CLINICAL TRIAL PROTOCOL

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

Investigational Product: ADX-629
Protocol Number: ADX-629-COVID-19-001

Sponsor:
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SIGNATURE PAGE

CLINICAL TRIAL 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

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

Signature Date

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 clinical trial as described. I will conduct this clinical trial in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the clinical trial within the time designated. I will provide copies of this protocol and access to all information furnished by Aldeyra Therapeutics, Inc. to clinical trial personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the clinical trial product and clinical trial 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 clinical trial 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 clinical trial subjects.

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

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

INVESTIGATIONAL PRODUCT: ADX-629

PHASE: 2a

INDICATION: The indication for this clinical trial is the treatment of inflammation associated with coronavirus disease 2019 (COVID-19).

OBJECTIVES:

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 prior to the requirement for mechanical ventilation.

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.

POPULATION:

Inclusion Criteria

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

1. Is a male or female ≥18 years of age at Screening;
2. Is willing and able to sign and date (or has a legally authorized representative willing to sign and date) a written (or electronic) informed consent form or provide equivalent consent per Food and Drug Administration guidelines on COVID-19 clinical trials;
3. Has a documented, laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as determined by polymerase chain reaction, a SARS-CoV-2 antigen test, or another commercial or public health assay, within 3 days (72 hours) of randomization;

4. Has COVID-19 of moderate severity, as defined by the following:
   - Positive testing by standard reverse transcription polymerase chain reaction assay or equivalent testing;
   - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion;
   - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, saturation of oxygen >93% on room air at sea level, or heart rate ≥90 beats per minute; and
   - No clinical signs indicative of severe or critical severity (see Appendix E);
5. [redacted]
6. Is willing to use an effective form of contraception (all women of childbearing potential [WCBP] or men with a female partner of childbearing potential) during the clinical trial and for 90 days after the last dose of study drug.

   Note: A WCBP is defined as any female, regardless of sexual orientation, who has not undergone a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation or has not been naturally postmenopausal for at least 12 consecutive months (i.e., 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 clinical trial and for 3 months after the last dose of study drug.

Exclusion Criteria

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

1. Has an NIAID ordinal scale score <5 (see Appendix C);
2. Is on high-flow oxygen or any form of noninvasive ventilation, excluding continuous positive airway pressure (CPAP) alone for sleep disorders (e.g., obstructive sleep apnea);
3. [redacted]
4. [redacted]
5. Has a history of chronic obstructive pulmonary disease or bronchial asthma requiring continuous treatment and/or intermittent or continuous oxygen within the last 90 days prior to

Screening or has significant infiltrates on chest X-ray (e.g., involving >50% of lung fields) at Screening as determined by the Investigator;

Note: Intermittent use of a β2-agonist inhaler is allowed.

6. Has had any form of mechanical ventilation (invasive or noninvasive, excluding CPAP alone) for structural lung disease, neuromuscular disease, or another condition requiring chronic mechanical ventilation;
7. [redacted]
8. [redacted]
9. [redacted]
10. Has a history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection or has a positive HIV antibody, hepatitis B surface antigen, or hepatitis C virus antibody result at Screening;
11. Has a current or previous severe allergy and/or hypersensitivity to ADX-629 or its excipients;
12. Is pregnant or lactating or plans to become pregnant during the clinical trial;

    Note: A serum human chorionic gonadotropin test will be performed in all WCBP at Screening.
13. Is male and has known hypogonadism and hypospermia;
14. Is currently on another systemic immunomodulatory therapy (e.g., corticosteroid, calcineurin inhibitor, hydroxychloroquine, anti-cytokine therapy, Janus kinase inhibitor) except for daily prednisone (or corticosteroid equivalent) ≤10 mg/day or inhaled or nasal corticosteroids;

    Note: Dexamethasone 6 mg daily or equivalent is permitted after randomization at the Investigator's discretion for progression to severe or critical COVID-19 requiring invasive ventilation or oxygen therapy for hypoxemia.
15. Is currently taking duloxetine, bupropion, a statin, a phosphodiesterase inhibitor, midazolam, fluoxetine, fluvoxamine, fluconazole, or ciprofloxacin; is on another cytochrome P450 (CYP)1A2, 2B6, or 3A4 sensitive substrate; or is on a CYP1A2, 2C19, or 3A4 inhibitor that, in the opinion of the Investigator in consultation with the Medical Monitor, would result in either supratherapeutic or subtherapeutic drug levels, placing the subject at undue risk by participating in the clinical trial;

    Note: ADX-629 may increase the metabolism of other sensitive CYP1A2, 2B6, or 3A4 substrates (see Appendix D), potentially leading to subtherapeutic drug levels. Subjects

taking these medications may be included; however, enrollment will be decided upon on an individual basis by the Investigator in consultation with the Medical Monitor.

16. Is currently taking any investigational products, other than the study drug;
17. Has participated in any other interventional clinical trial within the past 90 days or within 5 half-lives of the investigational therapy at Screening; or
18. Has any other condition that, in the opinion of the Investigator, could interfere with (or for which the treatment might interfere with) the conduct of the clinical trial or interpretation of the clinical trial results or that would place the subject at undue risk by participating in the clinical trial.

CLINICAL TRIAL DESIGN AND DURATION:

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 prior to the requirement for mechanical ventilation. 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.

The reason for hospital admission (for hospitalized subjects), the standard of care followed for each subject and site, and whether any care decisions were based on resource limitations will be clearly documented for all subjects.

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 (see Appendix C) 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.

DATA AND SAFETY MONITORING BOARD:

An independent Data and Safety Monitoring Board (DSMB) with multidisciplinary representation will be established to evaluate accumulating clinical trial data and to assess the ongoing safety of the clinical trial for the subjects enrolled. Interim safety assessments will be scheduled after the first group of 10 subjects has been enrolled and subsequently, as needed, to provide safety oversight for subjects in the clinical trial. Additional details will be provided in the DSMB charter.

STOPPING CRITERIA:

An independent DSMB will evaluate the safety and tolerability of the first 10 subjects after dosing and determine if it is acceptable to continue the clinical trial. However, safety and tolerability data will be reviewed on an ongoing basis by the Medical Monitor and stopping rules will be applicable starting with dosing of the first subject.

Subjects will be discontinued from dosing, but will continue to be followed in the clinical trial, if

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

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.

ADX-629 and the corresponding placebo will each be available as a tablet for oral administration. Additional details can be found in the Pharmacy Manual.

ENDPOINTS:

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

- AEs;
- Safety laboratory tests (including chemistry, hematology, coagulation parameters, and urinalysis);
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation);
- Physical examinations; and
- 12-lead electrocardiograms.

The key secondary endpoint is the NIAID ordinal scale score over Day 1 through Day 28.

Additional secondary 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 satisfies 1 of the following 3 categories from the NIAID ordinal scale:
  - Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;
  - Not hospitalized, limitation on activities and/or requiring home oxygen; or
  - Not hospitalized, no limitations on activities;
- 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 (e.g., NIAID scale 7 to 8);
- 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).

PHARMACODYNAMIC ENDPOINTS:

The PD endpoints will 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).

STATISTICAL ANALYSES:

The following analysis populations are defined for this clinical trial:

- Intent-to-Treat (ITT) Population: All randomized subjects;
- Safety Population: All randomized subjects who receive at least 1 dose of study drug;
- Per-Protocol Population: All subjects in the ITT Population without major protocol deviations; and
- PD Population: All subjects who have at least 1 PD measurement.

[redacted]

SAMPLE SIZE DETERMINATION:

[redacted] his clinical trial is exploratory in nature and is not formally powered.

SITES: The clinical trial will be conducted at approximately 3 sites in the United States.

SPONSOR:

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours
BID	*Bis in die* or twice daily
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CoV	Coronavirus(es)
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRA	Clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure *In Utero*
EMA	European Medicines Agency
EOT	End of Treatment
EUA	Emergency use authorization
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-Treat

Abbreviation	Definition
MAD	Multiple ascending dose
MDA	Malondialdehyde
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
NASH	Nonalcoholic steatohepatitis
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RASP	Reactive aldehyde species
SAD	Single ascending dose
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
Th	T-helper
UC	Ulcerative colitis
ULN	Upper limit of normal
WCBP	Women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

ADX-629, a small molecule therapy formulated for oral administration, is being developed for the treatment of chronic diseases with inflammatory and immune-mediated components. The target population in this clinical trial is non-ventilated adult subjects with coronavirus disease 2019 (COVID-19) of moderate severity. It is postulated that ADX-629 may mitigate the inflammatory response sufficiently in these subjects to lower levels of inflammatory mediators and potentially improve clinical outcomes.

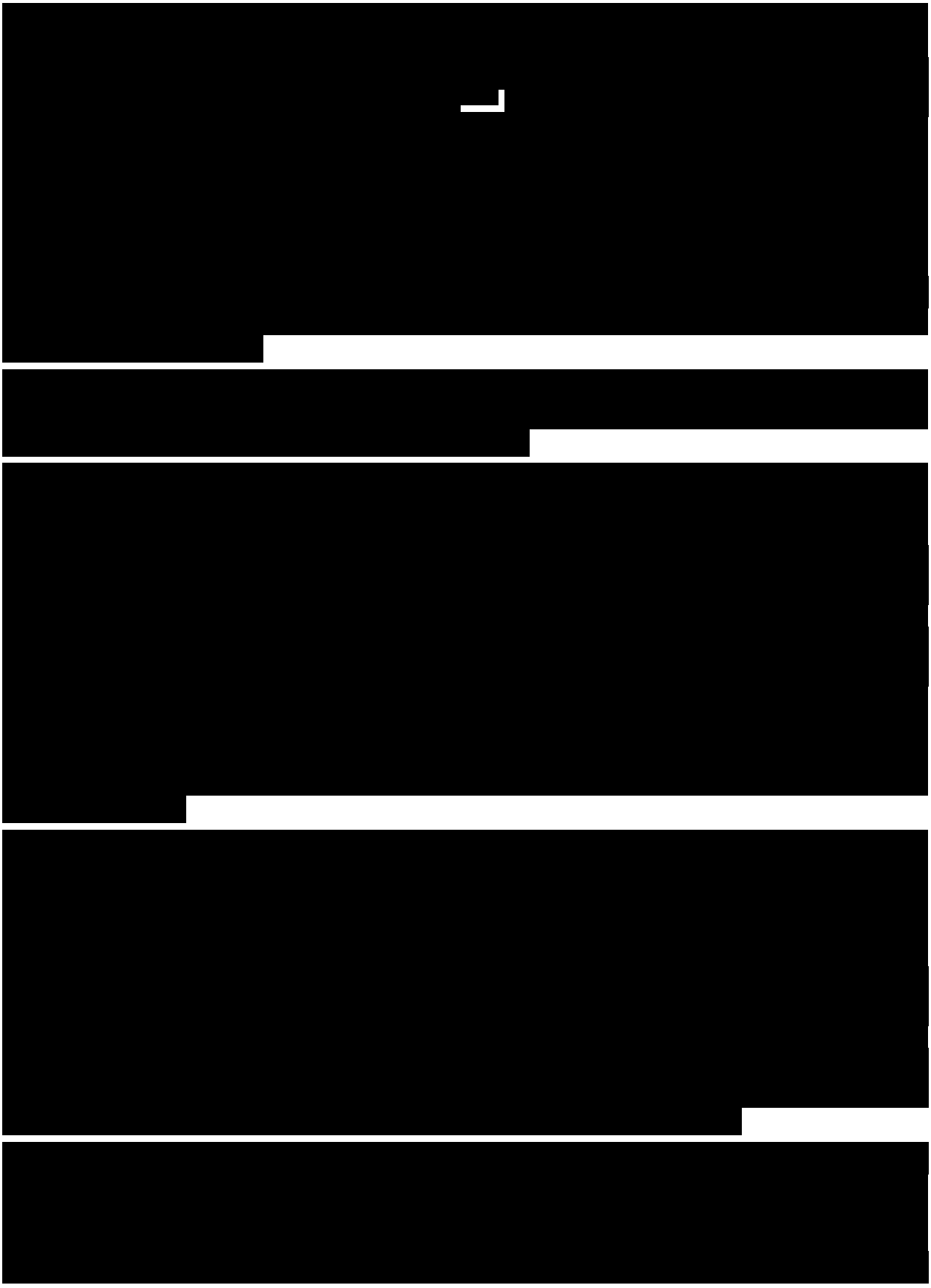
1.1 Background

Coronaviruses (CoV) are common causes of respiratory and gastrointestinal infections in a variety of animal species, including humans.[1] Numerous strains of CoV have been discovered, 7 of which have been identified to infect humans. Most of these strains cause mild respiratory symptoms in immunocompetent hosts; however, 3 strains, including the novel severe acute respiratory syndrome (SARS)-CoV-2 (SARS-CoV-2), cause severe respiratory syndromes. The SARS-CoV-1, Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2 can all result in severe pneumonia and acute respiratory distress syndrome (ARDS), a frequently fatal condition.[1,2] Although fatality rates from SARS-CoV-1 and MERS-CoV, 9.5% and 34.4% respectively[2], are higher than reported rates for SARS-CoV-2 (ranging from <1.0% to over 6% [as of 31 May 2020][3,4]), SARS-CoV-2 is more easily transmitted.[2]

SARS-CoV-2 originated in December 2019 in Wuhan, China. Secondary to its high reproductive number,[2] SARS-CoV-2 quickly spread across China and the world despite attempts at quarantining, social distancing, and using personal protective measures. The World Health Organization declared the SARS-CoV-2 and resulting COVID-19 as a pandemic and public health emergency of international concern on 30 January 2020.[5] As of 31 May 2020, the United States has reported 1,737,950 total cases of COVID-19 with 102,785 deaths from the disease.[6]

The COVID-19 pandemic has led to an urgent need for new therapies. Many patients diagnosed with COVID-19 will develop ARDS and require ventilatory support. In general, ARDS is associated with mortality rates up to 40%;[7] however, mortality from COVID-19-induced ARDS is even higher, with reported death rates over 50%.[8,9,10,11] The worst outcomes are observed in older patients and those with chronic diseases.[8] A treatment that could prevent the progression to severe COVID-19 could potentially reduce morbidity and mortality from the disease.

1.1.1 Nonclinical Studies of ADX-629



[redacted]

1.1.2 Clinical Trial of ADX-629

In addition to nonclinical safety studies, a Phase 1 safety clinical trial was conducted in 85 healthy human volunteers in a single ascending dose (SAD) clinical trial and a multiple ascending dose (MAD) clinical trial. In the SAD clinical trial, 41 subjects received ADX-629 and 13 subjects received placebo, across all dose cohorts. In the MAD clinical trial, 23 subjects received ADX-629 and 8 subjects received placebo across all cohorts. Overall, ADX-629 was found to be safe and tolerable at the doses explored, including the maximum dose of 600 mg *bis in die* or 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 a treatment-emergent AE (TEAE) compared to 4 (19.1%) subjects who received placebo. None of the subjects required an interruption or discontinuation of the study drug.

No clinically meaningful changes were observed in the hepatic and renal analytes, including transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase, amylase, gamma-glutamyl transferase, bilirubin, creatinine kinase, and creatinine. No changes in serum glucose were observed. Throughout the clinical trial period, there were no clinically meaningful changes observed in heart rate, blood pressure (systolic, diastolic, and orthostatic changes), respiratory rate, pulse oximetry, or temperature. No clinically significant hematology changes were observed. ADX-629 did not lead to a prolongation of heart rate-corrected QT interval using Fridericia's formula (QTcF). There were no subjects who had a QTcF >500 ms or a change of >60 ms from baseline. Five subjects had a change of >30 ms from baseline; however, no intervention or study drug interruption or discontinuation was required, and all subjects remained asymptomatic. Three of the 5 subjects were in the SAD portion of the clinical trial (1 each in of the 100 mg, 200 mg, and 700 mg dose cohorts) and the remaining 2 subjects were in the MAD portion of the clinical trial (1 in each of the 150 mg BID and 300 mg BID dose cohorts).

Although PK variability was observed, a linear correlation was evident in C_{max} and AUC as dose increased. The half-life was consistent across cohorts and days, with mean values in multiple day exposures ranging from 3.49 hours to 6.83 hours. Little to no accumulation of ADX-629 was observed across all cohorts. At the highest dose (600 mg BID), C_{max} was 1700 ng/mL (approximately 8.5 μM) and AUC from time 0 to 12 hours (AUC_{0-12}) was 7220 h*ng/mL. At the closest dose to the clinical dose (350 mg BID), a C_{max} of 1180 ng/mL (approximately 5.8 μM) and an AUC_{0-12} of 4110 h*ng/mL 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 oral dosing with ADX-629 600 mg BID that was statistically significantly greater than that of subjects treated with placebo. Following ingestion of a high-fat meal on Day 10 of dosing with ADX-629 600 mg BID or placebo, levels of free fatty acids were statistically significantly lower, and levels of HDL were statistically significantly higher, in ADX-629-treated subjects compared with placebo-treated subjects, potentially representing additional anti-inflammatory activity of ADX-629.

The Investigator's Brochure provides more details of the clinical trials conducted with ADX-629.

1.2 Rationale

This Phase 2a, randomized, double-blind, placebo-controlled, clinical trial will assess the safety, tolerability, efficacy, and pharmacodynamics (PD) of up to 28 days of treatment with ADX-629 300 mg BID in subjects with COVID-19 of moderate severity.

In summary, mechanistic and preclinical data suggest that administration of ADX-629 in non-ventilated subjects with COVID-19 of moderate severity may mitigate the inflammatory response sufficiently to lower levels of inflammatory mediators and potentially improve clinical outcomes. Consistent with nonclinical safety results, ADX-629 was deemed to be safe and well tolerated in Phase 1 clinical testing, with few and no greater than mild to moderate TEAEs at any dose tested.

1.3 Risk/Benefit

The ADX-629-COVID-19-001 clinical trial will evaluate the safety, tolerability, efficacy, and PD of ADX-629 in COVID-19-positive subjects with moderate severity prior to the requirement for mechanical ventilation. Scientific data suggest that a benefit to the subjects may exist from participating in the clinical trial.

The protocol design, dose selection, and safety monitoring are developed following the Food and Drug Administration (FDA) Guidance for Industry for Estimating Maximum Safe Starting Dose in Initial Clinical Trials, 2005; the FDA Guidance for Industry for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, 2007; the European Medicines Agency (EMA) guidance on first-in-human and early clinical trials (EMA, 2017); and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Safety of the clinical dosing regimen in this clinical trial is supported by a Phase 1 clinical trial in healthy volunteers and a number of preclinical toxicology and PK studies during which no serious safety concerns were noted at the projected therapeutic doses in humans.

Refer to the Investigator's Brochure for additional information.

2 CLINICAL TRIAL OBJECTIVES

2.1 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 prior to the requirement for mechanical ventilation.

2.2 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 PD by measuring plasma RASP in adult subjects with COVID-19 of moderate severity who were administered ADX-629 orally.

3 CLINICAL TRIAL DESCRIPTION

3.1 Summary of Clinical Trial Design

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 prior to the requirement for mechanical ventilation. Approximately 30 subjects will be randomized in a 2:1 ratio (ADX-629 to placebo) to receive either ADX-629 300 mg BID or placebo BID for up to 28 days.

The reason for hospital admission (for hospitalized subjects), the standard of care (see Section 5.6.3) followed for each subject and site, and whether any care decisions were based on resource limitations will be clearly documented for all subjects.

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 (see Appendix C) 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 clinical trial will be conducted at approximately 3 sites in the United States.

3.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) with multidisciplinary representation will be established to evaluate accumulating clinical trial data and to assess the ongoing safety of the clinical trial for the subjects enrolled. Interim safety assessments will be scheduled after the first group of 10 subjects has been enrolled and subsequently, as needed, to provide safety oversight for subjects in the clinical trial. Additional details will be provided in the DSMB charter.

3.3 Stopping Criteria

An independent DSMB will evaluate the safety and tolerability of the first 10 subjects after dosing and determine if it is acceptable to continue the clinical trial. However, safety and tolerability data will be reviewed on an ongoing basis by the Medical Monitor and stopping rules will be applicable starting with dosing of the first subject.

3.4 Clinical Trial Indication

The indication for this clinical trial is the treatment of inflammation associated with COVID-19.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Is a male or female ≥18 years of age at Screening;
2. Is willing and able to sign and date (or has a legally authorized representative willing to sign and date) a written (or electronic) informed consent form (ICF) or provide equivalent consent per FDA guidelines on COVID-19 clinical trials;
3. Has a documented, laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR), a SARS-CoV-2 antigen test, or another commercial or public health assay, within 3 days (72 hours) of randomization;
4. Has COVID-19 of moderate severity, as defined by the following:
   - Positive testing by standard reverse transcription PCR assay or equivalent testing;
   - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion;
   - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, saturation of oxygen >93% on room air at sea level, or heart rate ≥90 beats per minute; and
   - No clinical signs indicative of severe or critical severity (see Appendix E);
5. [redacted]
6. Is willing to use an effective form of contraception (all women of childbearing potential [WCBP] or men with a female partner of childbearing potential) during the clinical trial and for 90 days after the last dose of study drug.

   Note: A WCBP is defined as any female, regardless of sexual orientation, who has not undergone a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation or has not been naturally postmenopausal for at least 12 consecutive months (i.e., 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 clinical trial and for 3 months after the last dose of study drug.

4.2 Exclusion Criteria

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

1. Has an NIAID ordinal scale score <5 (see Appendix C);
2. Is on high-flow oxygen or any form of noninvasive ventilation, excluding continuous positive airway pressure (CPAP) alone for sleep disorders (e.g., obstructive sleep apnea);
3. [redacted]
4. [redacted]
5. Has a history of chronic obstructive pulmonary disease or bronchial asthma requiring continuous treatment and/or intermittent or continuous oxygen within the last 90 days prior to Screening or has significant lung infiltrates on chest X-ray (e.g., involving >50% of lung fields) at Screening as determined by the Investigator;

   Note: Intermittent use of a β2-agonist inhaler is allowed.
6. Has had any form of mechanical ventilation (invasive or noninvasive, excluding CPAP alone) for structural lung disease, neuromuscular disease, or another condition requiring chronic mechanical ventilation;
7. [redacted]
8. [redacted]
9. [redacted]
10. Has a history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection or has a positive HIV antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody result at Screening;
11. Has a current or previous severe allergy and/or hypersensitivity to ADX-629 or its excipients;
12. Is pregnant or lactating or plans to become pregnant during the clinical trial;

    Note: A serum human chorionic gonadotropin (hCG) test will be performed in all WCBP at Screening.
13. Is male and has known hypogonadism and hypospermia;

14. Is currently on another systemic immunomodulatory therapy (e.g., corticosteroid, calcineurin inhibitor, hydroxychloroquine, anti-cytokine therapy, Janus kinase inhibitor) except for daily prednisone (or corticosteroid equivalent) ≤10 mg/day or inhaled or nasal corticosteroids;

    Note: Dexamethasone 6 mg daily or equivalent is permitted after randomization at the Investigator's discretion for progression to severe or critical COVID-19 requiring invasive ventilation or oxygen therapy for hypoxemia.

15. Is currently taking duloxetine, bupropion, a statin, a phosphodiesterase inhibitor, midazolam, fluoxetine, fluvoxamine, fluconazole, or ciprofloxacin; is on another cytochrome P450 (CYP)1A2, 2B6, or 3A4 sensitive substrate; or is on a CYP1A2, 2C19, or 3A4 inhibitor that, in the opinion of the Investigator in consultation with the Medical Monitor, would result in either supratherapeutic or subtherapeutic drug levels, placing the subject at undue risk by participating in the clinical trial;

    Note: ADX-629 may increase the metabolism of other sensitive CYP1A2, 2B6, or 3A4 substrates (see Appendix D), potentially leading to subtherapeutic drug levels. Subjects taking these medications may be included; however, enrollment will be decided upon on an individual basis by the Investigator in consultation with the Medical Monitor.

16. Is currently taking any investigational products, other than the study drug;

17. Has participated in any other interventional clinical trial within the past 90 days or within 5 half-lives of the investigational therapy at Screening; or

18. Has any other condition that, in the opinion of the Investigator, could interfere with (or for which the treatment might interfere with) the conduct of the clinical trial or interpretation of the clinical trial results or that would place the subject at undue risk by participating in the clinical trial.

4.3 Withdrawal Criteria

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

- Withdrawal of consent or a subject request for discontinuation from the clinical trial 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 SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Subject failure to comply with protocol requirements or clinical trial-related procedures; or
- Termination of the clinical trial 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 with the clinical trial for acquisition of safety and efficacy assessments through the Day 60 telephone follow-up visit. If a subject withdraws prematurely from

the clinical trial prior to the EOT visit (Day 28), clinical trial staff should make every effort to complete the full panel of assessments scheduled for the EOT visit (Day 28). The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

Withdrawn subjects will not be replaced.

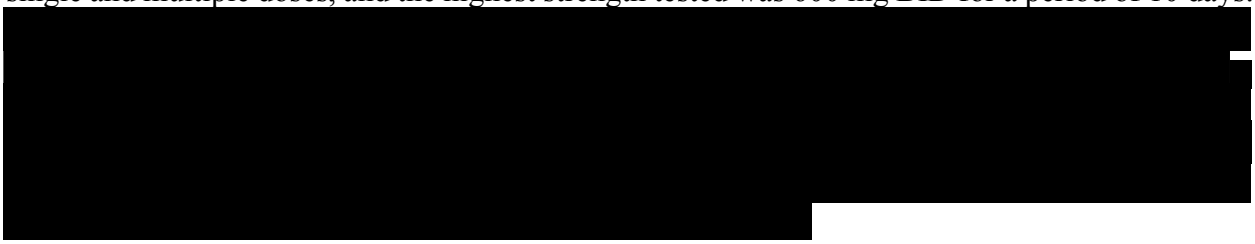
5 CLINICAL TRIAL TREATMENTS

5.1 Treatment Groups

All subjects will receive either ADX-629 300 mg BID or placebo BID for up to 28 days. The study drug will be administered orally as a tablet, at the discretion of the Investigator.

5.2 Rationale for Dosing

The starting dose for ADX-629 is based on the nonclinical studies conducted to-date and the doses used in the Phase 1 healthy volunteer clinical trial. Subjects in this clinical trial received escalating single and multiple doses, and the highest strength tested was 600 mg BID for a period of 10 days.



5.3 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.

5.4 Breaking the Blind

The Investigator is responsible for the medical care of subjects during the clinical trial. 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 an 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 clinical trial treatments, or as requested by local regulatory authorities.

If the clinical trial 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 clinical trial 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 matched placebo) to allow for completion of the clinical trial. The lot numbers will be recorded in the final clinical trial report.

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. See the Pharmacy Manual for further details.

5.5.2 Study Drug Preparation and Dispensing

[redacted]

5.5.3 Study Drug Administration

[redacted] 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.

5.5.4 Treatment Compliance

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

5.5.5 Storage and Accountability

The pharmacist (or designee) will acknowledge receipt of all shipments of the study drug and maintain an inventory. The study drugs 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 the study drugs dispensed and used by each subject. The clinical research associate (CRA) will periodically check the supplies of study drugs held by the pharmacist to verify accountability of all study drugs used.

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

[redacted]

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

[redacted]

5.6.2 Documentation of Prior and Concomitant Medication Use

Prior medications used within the 7 days prior to randomization will be recorded. Prior medications must be recorded on the appropriate eCRF along with the reason for use, dates of administration, and dosages.

[redacted]
decided upon on an individual basis by the Investigator in consultation with the Medical Monitor.

Any medication taken by the subject during the clinical trial, from the time of informed consent, should be considered a concomitant medication. All concomitant medications through and including Day 60 must be recorded in the subject's eCRF along with the reason for use, dates of administration, and dosages. Concomitant medications given to treat any SAEs will be recorded in the eCRF through the end of the clinical trial.

5.6.3 Documentation of Standard of Care Medications and Procedures

The standard of care that was followed for each subject and site must be recorded throughout the treatment period, from Day 1 through Day 28, and at the follow-up visit (Day 35). If standard of care therapies or procedures are not able to be delivered due to resource limitations, this should

also be recorded. The specific resource limitation, including subject-related limitations (e.g., financial, social) and/or healthcare-related limitations (e.g., equipment shortage, clinician shortage) will be recorded on the appropriate eCRF.

Data regarding the clinical decision making that guides removal from mechanical ventilation, in relation to clinical deterioration, lack of clinical response, or other reasons will be recorded on the appropriate eCRF.

6 CLINICAL TRIAL PROCEDURES

The clinical trial procedures are described in Appendix A.

6.1 Informed Consent

A written (or electronic) ICF, or equivalent consent per FDA guidelines on COVID-19 clinical trials, must be obtained from the subject, or a legally authorized representative, prior to performing any protocol-specific procedure. See Section 11.3.

6.2 Screening Visit (Day -3 to 1)

The following procedures will be performed at Screening (Day -3 to 1):

- Obtain informed consent;
- Review inclusion and exclusion criteria;
- Obtain demographic information;
- Obtain medical/surgical history;
- Assess NIAID score (see Appendix C);
- Measure weight and height and calculate body mass index;
- Perform full physical examination;
- Measure vital signs;
- Perform PCR or another commercial or public health assay for SARS-CoV-2, and perform a confirmatory test for SARS-CoV-2 (if not done within 3 days [72 hours] of randomization), only if no documented, laboratory-confirmed SARS-CoV-2 infection test result is available;
- Perform serum hCG test (WCBP only);
- Perform FSH testing (naturally postmenopausal women only);
- Perform HIV, HBsAg, and HCV testing, only if status is unknown;
- Perform clinical laboratory assessments;
- Perform 12-lead electrocardiogram (ECG);

  Note: ECG may be performed on Day 1, if not done at Screening, but it must be performed before the first dose of study drug is given.
- Perform chest X-ray;
- Record concomitant medications; and
- Record AEs.

6.3 Treatment Period – Days 1 Through 28/EOT

During the Treatment Period, all subjects will receive study drug (either ADX-629 or placebo) BID on Days 1 to 28/EOT. Treatment may commence whether a subject is hospitalized or is treated as an outpatient at Screening. 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. The study drugs will each be administered orally BID, 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. Inpatient subjects will receive the study drug in the hospital. Outpatient subjects will take the study drug at home according to their usual schedule, including on Days 1, 7, 13, 22, and 28.

All subjects will also have an assessment using the NIAID ordinal scale score (see Appendix C) 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. For outpatient subjects, the subject will receive instructions for subject diary completion on Day 1, while inpatient subjects will receive instructions on the day of discharge. Site personnel will monitor subject compliance between onsite study visits and contact subjects who are not compliant with diary completion. Subject compliance (for outpatient subjects only) for the subject diaries should be reviewed at the onsite visits at Days 7, 13, 22, and 28.

Inpatient subjects will have an assessment of standard of care (see Section 5.6.3) daily on Days 1 to 28/EOT (or until discharge). Outpatient subjects will have an assessment of standard of care (see Section 5.6.3) at each visit through Day 28.

In addition to study drug administration and NIAID score assessment, the procedures listed below will be performed on Days 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28/EOT (inpatients). Subjects who commence treatment as outpatients or who are discharged from the hospital prior to Day 28 will undergo a telephone visit on Day 4 to assess safety and weekly onsite visits through Day 28 (on Days 7, 13, 22, and 28), which will include vital sign assessments, physical examinations, and local laboratory evaluations, as indicated below.

6.3.1 Day 1 of Clinical Trial

The following procedures will be performed at Day 1:

- Review inclusion and exclusion criteria;
- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;
- Perform 12-lead ECGs at 1 hour and 6 hours post-dose;

  Note: If a 12-lead ECG was not performed at Screening, the subject should have a pre-dose ECG performed in addition to the post-dose ECGs.
- Obtain blood sample for PD analyses as follows: pre-dose (within 2 hours before the first dose of study drug) and post-dose (within 1 hour);

  Note: The exact time (in minutes) of the blood sample(s) must be recorded in the eCRF.
- Record concomitant medications;

- Record AEs;
- Assess NIAID score;
- Record standard of care received;
- Perform randomization; and
- Administer study drug (to hospitalized subjects only).

  Note: Outpatient subjects will take the study drug at home according to their usual schedule.

6.3.2 Day 4 of Clinical Trial

The following procedures will be performed at Day 4, for subjects who are currently admitted to the hospital as inpatients:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;
- Record concomitant medications;
- Assess NIAID score;
- Record standard of care received;
- Record AEs; and
- Administer study drug.

The following assessments will occur via telephone at Day 4, for subjects who are outpatients:

- Record concomitant medications;
- Record symptoms;
- Assess NIAID score;
- Record standard of care received; and
- Record AEs.

6.3.3 Day 7 of Clinical Trial

The following procedures will be performed at Day 7 for all subjects as indicated:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;

  Note: Subjects who are outpatients may use a local laboratory.
- Perform 12-lead ECG (inpatients only);

- Obtain blood sample for PD analyses post-dose (within 1 hour);

  Note: The exact time (in minutes) of the blood sample must be recorded in the eCRF.

  Note: Subjects who are outpatients may use a local laboratory.
- Record concomitant medications;
- Assess NIAID score;
- Assess subject diary compliance (for outpatient subjects only);
- Record standard of care received;
- Record AEs; and
- Administer study drug (to hospitalized subjects only).

  Note: Outpatient subjects will take the study drug at home according to their usual schedule.

6.3.4 Day 10 of Clinical Trial

The following procedures will be performed at Day 10 for subjects who are currently admitted to the hospital as inpatients:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;
- Record concomitant medications;
- Assess NIAID score;
- Record standard of care received;
- Record AEs; and
- Administer study drug.

6.3.5 Day 13 of Clinical Trial

The following procedures will be performed at Day 13 for all subjects as indicated:

- Measure weight;
- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;

  Note: Subjects who are outpatients may use a local laboratory.
- Obtain blood sample for PD analyses post-dose (within 1 hour);

  Note: The exact time (in minutes) of the blood sample must be recorded in the eCRF.

  Note: Subjects who are outpatients may use a local laboratory.

- Record concomitant medications;
- Assess NIAID score;
- Assess subject diary compliance (for outpatient subjects only);
- Record standard of care received;
- Record AEs; and
- Administer study drug (to hospitalized subjects only).

  Note: Outpatient subjects will take the study drug at home according to their usual schedule.

6.3.6 Day 16 of Clinical Trial

The following procedures will be performed at Day 16 for subjects who are currently admitted to the hospital as inpatients:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;
- Record concomitant medications;
- Assess NIAID score;
- Record standard of care received;
- Record AEs; and
- Administer study drug.

6.3.7 Day 19 of Clinical Trial

The following procedures will be performed at Day 19 for subjects who are currently admitted to the hospital as inpatients:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;
- Record concomitant medications;
- Assess NIAID score;
- Record standard of care received;
- Record AEs; and
- Administer study drug.

6.3.8 Day 22 of Clinical Trial

The following procedures will be performed at Day 22 for all subjects as indicated:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;

  Note: Subjects who are outpatients may use a local laboratory.
- Obtain blood sample for PD analyses post-dose (within 1 hour);

  Note: The exact time (in minutes) of the blood sample must be recorded in the eCRF.

  Note: Subjects who are outpatients may use a local laboratory.
- Record concomitant medications;
- Assess NIAID score;
- Assess subject diary compliance (for outpatient subjects only);
- Record standard of care received;
- Record AEs; and
- Administer study drug (to hospitalized subjects only).

  Note: Outpatient subjects will take the study drug at home according to their usual schedule.

6.3.9 Day 25 of Clinical Trial

The following procedures will be performed at Day 25 for subjects who are currently admitted to the hospital as inpatients:

- Perform targeted physical examination;
- Measure vital signs;
- Perform clinical laboratory assessments;
- Record concomitant medications;
- Assess NIAID score;
- Record standard of care received;
- Record AEs; and
- Administer study drug.

6.3.10 Day 28 (End of Treatment) of Clinical Trial

The following procedures will be performed at Day 28 for all subjects as indicated:

- Perform targeted physical examination;
- Measure vital signs;

- Perform clinical laboratory assessments;

  Note: The exact time of the blood sample (in minutes) must be recorded in the eCRF.

  Note: Subjects who are outpatients may use a local laboratory.
- Obtain blood sample for PD analyses post-dose (within 1 hour);

  Note: The exact time of the blood sample (in minutes) must be recorded in the eCRF.

  Note: Subjects who are outpatients may use a local laboratory.
- Record concomitant medications;
- Assess NIAID score;
- Assess subject diary compliance (for outpatient subjects only);
- Record standard of care received;
- Record AEs; and
- Administer study drug (to hospitalized subjects only).

  Note: Outpatient subjects will take the study drug at home according to their usual schedule.

6.4 Follow-Up Visit (Day 35)

The following procedures will be performed at the follow-up visit (Day 35):

- Perform targeted physical examination;
- Measure vital signs;
- Record concomitant medications;
- Record standard of care received; and
- Record AEs.

All subjects will undergo a follow-up visit at Day 35. 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. In that case, the procedures listed below in Section 6.5 will be performed.

6.5 Telephone Follow-Up (Day 60)

All subjects will undergo a telephone follow-up visit at Day 60. The purpose of the telephone follow-up is to assess survival status and evaluate for COVID-19 relapse. The following procedures will be performed during the telephone follow-up (Day 60):

- Record concomitant medications; and
- Record AEs.

6.6 Early Termination Visit and Withdrawal Procedures

The EOT for subjects completing the clinical trial is Day 28. For subjects who are withdrawn from the clinical trial prior to completion, all Day 28 procedures (see Section 6.3.10) will be performed at an early termination visit. Subjects who are withdrawn and complete an early termination visit will also undergo a telephone follow-up at Day 60.

7 ENDPOINTS

7.1 Primary Endpoint

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

- AEs;
- Safety laboratory tests (including chemistry, hematology, coagulation parameters, and urinalysis);
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation);
- Physical examinations; and
- 12-lead ECGs.

7.2 Secondary Endpoints

The key secondary endpoint is the NIAID ordinal scale score over Day 1 through Day 28.

Additional secondary 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 satisfies 1 of the following 3 categories from the NIAID ordinal scale:
  - Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;
  - Not hospitalized, limitation on activities and/or requiring home oxygen; or
  - Not hospitalized, no limitations on activities;
- 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 (e.g., NIAID scale 7 to 8);
- 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).

7.3 Pharmacodynamic Endpoints

The PD endpoints will include the following:

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

8 SAFETY ASSESSMENTS

The safety of ADX-629 will be determined by evaluation of the following:

- AEs;
- Safety laboratory tests (including chemistry, hematology, coagulation parameters, and urinalysis);
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation);
- Physical examinations; and
- 12-lead ECGs.

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 the last clinical trial visit, including the telephone follow-up. Subjects should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to clinical trial 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 (e.g., 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 should 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 clinical trial. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the clinical trial or are present at Screening and significantly worsen during the clinical trial 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 trial 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 test results that are abnormal, but not clinically significant

as determined by the Investigator, should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (e.g., 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 (i.e., 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 using the CTCAE version 5.0 and will also categorize each AE as to its potential relationship to study drug using the categories of "no" or "yes."

Severity assessment

The severity of all AEs should be graded according to the CTCAE version 5.0. 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, or 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 (e.g., concomitant drugs, therapies, complication) is suspected; or

- Yes (possibly related, probably related, 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 (e.g., concomitant drugs, therapies, complications) 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 when assessing the relationship of an AE to the study drug:

- 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 drugs;

  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.

8.2 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 (i.e., 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 1 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.

Note: Events related to progression of the subject's underlying COVID-19 diagnosis will be captured as endpoints; therefore, events clearly related to progression of the subject's underlying COVID-19 (signs or symptoms of progression) should not be reported as an SAE unless considered related to study drug or if the outcome is fatal during the clinical trial or within the safety reporting period. If the event has a fatal outcome during that timeframe, the event of "Progression of COVID-19" must be recorded as an SAE with a fatal outcome.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent 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 the study drug must be reported to the [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 clinical trial. When the form is completed, [redacted] Safety 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, [redacted] within 24 hours of awareness. 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 clinical trial and submit any supporting documentation (e.g., 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 clinical trial or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the subject should be withdrawn from the clinical trial. 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 (i.e., 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, but 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 regulations.

The requirements above refer to the requirements relating to investigational medicinal product.

8.6 Safety Contact Information

8.7 Clinical Laboratory Evaluations

All standard blood tests will be analyzed by the local laboratory. Blood samples will be collected and processed per institutional requirements and local processes.

Clinical laboratory tests are to be performed only if not done routinely as standard of care and only to the extent that the tests are missing to meet the clinical trial requirements. The Investigator will review laboratory values for those outside of the normal range and will be required to conduct clinically appropriate follow-up procedures. Clinical significance of the values outside of normal ranges will be assessed by the Investigator.

Clinical laboratory tests, including chemistry, hematology, coagulation parameters, and urinalyses, will be measured according to the timing specified in the Schedule of Procedures (Appendix A). For specifics of the analytes measured, see Appendix B.

8.8 Vital Signs

Vital signs will include temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation. Vital signs will be collected BID, both times prior to dosing with ADX-629. On Day 1, vital signs will also be collected at 2, 4, 6, and 8 hours post the morning dose.

8.9 Physical Examinations

A full physical examination will be performed only at Screening. Full physical examination will include the following systems: dermatological, head/eyes/ears/nose/throat, respiratory, cardiovascular, musculoskeletal, neurological, abdominal, and general appearance.

A targeted physical examination, driven by the subject's signs and symptoms, will be performed at the remaining visits, as specified in the Schedule of Procedures (Appendix A).

8.10 Electrocardiograms

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. Whenever ECGs and blood samples are specified to be collected at the same time, ECGs will be obtained before the blood samples. ECGs should be obtained in digital format when possible and archived.

Subjects should be in a supine position for at least 10 minutes prior to the ECG measurement. The ECG measurements will include heart rate, RR-interval, PR-interval, QT-interval, QRS-complex, and QTcF.

8.11 SARS-CoV-2 Testing

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 3 days (72 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.

8.12 Other Safety Assessment

A chest X-ray will be collected at Screening. Subjects will be excluded from the clinical trial if there are significant infiltrates on chest X-ray (e.g., involving >50% of lung fields) at Screening as determined by the Investigator.

9 STATISTICS

9.1 Analysis Populations

The following analysis populations are defined for this clinical trial:

- Intent-to-Treat (ITT) Population: All randomized subjects;
- Safety Population: All randomized subjects who receive at least 1 dose of study drug;
- Per-Protocol Population: All subjects in the ITT Population without major protocol deviations; and
- PD Population: All subjects who have at least 1 PD measurement.

9.2 Statistical Methods

9.2.1 Analysis of Endpoints

Clinical parameters will be assessed via linear models with repeated measures over 28 days. Sensitivity analyses will be performed using other techniques. The specific statistical analysis methods are detailed in the Statistical Analysis Plan.

9.2.2 Analysis of Safety

AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by counting the number of subjects reporting each event by treatment. The number (percentage) of subjects reporting TEAEs and SAEs for each preferred term will be tabulated by system organ class (SOC), by SOC and severity, and by SOC and relationship to the study drug. If more than 1 event occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity or relationship to study drug, respectively.

If specific AEs occur in a sufficient number of subjects, an exposure-response model may be developed as a secondary analysis.

Clinical laboratory values (excluding efficacy laboratory parameters) will be summarized by treatment arm, including changes from baseline at each visit.

Vital signs and change from baseline in vital signs will be summarized descriptively at each visit by treatment arm.

9.2.3 Interim Analysis

An independent DSMB with multidisciplinary representation will be established to evaluate accumulating clinical trial data and to assess the ongoing safety of the clinical trial for the subjects enrolled. Interim safety assessments will be scheduled after the first group of 10 subjects has been enrolled and subsequently, as needed, to provide safety oversight for subjects in the clinical trial. Additional details will be provided in the DSMB charter.

9.2.4 Sample Size Determination

[redacted] This clinical trial is exploratory in nature and is not formally powered.

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 clinical trial 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 clinical trial is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct clinical trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) Part 11 (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 thesauri will be used:

- MedDRA (latest version) for medical history and AEs; and
- World Health Organization Drug Dictionary (latest version) 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 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 clinical trial product, regulatory documents, and other Sponsor correspondence pertaining to the clinical trial must be kept in the appropriate clinical trial 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 trial necessary for the evaluation and reconstruction of the clinical trial. 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

Trial 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 Clinical Trial

The end of the clinical trial is defined as the date when the last subject for the clinical trial has completed the Day 60 telephone visit or otherwise terminates (withdraws, is withdrawn, or dies) before the Day 60 telephone visit.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Clinical Trial

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

11.2 Institutional Review Board

The IRB will review all appropriate clinical trial documentation in order to safeguard the rights, safety, and well-being of subjects. The clinical trial will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, 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 clinical trials. Prior to clinical trial onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this clinical trial 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

A written (or electronic) ICF, or equivalent consent per FDA guidelines on COVID-19 clinical trials, must be obtained from the subject, or a legally authorized representative, prior to performing any protocol-specific procedure.

The ICF and any changes to the ICF made during the course of the clinical trial 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 clinical trial subject is fully informed about the nature and objectives of the clinical trial 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 (or electronic) informed consent from each subject or legally authorized representative before any protocol-specific procedure is performed and should document in the source documentation that consent was obtained prior to enrollment in the clinical trial. 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 Clinical Trial Monitoring Requirements

It is the responsibility of the Investigator to ensure that the clinical trial 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 monitor'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 clinical trial, 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 clinical trial 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 trial. 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 monitor 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 clinical trial-specific monitoring log.

11.5 Disclosure of Data

Data generated by this clinical trial 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 that their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the clinical trial 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, [e.g., 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 Trial 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 clinical trial, the Sponsor should be prospectively notified. The clinical trial 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 clinical trial, 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 clinical trial confidential. The Investigator must consult with the Sponsor before

any clinical trial 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 clinical trial and for a period of 1 year after the completion of the clinical trial.

11.9 Insurance and Indemnity

In accordance with the relevant local, regional, and national regulations, the Sponsor has taken out subject liability insurance for all subjects who will give their consent to the clinical trial. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical trial's execution.

12 CLINICAL TRIAL ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

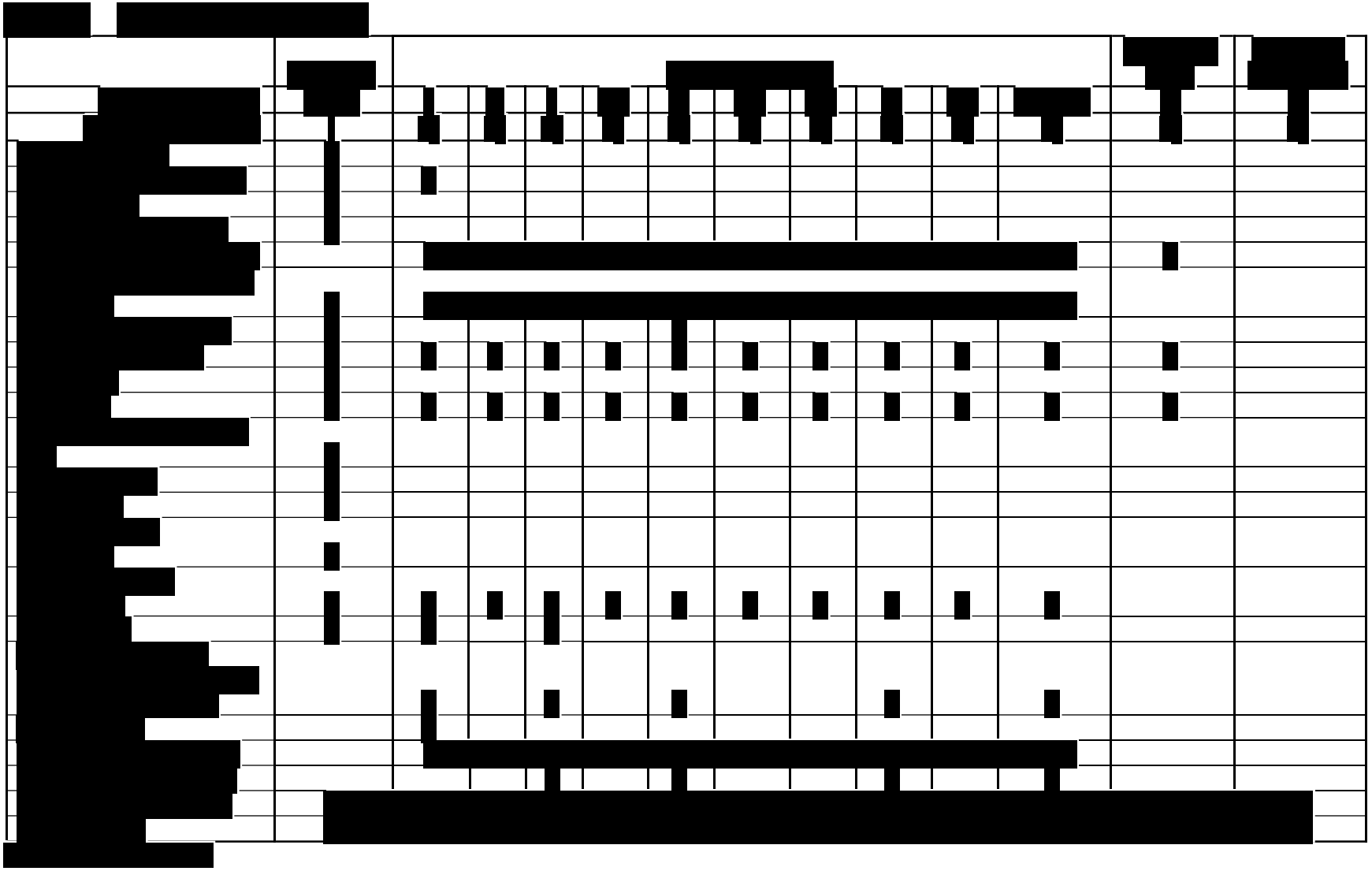
Any amendments to the clinical trial protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless 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.

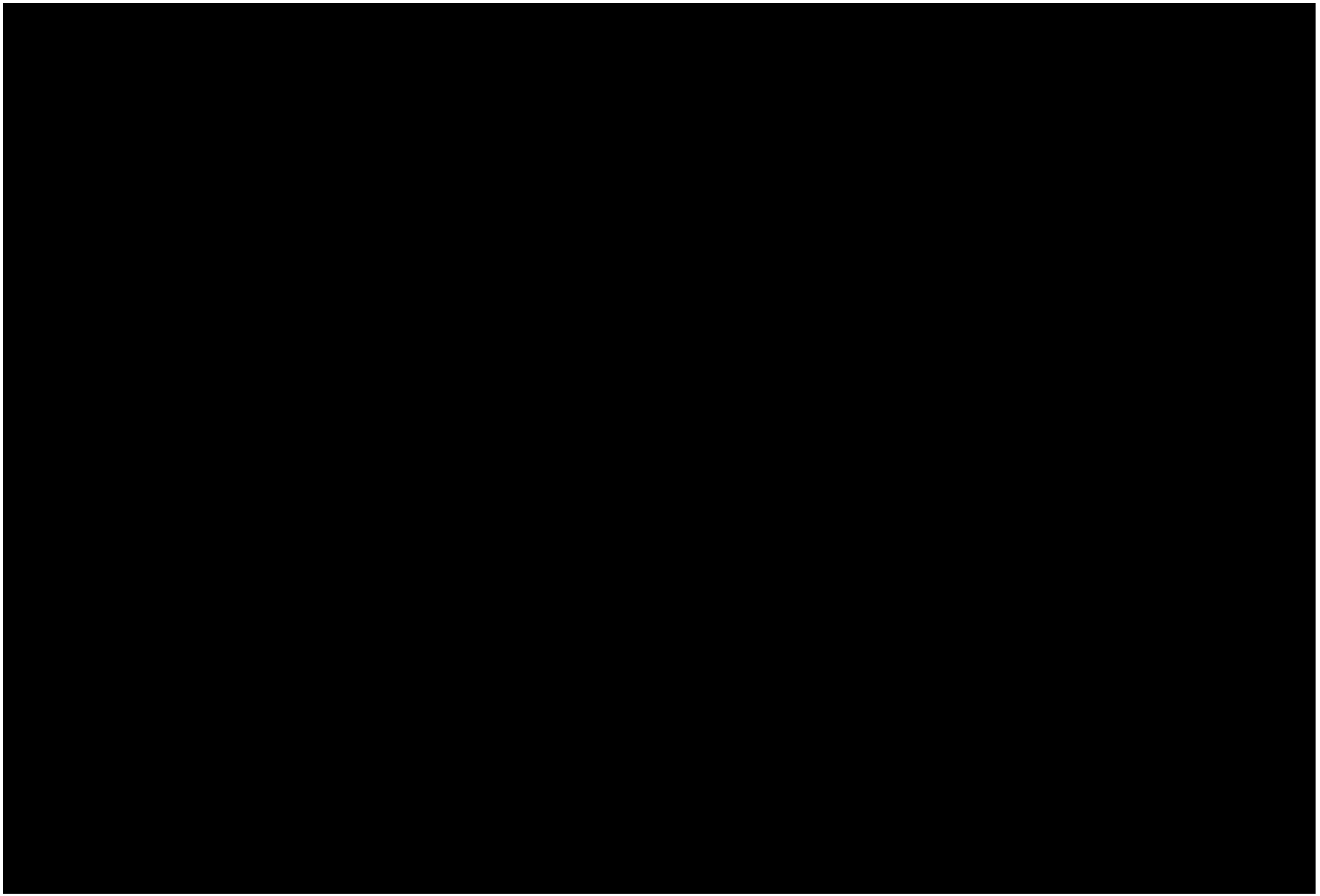
12.2 Protocol Deviations

Any deviations from the protocol will be recorded and reviewed routinely during the clinical trial period through monitoring activities. Training will be provided to an individual site or all sites upon identification of non-compliance with the protocol. The Investigator will submit a list of protocol deviations according to IRB requirements. The Sponsor will routinely monitor and assess deviations to identify if any serious breach of GCP has been incurred and will ultimately reconcile the list of protocol deviations to be included in the Clinical Study Report.

13 REFERENCES

APPENDIX A: SCHEDULE OF PROCEDURES





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	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 3 days (72 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

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.

APPENDIX C: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES 8-POINT ORDINAL SCALE FOR COVID-19

Table 2. 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

COVID-19 = coronavirus disease 2019; NIAID = National Institute of Allergy and Infectious Diseases.
Source: Adaptive COVID-19 treatment trial (ACTT). NIH clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT04280705. Accessed 30 May 2020

APPENDIX D: SUBSTRATES AND INHIBITORS OF CYTOCHROME P450

Table 3. Examples of Clinical Substrates for P450-Mediated Metabolism

	Sensitive Substrates	Moderate sensitive substrates
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine	Clozapine, pirfenidone, ramosetron, theophylline
CYP2B6	Buproprion	Efavirenz
CYP3A4	Alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil	Alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil
	Budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.
Note: This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list.
Note: This table has been modified from the original source for relevancy to this study.
AUC = area under the concentration-time curve; CYP = cytochrome P450; DDI = drug-drug interaction; OATP1B1 = organic anion transporting polypeptide 1B1.
Source: United States Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors, and inducers. Table 3-2. US Food and Drug Administration website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1.
Accessed 04 September 2020

Table 4. Examples of Clinical Inhibitors for P450-Mediated Metabolism

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives	Acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP2C19	Fluconazole, fluoxetine, fluvoxamine, ticlopidine	Felbamate	Omeprazole, voriconazole
CYP3A4	Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	Aprepitant, ciprofloxacin, conivapta, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor
	Clarithromycin, idelalisib, nefazodone, nelfinavir		

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. Strong inhibitors of CYP3A causing ≥10-fold increase in AUC of sensitive index substrate(s) are shown above the line.
Note: This table is prepared to provide examples of clinical inhibitors and is not intended to be an exhaustive list.
Note: This table has been modified from the original source for relevancy to this study.
AUC = area under the concentration-time curve; CYP = cytochrome P450; DDI = drug-drug interaction; HIV = human immunodeficiency virus; HCV = hepatitis C virus; P-gp = P-glycoprotein.
Source: United States Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors, and inducers. Table 3-2. US Food and Drug Administration website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.
Accessed 04 September 2020

APPENDIX E: FOOD AND DRUG ADMINISTRATION EXAMPLES OF BASELINE SEVERITY CATEGORIZATION

SARS-CoV-2 infection without symptoms

- Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test; and
- No symptoms.

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent test;
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, or gastrointestinal symptoms, without shortness of breath or dyspnea; and
- No clinical signs indicative of Moderate, Severe, or Critical severity.

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent test;
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion;
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, saturation of oxygen >93% on room air at sea level, or heart rate ≥90 beats per minute; and
- No clinical signs indicative of Severe or Critical severity.

Severe COVID-19

- Positive testing by standard RT-PCR assay or equivalent test;
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress;
- Symptoms suggestive of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, saturation of oxygen ≤93% on room air at sea level, heart rate ≥125 beats per minute, or partial pressure of oxygen/fraction of inspired oxygen <300; and
- No criteria for Critical severity.

Critical COVID-19

- Positive testing by standard RT-PCR assay or equivalent test; and
- Evidence of critical illness, defined by at least 1 of the following:
  - Respiratory failure defined based on resource utilization requiring at least 1 of the following:
    - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/minute with fraction of delivered oxygen ≥0.5), noninvasive positive pressure ventilation, extracorporeal membrane oxygenation, or clinical diagnosis of respiratory failure (i.e., clinical need for 1 of the preceding therapies, but preceding therapies are not able to be administered in setting of resource limitation);
  - Shock (defined by systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors); or
  - Multi-organ dysfunction/failure.

Note: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.

Source: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry: COVID-19: Developing drugs and biological products for treatment or prevention. May 2020