical examination results will be listed.

3.6.5 Electrocardiograms (ECG)

Twelve-lead ECGs will be performed at Screening or Day 1 (pre-dose), on Day 1 at 1 hour and 6 hours post-dose, and on Day 7.

ECG results (heart rate, PR, QRS, QT, QTcF, RR) will be summarized and listed for each treatment group by visit. Change from baseline to each scheduled post-dose time point will also be summarized. ECG overall interpretation will also be listed.

3.6.6 SARS-CoV-2 Testing

SARS-CoV-2 testing may be performed at Screening if needed. All available data will be listed.

4 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will monitor the safety of subjects over the course of the study. The DSMB will meet once or more during the subject enrollment period to examine the unblinded accumulated safety data. Subjects, investigators, site staff and in general all personnel directly involved in the conduct of the study will remain blinded to the subjects' treatment assignment until the completion of the study.

Details related to the DSMB responsibilities, authorities, and procedures will be documented in a DSMB charter which will be finalized prior the first subject being enrolled in the study.

5 ANALYSIS TIMING

5.1 Interim Analysis

No formal interim analysis is planned.

5.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated.

5.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final.

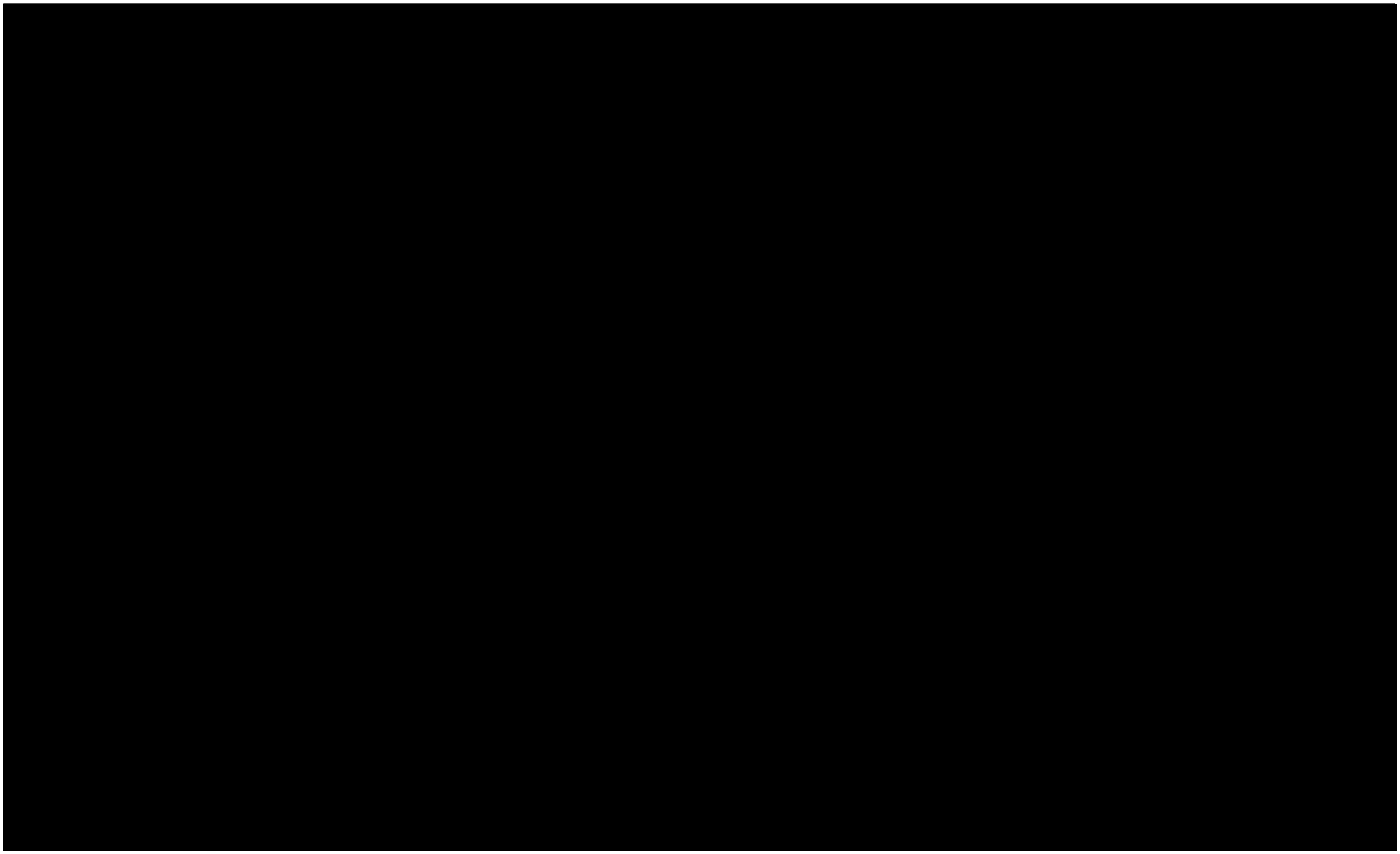
6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Laboratory assessments will be summarized by incidence of abnormalities instead of change from baseline values at each visit.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: SCHEDULE OF PROCEDURES



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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	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

Coagulation Parameters

Activated partial thromboplastin time	Fibrinogen
International normalized ratio	

Endocrinology

Follicle-stimulating hormone (FSH) [1]
Human chorionic gonadotropin (hCG) [2]

1. An FSH test will be performed at Screening in all naturally postmenopausal women to confirm postmenopausal status at Screening.
2. A serum hCG test will be performed in all women of childbearing potential at Screening.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

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

Urinalysis

Albumin	Bilirubin
Blood	Creatinine [1]
Glucose	Ketones
Leukocyte esterase	Microalbumin
Microscopy [2]	Nitrite
pH	Protein [1]
Specific gravity	Urobilinogen

1. Urine protein/creatinine ratio will also be calculated.
2. Microscopy will be performed only as needed based on positive dipstick test results.

Viral Serology

Hepatitis B surface antigen (HBsAg) [1]
Hepatitis C virus (HCV) antibody [1]
Human immunodeficiency virus (HIV) antibody testing [1]

1. HIV antibody, HBsAg, and HCV antibody testing will be performed at Screening, only if status is unknown.

Severe acute respiratory syndrome coronavirus-2 testing

Polymerase chain reaction (PCR), a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antigen test, or another commercial or public health assay, testing for SARS-CoV-2 [1]

1. SARS-CoV-2 testing may be performed at Screening if needed. The subject must have a documented, laboratory-confirmed SARS-CoV-2 infection, as determined by PCR or another commercial or public health assay, and a confirmatory test for SARS-CoV-2 within 2 days (48 hours) of randomization to be included in the clinical trial. A verbal report of infection will not suffice. This will be performed at Screening only if a documented result is unavailable.

Exploratory Biomarkers

D-dimer
Ferritin
Interleukin (IL)-1β
IL-6
IL-10
Reactive aldehyde species [1]
Tumor necrosis factor alpha

1. Reactive aldehyde species will potentially include malondialdehyde and 4-hydroxynonenal.