RIDGEBACKBIO

Long title: The Safety of EIDD-2801 and Its Effect on Viral Shedding of SARS-CoV-2

Short title: The Safety of EIDD-2801 and Its Effect on Viral Shedding of SARS-CoV-2 (The END-COVID Study)

Ridgeback Biotherapeutics Protocol #: EIDD-2801-2004

Clinical Phase: 2

ClinicalTrials.gov Identifier: NCT04405739

IND Sponsor/Principal Investigator:

Sponsor: Ridgeback Biotherapeutics LP

Principal Investigator: Ashwin Balagopal, MD

IND Number: 147734

Study Drug: EIDD-2801 and Placebo Capsules

Version/Date of Issue: Amendment 6, Version 7.0, 18 May 2021

PROTOCOL SUMMARY

Sample Size: 84 with allowance to increase up to 15% over as needed for dropouts or logistics considerations.

Study Population:

Adults aged 18 years or older who are hospitalized with a new diagnosis of coronavirus disease-2019 (COVID-19) with a duration of symptoms ≤7 days. Patients requiring admission to an intensive care unit or mechanical ventilation are not eligible.

Study Duration:

Length of study: Approximately 10 months from First Participant First Visit to Last Participant Last Visit

Length of participation of study participants: Up to 30 days, including a 0 to 2-day screening window, 5 days of dosing with study drug, and 23 days of post-dosing follow-up.

Locations:

Johns Hopkins Health System, The University of California, Los Angeles, and up to 5 additional sites in the United States

Study Design:

Phase 2a randomized, placebo-controlled, double-blinded clinical trial of EIDD-2801 (also known as MK-4482) in adult men and women who have tested positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection by polymerase chain reaction (PCR) test within 6 days (144 hours) prior to randomization and are hospitalized with a diagnosis of COVID-19. Rapid enrollment and treatment will be initiated such that the first dose of EIDD-2801 or placebo will be administered as soon as possible and within 7 days of onset of symptoms.

Randomization

Participants will be enrolled in up to 4 sequential study parts. During Part 1, participants will be randomized in a 1:1:1 ratio to: 200 mg EIDD-2801:400 mg EIDD-2801:placebo. In Part 2 of the study, 21 participants will be randomized in a 2:1 ratio to receive EIDD-2801 400 mg or placebo and in Part 3 of the study, 21 participants will be randomized in a 2:1 ratio to receive EIDD-2801 800 mg or placebo. An optional Part 4 may be added during which 21 participants will be randomized in a 2:1 ratio to EIDD-2801:placebo and the dose of EIDD-2801 may be the same or lower than doses studied in previous Part(s), but not to exceed 800 mg BID.

The study parts will be conducted as follows: Enrollment into Part 1 of the study may be terminated upon approval and implementation of Protocol Amendment 3, and enrollment into Part 2 will be initiated immediately thereafter. Enrollment into Part 3 will be initiated once Part 2 has been fully enrolled. If initiated, Part 4 may begin enrolling participants as soon as Part 3 has been fully enrolled. Study Parts 2 and 3 may be terminated prematurely based on emerging data from this and other ongoing studies of EIDD-2801.

Study Drug:

- EIDD-2801 and matching placebo

Primary Efficacy Objective:

To test whether orally administered EIDD-2801 results in a greater proportion of clearance from nasopharyngeal (NP) swabs compared to placebo in hospitalized adults by achieving undetectable (below the limit of detection [LOD] of the assay) viral RNA by Day 5 after initiation of study drug.

Primary Efficacy Endpoint:

Achievement of undetectable (below the LOD of the assay) SARS-CoV-2 RNA by Day 5 in NP swabs by quantitative reverse transcription polymerase chain reaction (qPCR).

Primary Safety Objective:

To evaluate the safety of treatment with EIDD-2801 in participants diagnosed with COVID-19

Primary Safety Endpoints:

1. Adverse events (AEs)
2. Serious adverse events (SAEs)
3. Physical examination including vital signs
4. Safety laboratory assessments
   - complete blood counts (CBC) with differentials
     - decrease in hemoglobin (Hgb) by >1 g/dL, or to <9 g/dL
     - decrease in platelet count by 50,000/µL, or to <75,000/µL
   - comprehensive metabolic panels (CMP) including liver function tests
     - increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, or lipase to ≥3x the upper limit of normal (ULN)
   - urinalysis
5. Electrocardiograms (ECGs)

Secondary Virologic Objectives:

To evaluate the efficacy of EIDD-2801 on clearance of SARS-CoV-2 RNA.

Secondary Virologic Endpoints:

1. Time to clearance of viral RNA in NP swabs
   - by qPCR
2. The decline in viral RNA by Day 3, Day 5, Day 8, Day 11, Day 15, Day 19, and Day 28 after initiation of study drug in NP swabs
   - by qPCR

3. Rate of decline in viral RNA (change in log_{10} copies/mL per day) in NP swabs
   – by qPCR

Secondary Clinical Objective

To evaluate the effect of EIDD-2801 on improvement of clinical symptoms and signs of COVID-19.

Secondary Clinical Endpoints:

1. Peak stage on the World Health Organization (WHO) Ordinal Scale for Clinical Improvement (Appendix 1) OR clinical requirement for addition of other antivirals including but not limited to:
   – Pegylated interferon alpha
   – Inhaled interferon beta1
   – Ribavirin (any formulation)
   – Any interleukin (IL)-6 inhibitor
2. Number of days of supplemental oxygen
3. Number of days of mechanical ventilation
4. Number of days in the Intensive Care Unit (ICU)
5. Death

Exploratory Virologic Objective

To evaluate the efficacy of EIDD-2801 to clear SARS-CoV-2 RNA and infectious virus.

Exploratory Virologic Endpoints:

1. Achievement of undetectable(below the LOD of the assay) viral titers by Day 5 in NP swabs
   – by infectivity assay
2. Time to clearance of infectious virus in NP swabs
   – by infectivity assay
3. Clearance of infectious virus by Day 3 and Day 5 in NP swabs
   – by infectivity assay
4. The number of acquired single-nucleotide polymorphisms in SARS-CoV-2 genomes by Day 5 or Day 11 in NP swabs
   – by viral sequencing

Exploratory Clinical Objective

To ascertain the role of EIDD-2801 in improvement of clinical symptoms and signs of COVID-19.

Exploratory Clinical Endpoints:

1. Days of hospitalization
2. Time until on room air without requirement for supplemental oxygen
3. Time to resolution of COVID-19 symptoms defined as:
   – Fevers OR

- At least one of the following symptoms: cough, shortness of breath, respiratory rate ≥20, radiographic evidence of pneumonia OR
- other clinical symptoms or signs of pneumonia that are not otherwise explained by comorbidities or co-diagnoses

4. Number of days until a 2-point decrease in stage according to the WHO Ordinal Scale for Clinical Improvement (Appendix 1).
5. Radiologic improvement by grading chest diagnostics (when radiography is available)
6. Change in interleukin (IL)-6 levels by Day 5

Pharmacokinetic Objectives

(To be conducted in a subset of participants at clinical sites that can participate, including but not limited to on Days 3 to 4 of dosing):

Secondary:

To evaluate EIDD-1931 pharmacokinetics in plasma.

Exploratory:

To characterize the pharmacokinetics of EIDD-2061 (NHC-TP) in peripheral blood mononuclear cells (PBMC) in a subset of participants.

Pharmacokinetic Endpoints:

Secondary (plasma analysis):

1. Maximum EIDD-1931 concentration (C_{max})
2. 1.5-hour EIDD-1931 concentration ($C_{1.5}$)
3. 3-hour EIDD-1931 concentration (C_3)
4. Area under the concentration: time curve of EIDD-1931 (AUC)
5. Elimination half-life ($t_{1/2}$) of EIDD-1931

Exploratory (PBMC analysis):

1. Maximum EIDD-2061 concentration (C_{max})
2. EIDD-2061 time of maximal concentration (t_{max})
3. Elimination half-life of EIDD-2061 ($t_{1/2}$)
4. Area under the concentration: time curve of EIDD-2061 (AUC_{0-12})
5. Parent: metabolite (EIDD-1931:EIDD-2061) concentration ratio at each time point, in which both plasma and PBMC are processed for PK analysis

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
AE: Adverse Event/Adverse Experience
ALT: Alanine aminotransferase
ARDS: Acute Respiratory Distress Syndrome
AST: Aspartate aminotransferase
AUC: Area under the curve
AUC_{0-12}: Area under the concentration-time curve throughout 12-hour dosing interval
AUC_{0-24}: Area under the concentration-time curve throughout 24-hour dosing interval
AUC_{0-8}: Area under the concentration-time curve throughout 8-hour dosing interval
BID: Bis in die, or twice daily
BiPAP: Bilevel positive airway pressure
BMI: Body mass index, or weight in kilograms divided by height in meters squared
$C_{1.5}$: One point five-hour concentration
C_3: Three-hour concentration
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CHKV: Chikungunya virus
CLIA: Clinical Laboratory Improvement Amendment of 1988
C_{max}: Maximum concentration
COI: Conflict of Interest
CoV: Coronavirus
COVID-19: Coronavirus Disease
CRF: Case Report Form
CRS: Cytokine Release Syndrome
DMC: Data Management Center
DRF: Dose range finding

ECG: Electrocardiogram
EEEV: Eastern equine encephalitis virus
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
IB: Investigator's Brochure
I/E: Inclusion and exclusion
ICF: Informed Consent (Informed Consent Form)
ICU: Intensive Care Unit
IEC: Independent ethics committee
IRB: Institutional review board

IWRS: Interactive web response system
LOD: Limit of detection
MAD: Multiple ascending dose
MERS: Middle East Respiratory Syndrome
MERS-CoV: Middle East Respiratory Syndrome Coronavirus
MTD: Maximum tolerated dose
NOAEL: No observed adverse effect level
NP: Nasopharyngeal
PFA: Plaque forming assay
PO2: Partial pressure of oxygen
QD: Quaque die, or once daily
QOD: Quaque altera die, or once every other day
qPCR: Quantitative polymerase chain reaction
RSV: Respiratory syncytial virus
RT-PCR: Reverse transcriptase polymerase chain reaction
SAD: Single ascending dose
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SOC: Standard of care
SRC: Safety review committee
$t_{1/2}$: half-life
VEEV: Venezuelan equine encephalitis virus
ZIKV: Zika virus

1. STUDY OBJECTIVES

1.1. Primary Efficacy Objective

Primary Efficacy Objective:

To test whether orally administered EIDD-2801 results in a greater proportion of clearance from nasopharyngeal (NP) swabs compared to placebo in hospitalized adults by achieving undetectable (below the limit of detection [LOD] of the assay) viral RNA by Day 5 after initiation of study drug.

Primary Efficacy Endpoint:

Achievement of undetectable (below the LOD of the assay) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) RNA by Day 5 in NP swabs by quantitative reverse transcription polymerase chain reaction (qPCR).

1.2. Primary Safety Objective

Primary Safety Objective:

To evaluate the safety of treatment with EIDD-2801 in participants diagnosed with COVID-19

Primary Safety Endpoints:

1. Adverse events (AEs)
2. Serious adverse events (SAE)
3. Physical examination including vital signs
4. Safety laboratory assessments:
    - complete blood counts (CBC) with differentials
        - decrease in hemoglobin (Hgb) by >1 g/dL, or to <9 g/dL
        - decrease in platelet count by 50,000/µL, or to <75,000/µL
    - comprehensive metabolic panels (CMP) including liver function tests
        - increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, or lipase to ≥3x the upper limit of normal (ULN)
    - urinalysis
5. Electrocardiograms (ECGs)

1.3. Secondary Virologic Objective

To evaluate the efficacy of EIDD-2801 on clearance of SARS-CoV-2 RNA.

Secondary Virologic Endpoints:

1. Time to clearance of viral RNA in NP swabs
   - by qPCR
2. The decline in viral RNA by Day 3, Day 5, Day 8, Day 11, Day 15, Day 19, and Day 28 after initiation of study drug in NP swabs
   - - by qPCR
3. Rate of decline in viral RNA, (change in $\log_{10}$ copies/mL per day) in NP swabs
   - - by qPCR

1.4. Secondary Clinical Objectives

To evaluate the effect of EIDD-2801 on improvement of clinical symptoms and signs of COVID-19.

Secondary Clinical Endpoints:

1. Peak stage on the World Health Organization (WHO) Ordinal Scale for Clinical Improvement (Appendix 1) OR clinical requirement for addition of other antivirals including but not limited to:
   - Pegylated interferon alpha
   - Inhaled interferon beta1
   - Ribavirin (any formulation)
   - Any interleukin (IL)-6 inhibitor
2. Number of days of supplemental oxygen
3. Number of days of mechanical ventilation
4. Number of days in the Intensive Care Unit (ICU)
5. Death

1.5. Exploratory Virologic Objective

To evaluate the efficacy of EIDD-2801 to clear SARS-CoV-2 RNA and infectious virus .

Exploratory Virologic Endpoints:

1. Achievement of undetectable (below the LOD of the assay) viral RNA titers by Day 5 in NP swabs
   - by infectivity assay
2. Time to clearance of infectious virus in NP swabs
   - by infectivity assay
3. Clearance of infectious virus by Day 3 and Day 5 in NP swabs
   - by infectivity assay
4. The number of acquired single-nucleotide polymorphisms in SARS-CoV-2 genomes by Day 5 or Day 11 in NP swabs
   - by viral sequencing

1.6. Exploratory Clinical Objective

To ascertain the role of EIDD-2801 in improvement of clinical symptoms and signs of EIDD-2801.

Exploratory Clinical Endpoints:

1. Days of hospitalization
2. Time until on room air without requirement for supplemental oxygen
3. Time to resolution of COVID-19 symptoms defined as:
   - Fevers OR
   - At least one of the following symptoms: cough, shortness of breath, respiratory rate ≥20, radiographic evidence of pneumonia OR
   - other clinical symptoms or signs that are not otherwise explained by comorbidities or co-diagnoses
4. Number of days until a 2-point decrease in stage according to the WHO Ordinal Scale for Clinical Improvement (Appendix 1).
5. Radiologic improvement by grading chest diagnostics (when radiography is available)
6. Change in IL-6 levels by Day 5

1.7. Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives will be assessed on dosing Days 3 and 4 in participants enrolled at clinical sites able to conduct the collections. These sites include but are not limited to

Secondary:

To evaluate EIDD-1931 PK in plasma in a subset of participants.

Exploratory:

To characterize the PK of EIDD-2061 (NHC-TP) in peripheral blood mononuclear cells (PBMC) in a subset of participants.

Pharmacokinetic Endpoints:

Secondary (plasma analysis):

1. Maximum EIDD-1931 concentration (C_{max})
2. 1.5-hour EIDD-1931 concentration ($C_{1.5}$)
3. 3-hour EIDD-1931 concentration (C_3)
4. Area under the concentration: time curve of EIDD-1931 (AUC)
5. Elimination half-life ($t_{1/2}$) EIDD-1931

Exploratory (PBMC analysis):

1. Maximum EIDD-2061 concentration (C_{max})
2. EIDD-2061 time of maximal concentration (t_{max})
3. Elimination half-life of EIDD-2061 ($t_{1/2}$)
4. Area under the concentration: time curve of EIDD-2061 (AUC_{0-12})
5. Parent: metabolite (EIDD-1931:EIDD-2061) concentration ratio at each time point, in which both plasma and PBMC are processed for PK analysis

2. BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Abstract

SARS-CoV-2 has infected over 5 million people worldwide since December 2019, with >300,000 fatalities reported as of the date of this protocol (Johns Hopkins University Coronavirus Resource Center: https://coronavirus.jhu.edu/map.html). In this unprecedented global crisis, the medical community is lacking adequate tools to combat the severe outcomes of COVID-19: respiratory collapse, multi-system organ failure, and death. There is a desperate need for safe and effective antiviral therapies to mitigate the natural course of COVID-19, especially in those who are at high risk for severe disease. Currently, there are no approved therapeutics specific for COVID-19.

EIDD-2801 (also known as MK-4482) is an orally bioavailable prodrug of EIDD-1931, a small molecule ribonucleoside analogue that was developed for respiratory viruses. EIDD-2801 has demonstrated potent in vitro antiviral activity against a broad array of coronaviruses including SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome-coronavirus (MERS-CoV), and it has shown in vivo activity in animal models of SARS-CoV and MERS-CoV (Agostini et al, 2019; Sheahan et al, 2020). EIDD-2801 is currently in Phase 1 clinical trials.

We propose a Phase 2a randomized, placebo-controlled, double-blinded clinical trial of EIDD-2801 in hospitalized men and women (aged 18+ years) with PCR-confirmed SARS-CoV-2 infection who also have evidence of symptomatic COVID-19. We plan to enroll hospitalized patients who present within 7 days of symptom onset for a 5-day course of twice daily (BID) dosing of EIDD-2801 or placebo. We will follow participants for every hospitalized day and after they are discharged, for 28 days after the first dose. The primary endpoint will be the achievement of undetectable (below the LOD of the assay) SARS-CoV-2 RNA in NP swabs by Day 5 (end-of-treatment). Secondary clinical endpoints will include the time until virologic clearance (by RNA testing), rate of decline in viral RNA, peak stage on the WHO Ordinal Scale for Clinical Improvement, requirement for additional antivirals, duration of ICU stay, duration of mechanical ventilation, or death. Safety outcomes will include AEs, SAEs, physical examination with vital signs, ECGs, and laboratory measurements (including CBC, CMP, and urinalysis). We will measure the PK of EIDD-1931, the primary circulating form of EIDD-2801, in plasma. We will also collect PBMCs for measurement of EIDD-2061 (NHC-TP), as an exploratory objective. PK sampling will be assessed on dosing days 3 and 4 in participants enrolled at clinical sites able to conduct the collections. These sites include but are not limited to

. We anticipate enrollment of 80 participants in this trial at the following dose levels: EIDD-2801 200 mg, EIDD-2801 400 mg, EIDD-2801 800 mg, and placebo. In the primary analysis, we will compare the proportion of participants in each EIDD-2801 and placebo groups who achieve virological clearance.

2.2. Background

COVID-19 is a disease caused by the SARS-CoV-2 that was first detected in China's Hubei province in December 2019. It is a systemic disease with influenza-like symptoms; a subset of patients with severe disease can experience respiratory decline, acute respiratory distress syndrome (ARDS), multi-system organ failure, and death. SARS-CoV-2 has infected over 5 million people worldwide since its emergence, with >300,000 fatalities reported as of the date of this study protocol (Johns Hopkins University Coronavirus Resource Center: https://coronavirus.jhu.edu/map.html).

There have been suggestions that the worst consequences of SARS-CoV-2 are seen in people with the highest viral burden (Wolfel et al. 2020). Although numerous agents are currently being tested in clinical trials, the majority of these are re-purposed drugs that are not specifically developed for SARS-CoV-2 or other coronaviruses. There is an urgent need for direct-acting SARS-CoV-2 antiviral agents that can be used in patients to mitigate the worst complications of the infection.

SARS-CoV-2 is an enveloped, positive-sense, single-strand RNA beta-coronavirus that is related to SARS-CoV and distantly to MERS-CoV. SARS-CoV-2 has a genome of ~30kb which comprises 4 structural proteins and 16 non-structural proteins. Among the non-structural proteins is nsp12, the RNA-dependent RNA polymerase (RdRp) that is required to replicate the viral genome. Many successful antivirals for other viruses target the RdRp: nucleos(t)ide inhibitors for Human Immunodeficiency Virus (HIV)-1 and hepatitis B, NS5B inhibitors for hepatitis C. However, many nucleoside analogues fail to inhibit coronaviruses because of the unique coronavirus 3'-5' exoribonuclease (nsp14) that confers proofreading activity to the CoV RdRp. Only 2 nucleoside analogues to date have been shown to overcome the coronavirus proofreading activity and inhibit a broad range of coronaviruses: remdesivir and EIDD-2801/EIDD-1931 (Agostini et al, 2018; Agostini et al, 2019).

EIDD-2801 (also known as MK-4482) is an oral prodrug of EIDD-1931 ([N4-HYDROXY-5′-O-(2-METHYLPROPANOYL)CYTIDINE, NHC], a novel small molecule ribonucleoside analogue with potent *in vitro* inhibition of a broad array of coronaviruses including SARS-CoV-2, SARS-CoV, and MERS-CoV (Sheahan et al, 2020). EIDD-2801 is converted into its circulating intermediate form, EIDD-1931, by non-specific esterases in plasma—this is the primary form found in systemic circulation. EIDD-1931 is then taken up by target mononuclear cells and enzymatically converted by host kinases to the metabolites 5'-monophosphate EIDD-1931 and 5'-triphosphate EIDD-1931 (also called EIDD-2061, or NHC-TP). The 5'-triphosphate form is a competitive antagonist of the RNA-dependent RNA polymerase (RdRp), while the 5'-monophosphate form promotes lethal mutagenesis in the nascent viral RNA strand, thus impacting downstream viral processes. EIDD-1931 has a median effective concentration (EC_{50}) of 0.3 micromolar against SARS-CoV-2 *in vitro*, demonstrating a 1000-fold reduction in SARS-CoV-2 viral titers, as well as reduced lung hemorrhage and damage in a murine model of SARS-CoV.

Pharmacologic aspects of EIDD-1931 and its metabolites have been evaluated in *in vitro* cell culture systems, as well as pre-clinical animal models. Anabolic PK assessments were characterized in cultured human bronchial tracheal epithelial cells. Following ex vivo incubation of epithelial cells with 20 µM EIDD-1931, there was rapid conversion to the EIDD-1931 metabolite (EIDD-Triphosphate, EIDD-TP) within the first 60 minutes. Plateau concentrations of EIDD-TP (4 nmol/10^6 cells) were achieved within 4 hours and remained stable for 24 hours. Removal of drug led to persistence of the metabolite over a 24-hour period. The estimated intracellular half-life ($t_{1/2}$) of EIDD-TP was 4 hours. Comparable kinetics were observed in mouse lung tissue post-administration of an oral 500 mg/kg dose.

The orally bioavailable isopropylester compound, EIDD-2801, has been evaluated in an ongoing, Phase 1, randomized, double-blind, placebo-controlled single-ascending and multiple-ascending dose first in-human study to assess its safety, tolerability, and PK. A total of 130 healthy participants (109 males and 21 females) received at least 1 dose of EIDD-2801 or placebo in the Phase 1 trial EIDD-2801-1001. Preliminary, unblinded safety data are available for all subjects. Review of these safety data indicates that single oral doses of up to 1600 mg EIDD-2801 or placebo and multiple oral doses of up to 800 mg EIDD-2801 or placebo Q12H for 5.5 days have been generally well tolerated in healthy participants. Further details are provided in Section 2.3.1.

The prodrug (EIDD-2801) was generally not detectable in plasma following single (50 to 1600 mg) or multiple doses (50 to 800 mg BID for 5.5 days) of MK-4482. Plasma concentrations of the nucleoside metabolite (EIDD-1931) were detectable. T_{max} occurred approximately 1 hour post dose. Plasma EIDD-1931 concentrations generally declined in a monophasic manner, with a $t_{1/2}$ of approximately 1 hour. A biphasic profile with a later, slower elimination phase ($t_{1/2}$ ranging from 1.47 to 19.2 hours) was observed in some participants (following single doses of 1200 mg and 1600 mg and following multiple doses of 600 mg and 800 mg). C_{max} and AUC increased in an approximately dose-proportional manner across the range of doses tested. No accumulation occurred following multiple dosing (Q12H for 5.5 days), and administration in the fed state did not meaningfully impact plasma exposure of EIDD-1931. There were no significant detectable concentrations of EIDD-2801; initial PK parameters were identified for EIDD-1931 concentrations in plasma. Following multiple doses of 100 mg BID EIDD-2801 orally in the fasted state, median t_{max} was 1.25 hours post-dose (range 1-2 hours), and concentrations declined monophasically and were quantifiable until the 6 to 9-hour time points. The apparent terminal half-life ($t_{1/2}$) was 0.918 and 0.969 hours on Days 1 and 6, respectively. AUC_{tau} was 853 ng*h/mL (%CV 19.9), and C_{max} was 395 ng/mL (%CV 18.5). The increase in exposure between the 50 mg and 100 mg doses was slightly supraproportional with the 2-fold increase in dose resulting in a 2.23-fold increase in AUC_{tau} and 2.31-fold increase in Cmax. (EIDD-2801 Investigator's Brochure, V3.0, 2020).

2.3. Known Potential Risks

2.3.1. Clinical Findings

EIDD-2801 has been studied in a single and multiple dose escalation study in humans that includes a food effect cohort. All subjects have completed participation in the study and preliminary data are available.

A total of 130 healthy volunteers were enrolled in this study. Sixty-four participants received a single dose between 50 and 1600 mg EIDD-2801 or placebo; 56 participants received multiple doses between 50 and 800 mg EIDD-2801 or placebo BID for 5.5 days; and 10 participants received a single dose of

200 mg EIDD-2801 in the fed state followed by a single dose of 200 mg EIDD-2801 in the fasted state after a washout period of 14 days, or vice versa.

Among participants who received single doses of EIDD-1801 or placebo, a greater proportion of participants reported AEs following administration of placebo (43.8%) than following administration of EIDD 2801 (35.4%). One moderate AE (headache) was reported by 1 participant following administration of EIDD-2801 at the 400-mg dose level, and 2 moderate AEs (nausea and headache) were reported by 1 participant following administration of placebo. No severe AEs were reported. The most frequently reported AE was headache, which was reported by 18.8% of participants who were administered placebo and 12.5% of participants who were administered EIDD-2801.

Among participants who received multiple ascending doses of EIDD-2801 or placebo BID over 5.5 days, a greater proportion reported AEs following administration of placebo (50.0%) than following administration of EIDD-2801 (42.9%). With the exception of 1 participant in the 200 mg BID group who reported moderate AEs of sore throat, aching limbs, and flu-like symptoms, all other AEs were mild in severity. The most frequently reported AE was diarrhea, which was reported by 7.1% of participants who were administered EIDD-2801 and 7.1% of participants who were administered placebo. One participant had an AE of mild, truncal, maculopapular, pruritic rash following multiple doses of 800-mg EIDD 2801, which was considered by the investigator to be related to the study drug; this AE resulted in early discontinuation of the study drug dosing on Day 3. The participant was administered a topical steroid and anti-histamines, and the AE resolved after 18 days.

Among participants in the food-effect evaluation, 3 participants reported 1 AE each, all of which were mild in severity.

There were no serious AEs reported in this study and there were no trends of increased frequency or severity of AEs with higher doses of EIDD-2801.

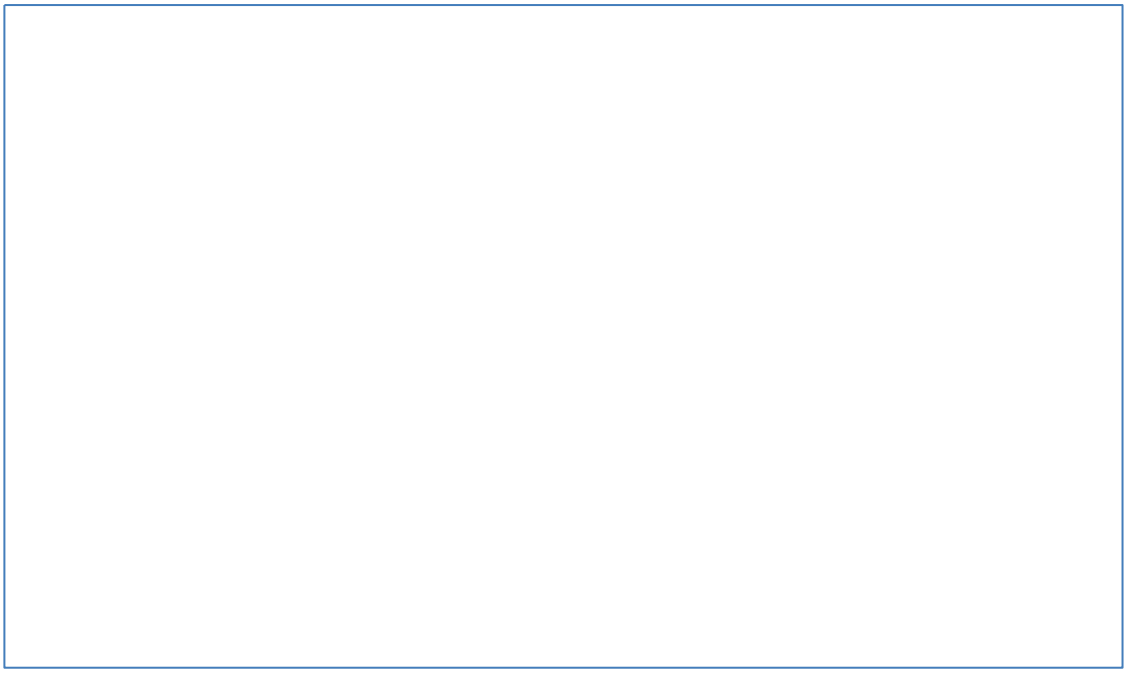
There were no clinically significant findings in clinical laboratory, vital signs, or ECG data.

(Section 2.3.2.2). However, no clinically significant changes in hematological parameters were seen in the Phase 1 study.

2.3.2. Nonclinical Findings

2.3.2.1. Effects on the Gastrointestinal Tract

2.3.2.2.



2.3.2.4.

2.3.2.5.

2.3.2.5.1.

2.3.2.5.2.

2.3.2.5.3.

2.3.3.

2.4. Known Potential Benefits

EIDD-2801 has been administered to COVID-19 patients in ongoing studies and the safety and tolerability of single and multiple ascending doses has been tested in healthy adult volunteers (See Section 2.3.1).

After oral delivery, EIDD-2801 is rapidly hydrolyzed by circulating esterases to produce high circulating (plasma) levels of EIDD-1931. In cell culture systems, EIDD-1931 has been shown to inhibit replication of multiple viral pathogens from multiple RNA virus families including pathogenic CoV (e.g., SARS-CoV-2, severe acute respiratory syndrome (SARS-CoV), and Middle East Respiratory Syndrome (MERS)), influenza viruses (seasonal, pandemic, and avian subtypes), respiratory syncytial virus (RSV), alphaviruses (e.g., Eastern equine encephalitis virus (EEEV), Venezuelan equine encephalitis virus (VEEV), and Chickungunya virus (CHKV)), Filoviruses (e.g., Ebola virus (EBOV), and Zika virus (ZIKV)). In addition, EIDD-2801 is active against orthopox viruses probably because orthopox viruses encode their own unique RNA polymerase. Antiviral activity has been verified in animal models of CoV (MERS- and SARS-CoV), influenza, RSV, VEEV, CHKV, and EBOV. The primary mechanism of action of EIDD-2801 is inhibition of viral RNA replication by incorporation of EIDD-1931 monophosphate metabolite into the viral RNA genome resulting in induction of viral error catastrophe.

2.4.1. Potential Benefits of Treatment

EIDD-2801 has demonstrated activity against SARS-CoV-2 in vitro, and SARS-CoV as well as MERS-CoV in vitro and in vivo. EIDD-2801 has shown efficacy against CoV in animal models. In mice, EIDD-2801 was active in both a prophylactic and therapeutic setting (Painter et al, 2019). When EIDD-2801 was administered up to 24 hours after infection with SARS-CoV or up to 12 hours after infection with MERS-CoV, a reduction in viral lung titers, protection from both lung hemorrhage and weight loss, and improvements in pulmonary function were seen, compared to vehicle-treated (control) animals.

Nonclinical findings suggest that it will be active against SARS-CoV-2. More information regarding nonclinical activity of EIDD-2801 can be found in the Investigators' Brochure.

2.4.2. Potential Benefits of Clinical Monitoring and Virologic Testing

Participants enrolled in the study will undergo close clinical and laboratory monitoring that could facilitate improved management of COVID-19 with associated benefit to the individual, their family, and the community at large.

3. PATIENT POPULATION

Adults aged 18 years or older who are hospitalized with a new diagnosis of COVID-19 with a duration of symptoms ≤7 days. Patients requiring admission to an intensive care unit for mechanical ventilation are not eligible. Persons with Low English Proficiency (LEP) and who are non-English Speakers may join.

3.1. Inclusion Criteria for Enrollment

Participants who meet all the following criteria will be eligible for study participation:

1. Has COVID-19 disease, defined by having one or more of the following new symptoms and signs (within 7 days):
   - Fevers OR
   - At least one of the following: cough, sore throat, shortness of breath, respiratory rate ≥ 20, radiographic evidence of pneumonia OR
   - Anosmia OR
   - other clinical symptoms or signs of COVID-19 that are not otherwise explained by comorbidities or co-diagnoses
2. PCR+ test for SARS-CoV-2 within 6 days prior to randomization.
3. Has new signs or symptoms of COVID-19 that began ≤7 days of anticipated first dose of study drug.
4. Persons ≥18 years old.
5. Is an inpatient at the time of first dose.
6. Is willing and able to comply with all study procedures including providing informed consent firsthand or via a legally authorized representative, collection of virology samples, and any safety tests that are not included as part of standard of care (SOC).
7. Is willing and able to take oral medications and is anticipated to be able to take the full course of 5 days of study drug.

Pregnancy and Contraception:

Therefore, treatment with EIDD-2801 is contraindicated in women who are pregnant or nursing and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during the study and for 4 days after completion of EIDD-2801 dosing in female participants and for 4 days after completion of EIDD-2801 dosing in female partners of male participants.

8. A female participant is eligible to participate if she is not pregnant or breastfeeding and at least one of the following conditions applies:
   - Is not a woman of childbearing potential (WOCBP)

   OR
   - Is a WOCBP and using a contraceptive method that is highly effective (a low user dependency method OR a user-dependent method in combination with a barrier method),

or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 2 during the intervention period and for at least 4 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (serum test is required) within 24 hours before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 4.4.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Given the elevated risk of venous thrombotic events in patients hospitalized with COVID-19 (Benson et al 2020; Spratt et al 2020), estrogen-containing contraceptives must not be started to fulfill the contraceptive requirement of this study at any time during participant's hospitalization. If contraceptives are interrupted as standard of care management of COVID-19 patients and resumed at a later time point, such as at hospital discharge, then abstinence must be practiced for the defined period of back-up contraception per the contraceptive product labeling. After this period, contraceptive use must adhere to Appendix 2.

9. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 4 days after the last dose of study intervention:
    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

    OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 2]) as detailed below:

    Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

3.2. Exclusion Criteria for Enrollment

Participants who meet any of the following criteria will not be eligible for participation

1. Is anticipated to require ICU admission for mechanical ventilation within 24 hours of enrollment.
2. Requires more than 6 liters/minute of oxygen to maintain O_2 saturation above 95%.
3. Is not expected to survive longer than 24 hours.

4. Has a platelet count less than 100,000/µL, hemoglobin <9 g/dL, or has a disorder of the hematologic system including anemic disorder or other blood dyscrasia, cancer of the hematologic system, history of bone marrow transplant, or other significant hematologic disease.
5. Women who are pregnant or breastfeeding.
6. Is experiencing DAIDS AE grading scale grade 4 baseline medical conditions or laboratory abnormalities.
7. Has received a vaccine for COVID-19 prior to enrollment, or plans to receive a vaccine for COVID-19 before the end-of-study visit.
8. Has received an experimental antiviral treatment for COVID-19 prior to enrollment.
9. Has received convalescent plasma or other monoclonal antibodies prior to enrollment.
10. Is participating in another clinical study that involves pharmacologic intervention or has participated in another study within 30 days of 5 half-lives of the investigational agent (observational study participation is permitted).
11. In the opinion of the investigator, has end-organ disease as a result of relevant comorbidities: chronic kidney disease (reduced glomerular filtration rate [GFR] <30 mL/min by the Modification of Diet in Renal Disease (MDRD) study equation prior to COVID-19 symptom onset), decompensated chronic liver disease or cirrhosis, decompensated congestive heart failure, active peripheral vascular disease including active diabetic ulcers, chronic pulmonary disease prior to COVID-19 symptom onset requiring bilevel positive airway pressure (BiPAP) or >4 L/min supplemental oxygen at baseline; if using ≤4 L/min supplemental oxygen at baseline, consultation with and approval of the sponsor is required prior to enrollment.
12. Has a diagnosis of cancer that is not in remission. Noninvasive cancers, such as basal and squamous cell carcinoma or history of in situ tumors are allowed at the discretion of the investigator after discussion with the sponsor.
13. Has received an organ transplantation.
14. Has received a bone marrow transplantation.
15. Has been on immunosuppressive medications within 1 month prior to enrollment.
16. Has any condition that would, in the opinion of the investigator, put the participant at increased risk for participation in a clinical trial.
17. Has known active hepatitis C (HCV RNA positive), active hepatitis B (hepatitis B surface antigen positive), or HIV (ELISA and confirmatory Western blotting). New screening tests not required.
18. Is currently taking nucleos(t)ide analogues for HIV or hepatitis B, or for their prevention, within 30 days of study enrollment.
19. Is currently taking systemic corticosteroids other than replacement doses or for treatment of COVID-19.
20. Has a body mass index (BMI) >50 kg/m^2.
21. Is anticipated to require surgery within 48 hours after hospital admission.

22. Is anticipated to have an NPO (nothing per mouth) order placed within 48 hours after hospital admission that is expected to last for ≥24 hours.

4. INVESTIGATIONAL PLAN

4.1. Definitions

I. Enrolled: From time consented to initiation of study drug until designated as off study either through discontinuation or completion of the study.
II. Randomized: when a patient identification (ID) number is assigned through randomization.
III. Screen Failures: signed informed consent, but then determined to be ineligible or withdraws before initiation of study drug.
IV. Discontinued: randomized, but then withdrawn by investigator or withdraws consent.
V. Completed: Participants are considered completed when they are followed through to Day 28 or died before that.

4.2. Randomization and Blinding

This study will be conducted in up to 4 parts. During Part 1, participants will be randomized in a 1:1:1 ratio to EIDD-2801 200 mg BID, EIDD-2801 400 mg BID, or placebo BID; during Part 2, approximately 21 participants will be randomized in a 2:1 ratio to EIDD-2801 400 mg BID:placebo BID; during Part 3, approximately 21 participants will be randomized in a 2:1 ratio to EIDD-2801 800 mg BID:placebo BID. An optional Part 4 may be added during which approximately 21 participants will be randomized in a 2:1 ratio to EIDD-2801 BID:placebo BID and the dose of EIDD-2801 may be the same or lower than doses studied in previous Part(s), but not to exceed 800 mg BID.

The study parts will be conducted as follows: Part 1 of the study may be terminated upon approval and implementation of Protocol Amendment 3, and Part 2 will be initiated immediately thereafter. Part 3 will be initiated once Part 2 has been fully enrolled. If initiated, Part 4 may begin enrolling participants as soon as Part 3 has been fully enrolled. Study Parts 2 and 3 may be terminated prematurely based on emerging data from this and other ongoing studies of EIDD-2801.

On Day 1, participants will be assigned a unique ID number (randomization number). The randomization number encodes the participant's assignment to one of the groups of the study, according to a randomization schedule generated prior to the start of each individual study part. Each participant will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' study drug assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study drug assignment unless this could delay emergency treatment of the participant. If a participant's study drug assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. If the investigator decides that unblinding is warranted, unblinding of a participant's study drug assignment will be coordinated by the unblinded pharmacist for the study.

4.3. Intervention

4.3.1. Screening

Adult patients who are newly hospitalized with PCR-confirmed SARS-CoV-2 and evidence of symptomatic COVID-19 will be invited to participate in the study. Those who express interest will undergo the informed consent process and be given the chance to ask any questions before agreeing to participate. Those who consent to participate will undergo screening for study entry; the time between screening and study entry should be as short as possible (ideally the same day, but no longer than 48 hours). Screening assessments will include demographics, medical history, concomitant medications, review of inclusion and exclusion criteria, height, weight, BMI, physical examination including vital signs, clinical chemistry labs (CMP), hematology (CBC with differential), high sensitivity serum beta-human chorionic gonadotropin (HCG) (to rule out pregnancy) as applicable, urinalysis, electrocardiogram (ECG), and pulse oximetry. It is expected that measurements/values will have been obtained as SOC, and medical chart extraction will be performed. Missing values will be obtained as part of study procedures. Any chest radiography results from hospital admission will be recorded.

4.3.2. Administration of Study Drugs

Upon completion of baseline assessments (including virologic assessments below), participants will then be administered the first dose of study drug (EIDD-2801 or placebo). Each participant will begin study treatment dosing with the first dose on the morning of Day 1, if possible. If the first dose is given later in the day, the second dose may be given at least 4 hours later on Day 1. Study drug administration will continue BID for a total of 5 days (10 doses). If the first dose on Day 1 is given in the late evening, the second dose may be taken on the morning of Day 2, in which case the final dose will be taken on the morning of Day 6.

In the event of missed doses, if the total number of missed doses is 4 or fewer, the number of days of study drug can be extended by no more than 1 day (through Day 6) with the equivalent of missed doses up to 2 doses. If the participant misses more than 4 consecutive doses, or more than 5 total doses, then the participant will be discontinued from any further study drug administration and followed for safety for the remainder of the study. Missed doses and times of administration will be recorded.

If a participant cannot ingest capsules orally during the study period, capsules will be opened, and the powder will be mixed with water and administered by mouth or through a nasogastric, percutaneous endoscopic gastrostomy (PEG) or orogastric tube.

4.3.3. Virologic Assessments

Upon enrollment, participants will have 2 NP swabs performed, one in each nostril (R or L to be documented), accessing the posterior nasopharynx. The NP swabs will be collected and stored separately for laboratory analysis. On Days 3, 5, 8, 11, 15 (inpatients only), 19 (inpatients only), and 28, participants will also have 2 NP swabs performed in the same way, collected and stored identically and individually. One swab will be sent to an infectivity lab for analysis. The other swab will be sent to for PCR sequencing. Detailed instructions for preparation and shipment of samples will be provided in a separate document.

In the setting of bronchoalveolar fluid lavage with sampling, or in participants who require mechanical ventilation who have endotracheal tube fluid sampling, we will collect a portion to perform viral RNA testing and the infectivity assay on the sample. If available from SOC procedures, a sample of sputum will also be collected if the participant has a productive cough and used to perform viral RNA testing and infectivity assays. In addition, a portion of material from NP swabs will be archived and frozen for viral sequencing.

4.3.4. Clinical Assessments

On each day that virology samples are obtained, participants will be assessed for clinical endpoints and interim AEs (and SAEs). Chart review will occur on structured days to perform safety assessments and record concomitant medications (including antivirals). CMP, CBC with differential, and urinalysis will be recorded at regular intervals during the study as indicated in the Schedule of Events (see Section 7.1). Any results that are not available will be obtained on the applicable chart extraction day.

Participants who are discharged from the hospital during study participation will return to the clinic for study visits through the Day 28 visit. Clinic visits will occur on Days 3, 5, 8, 11, and 28. On Day 15 (±1 day), a member of the study staff will contact the participant by telephone to query them about symptoms, study drug adherence, and concomitant medications. Outpatients will be seen in one of several locations, including but not limited to COVID-19 ambulatory pods, COVID-19 ambulatory clinics and clinical research units, and home visits. In all cases, visits will conform to infection control practices that are established by the institution. If the participant is discharged to a secondary care facility, study site staff will take measures to meet institutional regulatory requirements of the primary site as well as the receiving site to continue collecting study-related samples where allowed.

During in-clinic study visits, partial pressure of oxygen (PO2) will be measured by oximetry, and oral temperature will be documented. Other vital signs will be assessed, and a targeted physical examination will be conducted as needed. AEs and concomitant medications will be collected that have occurred since the last visit/report. Safety lab assessment (CBC with differential, CMP, and urinalysis) will be conducted, and for women of childbearing potential, a high sensitivity serum pregnancy test will be performed at the end-of-study (EOS) visit or at early discontinuation. Results of a single post-dose ECG should be recorded. If the participant is discharged from the hospital before a post-dose ECG is recorded, and recording of an outpatient ECG is not feasible, then results of the last recorded ECG before hospital discharged will be entered into the CRF. The results of any chest diagnostics done as part of SOC will be recorded. Any SAEs will be followed for 30 days after the end of study participation as detailed in Section 8.10.3.

Participants who are discharged from the hospital before the EOS visit will continue to take study drug at home for the full 5 day course, and drug accountability will be conducted at the Day 5 and/or Day 8 interim study visits, where allowed by the study institution. Participants will be instructed on how to report worsening of disease, including development of any additional symptoms of pneumonia or other concerning illness that may require interim assessment including clinic or urgent visits.

4.4. Pregnancy Testing

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 3.1.
- High sensitivity pregnancy testing should be conducted at screening (a serum test is required) within 24 hours of the first dose of study drug and on Day 28 approximately 23 days after the last dose of study intervention.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

4.5. Serology

Serology testing will be performed on plasma for IL-6 levels on Day 1 (pre-dose), Day 5, and Day 19. Samples will be archived for further cytokine testing in the future.

4.6. Rationale for Medication Dosing

Although 3 doses were effective in influenza models, the prolonged viral shedding that has been described in COVID-19 indicates that a longer dosing period may be beneficial. Also, allowing for differences between animal models and human disease, a margin of exposure at the top end of the range is desirable. Doses up to 800 mg twice daily are considered important to study in order to allow for sufficient exposure based on the use of data extrapolated from other species. Exploring a range of doses will allow for the selection of the best dose(s) to carry forward into subsequent studies.

Review of preliminary, unblinded data indicates that a treatment course of 5.5 days has been generally safe and well tolerated at multiple ascending doses (MAD) up to 800 mg, covering the doses planned for this efficacy/safety study. Also, single ascending doses (SAD) up to 1600 mg were similarly well tolerated, and PK has been dose-proportional in all cohorts. Refer to the IB for full information regarding animal efficacy studies and scaling to humans. Definition of an Overdose for this Protocol

For purposes of this protocol, an overdose is a single dose of more than 800 mg.

4.7. Concomitant Medications

Nucleos(t)ide analog drugs that are used for the treatment or prevention of HIV or hepatitis B virus are prohibited during the study, as are vaccines against COVID-19.

Remdesivir will be permitted. Corticosteroids for the treatment of COVID-19 will be permitted.

4.8. Study Discontinuation

If a participant is withdrawn from the study, the reason for withdrawal and the date the participant was removed will be documented in the case report form (CRF). A participant must be discontinued from the trial for any of the following reasons:

- The participant or legal representative (such as legal guardian) withdraws consent.
- Intercurrent illness that prevents further administration of treatment.
- Severe or life-threatening EIDD-2801-related AE(s).
- If in the opinion of the Investigator, a change or temporary or permanent discontinuation of therapy would be in the best interest of the participant.
- Noncompliance with trial treatment or procedure requirements.
- Participant is lost to follow-up.
- Participant becomes pregnant.

If a randomized participant withdraws from the study and has not been administered a dose of study drug or placebo, they will be replaced. Additional participants may be randomized, if needed, to ensure that an adequate number of participants provide Day 5 efficacy data.

Whenever possible, participants should continue to be monitored for safety through the remainder of the study.

The investigator should make every effort to perform the assessments indicated for the End-of-Study visit (see the Schedule of Events; Section 7.1) for participants who discontinue early from the study.

5. PHARMACEUTICAL INFORMATION

5.1. Agent Accountability

The study drug will be provided by the sponsor.

The study site will acknowledge receipt of study drug supplied by the sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

An accurate drug disposition record will be kept, specifying all study drug received, dispensed, returned to the sponsor, and disposed of by the study site. This drug accountability record will be available for inspection at any time, and at the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

5.2. Mode of Action

The mechanism of antiviral activity of EIDD-2801 is 'lethal mutagenesis', a concept that is predicated on increasing the viral mutation rate beyond a biologically tolerable threshold, resulting in impairment of viral fitness and leading to viral extinction.

The specifics of the mechanism are as follows: EIDD-2801 is rapidly taken up by cells and the 5′isopropylester cleaved to liberate EIDD-1931, which is in turn phosphorylated to EIDD-2061 by host kinases. The 5′triphosphate, EIDD-2061, acts as a competitive, alternative substrate for virally-encoded RNA-dependent RNA polymerases, and EIDD-2061 is incorporated into nascent viral RNA. Owing to the ability of the N4hydroxycytosine base of EIDD-1931 to tautomerize, EIDD-2061 can pair with either guanosine or adenosine, and consequently can substitute for either cytidine triphosphate (CTP) or uridine triphosphate (UTP), respectively. This results in an accumulation of mutations, which increase with each cycle of viral replication. The process whereby the mutation rate is increased by exposure to a drug is referred to as viral decay acceleration and results in viral ablation.

Significant work has gone into validating this mechanism of action for EIDD-2801/1931, and it has been shown for MERS-CoV, VEEV, and influenza A virus (IAV) that viruses grown in the presence of EIDD-1931 have significantly increased levels of transition mutations. Multi-log decreases in virus yields were observed after treatment with EIDD-1931. Additionally, it was demonstrated for VEEV that the infectivity of virions formed in the presence of EIDD-1931 decreases from approximately 20% to <0.2%, and that the infectious virions are significantly impaired in their replication ability. As a consequence of this mechanism of action, the generation of drug-resistant escape mutants is practically impossible. This same effect was demonstrated for CoV and influenza virus. Furthermore, given the unique mechanism of action, EIDD-2801 is expected to be active against viruses resistant to other antiviral agents which have a different mechanism of action. The only data generated to date regarding the activity of EIDD-1931 against viruses resistant to other nucleoside analogs found that EIDD-1931 was active against CoV resistant to remdesivir in cell culture assays.

As an alternative or additional mechanism of action, it has been theorized that incorporation of EIDD-2061 into viral genomic RNA can change the thermodynamics of RNA secondary structure and

thus decrease the efficiency of the promoter regions involved in RNA genome replication. Further details regarding the mechanism of action of EIDD-2801 are provided in the IB.

5.3. Description

EIDD-2801 is a white to off white solid.

EIDD 2801 (100- and 200-mg capsules) and matching placebo will be supplied as dry filled capsules for oral administration, along with the batch/lot numbers and Certificates of Analysis. Doses of EIDD-2801 or matching placebo will be administered as combinations of 100- and 200-mg capsules in such a way as to preserve the study blind and as appropriate for the dose level.

5.4. Packaging

The study drug will be labeled in accordance with regulatory requirements and will be stored according to the instructions on the label, in a location that is locked with restricted access.

5.5. Storage

Study drug should be stored in a secure, locked, restricted access facility at controlled room temperature defined as 15°C to 25°C (59°F to 77°F). Excursions are permitted up to 30°C (86°F) for up to 24 hours. If excursions occur which are outside of this range, the pharmacy staff should contact the sponsor to determine the course of action. Additional stability data may be available which would allow continued use of the study drug, or study drug may need to be replaced.

5.6. Route of Administration

EIDD-2801 is administered orally.

5.7. Participant Care Implications

Participants who receive EIDD-2801 during this study will be monitored for AEs and other safety findings. Virology samples will be collected and SOC for COVID-19 will be administered. Participation in this study will not alter clinical decisions with regards to hospital treatment, discharge, or outpatient management.

Participants who are admitted and enrolled at one participating site who are then transferred to another participating site, will continue to remain on study and will continue to receive study drug or placebo as initially assigned.

5.8. Returns and Reconciliations

At completion of the study, study drug will either be disposed of at the study site according to the study site's standard operating procedure or will be returned to the sponsor with the appropriate documentation. The site's method of destroying sponsor-supplied study drug must be agreed to by the sponsor. The site must obtain written authorization from the sponsor before any sponsor-supplied study drug is destroyed, and study drug destruction must be documented on the appropriate form.

5.9. Pharmacokinetics

Pharmacokinetic analysis will be performed in a subset of study participants and will be conducted based on local laboratory capacity. The PK secondary (plasma) and exploratory (PBMC) objectives will be limited to clinical sites that are able to participate, including but not limited to

Blood samples will be collected for plasma isolation and PBMC preparation to characterize EIDD-2801/EIDD-1931 and EIDD-2061 PK parameters. Previous studies demonstrated an EIDD-1931 PK $t_{1/2}$ of 0.969 hours in healthy human subjects (EIDD-2801 Investigator's Brochure, V3.0, 2020). The calculated $t_{1/2}$ of the EIDD-2061 metabolite is 4 hours, based on *ex vivo* incubation studies. Based on currently available PK data, additional pharmacologic analyses will be conducted in a subset of SARS-CoV-2-infected individuals.

Post-enrollment and initiation of therapy, and after an overnight fast (i.e., no food or liquid except for water after midnight), PK assessment will initiate on Day 3 for participants who are still inpatients. For EIDD-2801/EIDD-1931 analysis, blood will be collected on Day 3 at pre-dose, as well as 0.5 hours, 1.5 hours, 3 hours, 6 hours, 8 hours, on Day 3 and 24 hours post-Day 3 dose on Day 4 where possible. If a participant is scheduled to be discharged, then PK samples should be collected at all scheduled time points up to the time of discharge. In addition, if a participant is discharged prior to the 24-hour PK sample, a 12-hour PK sample on Day 3 should be collected, when possible.

Blood sampling for PBMC isolation and EIDD-2061 measurements will occur at pre-dose, as well as 0.5 hours, 1.5 hours, 3 hours, 6 hours, 8 hours, and 24 hours post-dose on Day 3 where possible, as described in the previous paragraph. Time of dose will be recorded on eCRFs.

Sparse PBMC sampling will be conducted to estimate EIDD-2061 $t_{1/2}$ and AUC_{tau}. C_{max} and t_{max} will be estimated. PK analyses in PBMC will be conducted as an exploratory objective to understand and characterize parent: metabolite (EIDD-1931:EIDD-2061) ratios at each time point, as well as persistence of EIDD-2061 after EIDD-1931 clearance from plasma.

Samples may be collected within a ± 15 minute window (for timepoints up to 3 hours post dose), ±30 minutes (for timepoints 6-8 hours post dose); and ± 1 hour (for timepoints 12-24 hours post dose).

Full processing details for plasma and PBMC PK will be provided within the study specific manual.

Sample Analysis

Plasma PK analysis will be performed at
. PBMC analysis will be performed under the control of the

The details of sample collection and analysis will be included in the Laboratory Manual and standard operating procedures (SOPs). Raw data will be archived at the bioanalytical site.

6. STATISTICAL CONSIDERATIONS

6.1. Sample Size and Power Considerations

We will test the hypothesis that EIDD-2801 will result in a larger proportion of NP swabs from recipients becoming undetectable (below the LOD of the assay) for SARS-CoV-2 RNA at Day 5 of EIDD-2801 administration compared to placebo. Participants receiving the same dose across the study parts will be pooled together in the final analysis. It is expected that 14 or more participants will receive EIDD-2801 in the higher dose groups, and at least 14 participants will receive placebo across the study parts. The power calculations were based on an individual dose arm versus placebo comparison, using a Fisher's exact test. Based on previous data (Wolfel, *Nature,* 2020), if we assume that 80% of the placebo arm and 20% of an EIDD-2801 arm are detectable at Day 5, we will have 83% power to detect a difference with α=0.05.

6.2. Statistical Analysis

6.2.1. Analysis Populations

Screened

All patients who consent to participate and who undergo screening will be included in the Screened population.

Safety

All patients treated with at least one dose of study drug will be included in the Safety population. Safety patients are analyzed according to their actual treatment received.

Intent-to-treat Set

The Intent-to-treat set (ITT) will consist of all randomized patients. ITT patients are analyzed according to their randomized treatment.

Efficacy Analysis Set

The Efficacy Analysis Set (EAS) will consist of all participants treated with at least one dose of study drug and with at least 1 post baseline assessment of SARS-CoV-2 RNA in NP swabs by qPCR. Efficacy analysis set participants are analyzed according to their actual treatment received.

Per Protocol Set

The Per-Protocol Set (PPS) will consist of all participants in the ITT population who do not have any important protocol deviations leading to exclusion from the PPS.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the participants from the PPS. Details will be provided in a Statistical Analysis Plan (SAP).

Pharmacokinetic

All participants treated with at least one dose of study drug with at least 1 reportable concentration of EIDD-will be included in the Pharmacokinetic (PK) population.

6.2.2. Data Handling

Day 1 is defined as the day of first dose of study drug. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis. Unscheduled visits will be listed but not tabulated.

Participants who received the same dose (i.e., placebo) across study parts will be combined into the same dose group. Data from the active treatment arms may be combined for analysis, when appropriate in comparison with the pooled placebo group.

6.2.3. Handling of Dropouts, Missing Data, and Outliers

Participants who prematurely discontinue from the study without receiving a single dose of study drug or placebo will be replaced. Participants who receive at least a single dose of study drug who prematurely discontinue study drug should continue to undergo regularly scheduled visits, including an end of study visit at Day 28, to evaluate clinical assessments, AEs, and SAEs for the analysis of the primary efficacy endpoint, if there is no swab is available for analysis then the patient's response will be imputed to have a detectable level of SARS-CoV-2 RNA by qPCR (non-response). Longitudinal analyses of secondary endpoints, such as the rate of decline of $\log_{10}$ viral RNA copies/mL for each method of sample collection, will use mixed effect models which are robust for missing data when this is missing completely at random (MCAR) or missing at random (MAR). Missing safety data will generally not be imputed. Details and exceptions will be provided in the SAP. No rules for outlier detection are planned.

6.2.4. Analysis of Primary Endpoint

To address the primary endpoint, we will use a Fisher's exact test to calculate the likelihood that a difference in detectable SARS-CoV-2 between a given dose of study drug (EIDD-2801 400 mg up to 800 mg) versus placebo, occurs by chance. Because the current SARS-CoV-2 RNA test is only 70% sensitive, we will perform 2 NP swabs at baseline and 2 NP swabs on Day 5, each analyzed separately (4 total NP swab measurements). Thus, an undetectable result at a given time point will be determined when neither NP swab has detectable (below the LOD of the assay) viral RNA at that time point. To graphically present the results, we will show individual points and smoothed curves to fully account for individual negative tests that are contemporaneously observed with positive tests.

6.2.5. Analysis of Secondary Endpoints

Secondary Virologic Endpoints:

1. Time to clearance of viral RNA in NP swabs
   - by qPCR
2. The decline in viral RNA by Day 3, Day 5, Day 8, Day 11, Day 15, Day 19, and Day 28 after initiation of study drug in NP swabs
   - - by qPCR
3. Rate of decline in viral RNA (change in log_{10} copies/mL per day) in NP swabs
   - - by qPCR

The time to clearance of viral RNA will be analyzed using the Kaplan-Meier method. The event time of median, 25th, 75th percentiles and associated 95% confidence intervals will be provided by dose group. The cumulative probability of BLOQ and the associated 95% confidence interval for the scheduled visit will also be provided by dose group.

The decline in viral RNA over time will be analyzed using a mixed effect of repeated measure model (MMRM). The model estimated between-group differences and associated 95% confidence intervals will be provided by scheduled visits. The rate of decline for each dose group will be estimated using a mixed effect linear model.

Additional details will be described in a SAP and finalized before database lock.

Details for the analyses of exploratory virologic endpoints will be described in the SAP.

6.2.6. Analysis of Adverse Event Data

Analysis of AE data will primarily be descriptive based on the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE is considered treatment-emergent if it begins or worsens in severity after the first dose of randomized study drug. The number and percentage of participants with treatment-emergent AEs will be tabulated by system organ class (SOC) and preferred term. Additional AE summaries will be provided by severity, drug related AEs, AEs leading to study drug discontinuation, and serious AEs.

6.2.7. Analysis of Other Safety and Clinical Data

Other safety and clinical endpoints will be provided descriptively by dose group and scheduled time of assessment where appropriate. Details will be provided in the SAP.

6.2.8. Analysis of Pharmacokinetic Data

Plasma EIDD-1931 PK Endpoints:

1. Maximum EIDD-1931 concentration (C_{max})
2. 1.5-hour EIDD-1931 concentration ($C_{1.5}$)
3. 3-hour EIDD-1931 concentration (C_3)
4. Area under the concentration: time curve EIDD-1931 (AUC_{0-8})
5. Elimination half-life ($t_{1/2}$) EIDD-1931

PBMC EIDD-2061 PK Endpoints:

1. Maximum EIDD-2061 concentration (C_{max})
2. EIDD-2061 time of maximal concentration (t_{max})
3. Elimination half-life of EIDD-2061 ($t_{1/2}$)
4. Area under the concentration: time curve EIDD-2061 (AUC_{0-12})
5. Parent: metabolite (Plasma EIDD-1931:PBMC EIDD-2061) concentration ratio at each time point

PK data will be summarized by dose group and scheduled time of assessment where appropriate. If data permit, assessment of dose proportionality will be performed and the relationship between the exposure parameters and virologic endpoints will be explored. Details will be described in the SAP.

7. STUDY PROCEDURES

7.1. Schedule of Events

	Inpatient										
Study Procedures	**Screening[a] Day -2 to 1**	**Day 1**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 11**	**Day 15**	**Day 19**	**Day 28 (EOS)**	**Early Discontin-uation**
Informed Consent	X										
Demographic data	X										
Inclusion/Exclusion Criteria	X										
Randomization [b]		X									
Medical History	X										
Pregnancy test[c]	X									X	X
Serology (plasma)[d]		X[e]			X				X		
Height, weight, BMI	X										
Study residency											
Visit while hospitalized for MR review	X	X	X		X	X	X	X	X	X	X
Prior/Concomitant medication review	X	X	X		X	X	X	X	X		
Study drug vs. placebo											
EIDD-2801 or PBO administration[f]		BID on Days 1-5	BID on Days 1-5	BID on Days 1-5	BID on Days 1-5						
Virologic endpoints											
NP swabs[g]		X[e]	X[e]		X[e]	X	X	X	X		
BAL and/or sputum[h]		X	X		X	X	X	X	X		
Clinical endpoints											
WHO Ordinal Scale (Appendix 1)[i]		X[i]	X		X	X	X	X	X	X	X
Clinical assessments[j]		X	X		X	X	X	X	X	X	X
Safety and tolerability											
AE/SAE reporting		X	X		X	X	X	X	X	X	X
Vital signs (temperature, blood pressure, pulse, respiratory rate)	X	X	X		X	X	X	X	X	X	X
Pulse oximetry[k]	X	X	X		X	X	X	X	X	X	X
Full physical examination	X									X	
Targeted physical examination [l]		X	X		X	X	X	X	X		X
Laboratory[m]	X		X		X	X		X	X		

Inpatient											
Study Procedures	**Screening[a] Day -2 to 1**	**Day 1**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 11**	**Day 15**	**Day 19**	**Day 28 (EOS)**	**Early Discontin-uation**
12-lead ECG[n]	X						1 posttreatment ECG to be performed, as feasible [n]				
Chest radiography[o]		X	X		X	X	X	X	X	X	X
Pharmacokinetics											
Plasma[p]			X	X							
PBMCs[p]			X	X							

Abbreviations: AE = adverse event; BAL = bronchoalveolar lavage; BID = twice daily; CBC = complete blood count; CMP = complete metabolic panel; ECG = electrocardiogram; EOS = end of study; h = hours; ICU = intensive care unit; IL-6 = interleukin 6; MR = medical record; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PBO = placebo; PK = pharmacokinetic; QD = once daily; QOD = every other day; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; SOE = schedule of events; WHO = World Health Organization.

a. Screening and Day 1 procedures will occur on the same day whenever possible as soon as SARS-CoV-2 testing is determined to be positive. A window of up to 6 days is allowable if the participant has not had symptoms for more than 7 days prior to dosing.
b. Randomization can happen at Screening or Day 1
c. For women of child-bearing potential only, high sensitivity serum pregnancy tests are required at Screening within 24 hours of the first dose of study drug and on Day 28. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.
d. Serology testing will be performed on plasma for immune response on Day 1 (pre-dose), Day 5, and Day 19, and specimens will be archived for further cytokine testing in the future.
e. The sample should be collected pre-dose.
f. EIDD-2801 and PBO are to be administered BID on Days 1-5. The first dose will be administered in the morning of Day 1, if possible. If the first dose is given later in the day, the second dose may be given at least 4 hours later on Day 1. If the first dose on Day 1 is given in the late evening, the second dose may be taken on the morning of Day 2, in which case the final dose will be taken on the morning of Day 6. In the event of missed doses, if the total number of missed doses is 4 or fewer, the number of days of study drug can be extended by no more than 1 day (through Day 6) for the equivalent of missed doses up to 2 doses. If the participant misses more than 4 consecutive doses, or more than 5 total doses, then the participant will be discontinued from any further study drug administration and followed for safety for the remainder of the study.
g. One NP swab will be collected from each nostril at each time point for a total of 2 swabs per time point.
h. BAL and/or sputum fluid *may* be collected when available for viral RNA testing. No study specific interventions will be initiated for collection of BAL fluid and/or sputum if participant has a productive cough. If, during clinical care, BAL is performed and excess fluid is available, the study team will collect this fluid for testing.
i. Note that on Day 1, the WHO ordinal scale assessment should be performed before the first dose of EIDD-2801 is administered.
j. Clinical assessments will be ascertained by chart extraction and will include number of days in the hospital, maximum O_2 requirements daily, ICU admission and number of days in the ICU, mechanical ventilation and number of days requiring mechanical ventilation, death, and symptom reporting.

k. Oxygen saturation is to be recorded twice daily (morning and evening) and may be ascertained by chart extraction; if not available in the participant's chart, it should be measured by the study staff.
l. Targeted physical examinations should be done if indicated by an AE or as needed in the judgement of the investigator.
m. Laboratory measurements will include CBC with differentials, CMP (including amylase and lipase), and urinalysis.
n. For ECGs, a single post-dosing recording should be collected. If the participant is discharged from the hospital before a post-dose ECG is recorded, and recording of an outpatient ECG is not feasible, then results of the last recorded ECG before hospital discharge will be entered into the CRF.
o. Results of all chest radiography performed as part of routine clinical care during Study Days 1-28 should be recorded.
p. Plasma and PBMC samples for PK analysis will be collected from participants if they are still inpatients on Day 3. Samples will be collected before the morning dose on Day 3 and at the following times after the Day 3 morning dose: 0.5 hours, 1.5 hours, 3 hours, 6 hours, 8 hours, and 24 hours (i.e., on the morning of Day 4). If a participant is scheduled to be discharged, then PK samples should be collected at all scheduled time points up to the time of discharge; in addition, if a participants is discharged prior to the 24-hour PK sample, a 12-hour PK sample should be collected, when possible. PK measurements will be assessed in participants enrolled at clinical sites able to conduct the collections. These sites include, but are not limited to, Samples may be collected within a ± 15 minute window (up to 3 hours), ± 30 minutes (6-8 hours), or ± 1 hour (12-24 hours).

Outpatient[a]							
Study Procedures	**Day 3**	**Day 5[b]**	**Day 8 (±1 day)**	**Day 11 (±1 day)**	**Day 15 (±1 day)**	**Day 28 (EOS) (±2 days)**	**Early Discontin-uation**
Serology (plasma)[c]		X				X	X
Pregnancy test[d]						X	X
Study residency							
Outpatient visit	X	X	X	X		X	X
Phone call[e]					X		
Study drug vs. placebo							
EIDD-2801 or PBO administration[f]	BID on Days 1-5	BID on Days 1-5					
Virologic endpoints							
NP swabs [g, h]	X	X	X	X		X	X
Clinical endpoints							
WHO Ordinal Scale (**Appendix 1**)[h]	X	X	X	X	X	X	X
Safety and tolerability							
Concomitant medication review	X	X	X	X	X	X	X
AE/SAE reporting [h]	X	X	X	X	X	X	X
Vital signs (temperature, blood pressure, pulse, respiratory rate) [h]	X	X	X	X		X	X
Pulse oximetry[j]	X	X	X	X		X	X
Targeted physical examination[k]	X	X	X	X		X	X
Laboratory [l]	X	X	X	X		X	X
Chest radiography[m]	X	X	X	X		X	X

Abbreviations: AE = adverse event; BAL = bronchoalveolar; BID = twice daily; CBC = complete blood count; CMP = complete metabolic panel; ECG = electrocardiogram; EOS = end of study; ICU = intensive care unit; IL-6 = interleukin 6; ; MR = medical record; NP = nasopharyngeal; PBO = placebo; PK = pharmacokinetic; QD = once daily; QOD = every other day; SOE = schedule of events; WHO = World Health Organization.

a. For participants who are discharged from the hospital after randomization and administration of the first-dose of study drug or PBO, this schedule will apply. Day number will be counted from enrollment. Participants will enter the Outpatient SOE upon day of discharge. Outpatients will be seen in one of several locations, including but not limited to COVID-19 ambulatory pods, COVID-19 ambulatory clinics and clinical research units, and home visits. In all cases, visits will conform to infection control practices that are established by the institution.
b. If Day 5 falls on a Saturday, then a visit will occur on Day 4. If Day 5 falls on a Sunday, then a visit will occur on Day 6.

c. Serology testing will be performed on plasma for IL-6 levels on Day 1 (pre-dose), Day 5 and Day 28, and specimens will be archived for further cytokine testing in the future.
d. Pregnancy test is required for women of childbearing potential only. High sensitivity serum pregnancy tests are required on Day 28. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.
e. Phone calls will be used to query participants about symptoms, study drug adherence, concomitant medications and to assess WHO ordinal scale.
f. EIDD-2801 and PBO are to be administered BID on Days 1-5. The first dose will be administered in the morning of Day 1, if possible. If the first dose is given later in the day, the second dose may be given at least 4 hours later on Day 1. If the first dose on Day 1 is given in the late evening, the second dose may be taken on the morning of Day 2, in which case the final dose will be taken on the morning of Day 6. In addition, if a participant misses up to 2 doses during Days 1 to 5, dosing may be extended into Day 6. If discharge occurs prior to completion of study drug dosing (prior to Day 6), study drug will be administered in the hospital on the morning of discharge, and the remainder of the study drug will be dispensed for administration at home by the participant. Procedures will be put into place to ensure study drug compliance (e.g., telephone, eCollection) and drug accountability will be assessed on Days 5 and 8.
g. One NP swab will be collected from each nostril at each time point for a total of 2 swabs per time point.
h. Will be obtained at least once on the indicated day AND on the day of discharge from inpatient to outpatient, at the discretion of the investigator in consultation with the sponsor.
i. Clinical assessments will be ascertained by chart extraction, including number of days in the hospital, maximum O_2 requirements daily, ICU admission and number of days in the ICU, mechanical ventilation and number of days requiring mechanical ventilation, death, and symptom reporting.
j. If the oxygen saturation value is <92%, the measurement should be repeated once within 30 minutes.
k. Targeted physical examinations should be done if indicated by an AE or as needed in the judgement of the investigator.
l. Laboratory measurements will include CBC with differentials, CMP (including amylase and lipase), and urinalysis.
m. Results of all chest radiography performed as part of routine clinical care during Study Days 1-28 should be recorded.

8. ADVERSE EVENTS, RISKS, AND BENEFITS

8.1. Potential Benefits of treatment

Based on animal efficacy studies, it is expected that EIDD-2801 will be active against SARS-CoV-2 infection in humans. This study will examine virologic responses to treatment with EIDD-2801 and is not powered to detect clinical outcomes. However, clinical improvement will be recorded for secondary/exploratory analysis.

8.2. Potential benefits of clinical monitoring

Benefits of participation in this study include the increased clinical monitoring of study participants. Intensive virology testing will be conducted.

8.3. Potential risks

The AE profile for EIDD-2801 is preliminary and derives from a Phase 1 study that is ongoing. Thus far, AE that were determined to be attributable to EIDD-2801 include insomnia, headaches, nausea, vomiting, abdominal pain, and loose stools (*see* the EIDD-2801 Investigator's Brochure, V3.0, 2020*)*.

Gastrointestinal events and liver enzymes will also be monitored.

8.4. Alternatives

The alternative to participation in this study is routine care and monitoring of COVID-19, receipt of a SOC treatment for SARS-CoV-2 infection if available, or participation in a different clinical trial, if available.

8.5. Definitions

8.5.1. Adverse Event

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy/intervention) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered AEs if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require investigation or therapy (i.e., are considered to be clinically significant).

This study will use the descriptions and grading scales found in the DAIDS Adverse Event Grading Scale for AE reporting.

8.5.2. Serious Adverse Event

An SAE is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form, although participants must have a negative pregnancy test prior to therapy and use at least 2 forms of non-hormonal contraception. All participants (men and women) must state that they will use 2 forms of contraception during the study and for 4 days after completion of EIDD-2801 dosing in female participants and for 4 days after completion of EIDD-2801 dosing in female partners of male participants.
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Events **not** considered to be SAEs are hospitalizations for the:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

- Escalation of care that is considered part of the disease progression of COVID-19 (including but not limited to need for escalation in supplemental oxygen, need for mechanical ventilation, need for intubation, admission to the ICU, cytokine release syndrome [defined by an elevation in IL-6 and CRP levels], thromboembolic events) will not be collected as SAE.

- Pregnancies will be reported using the SAE reporting guidelines for expedited reports (Section 8.10.4).

8.6. Relationship

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

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

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

The following factors should also be considered:

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

- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.

- Concomitant medication - The other medications the participant is taking or the treatment the participant 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 - 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.

8.7. Assessment of Grade/Severity

The investigator will assess grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the participant.

8.8. Expectedness

Unexpected adverse event: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the IB, package insert or safety reports. Any AE that is not included in the informed consent is considered "unexpected". At the time of this protocol, no events are considered to be expected for safety reporting purposes.

Expected (known) adverse event: An AE, which has been reported in the package insert. An AE is considered "expected", only if it is included in the informed consent document as a risk.

8.9. Handling of Expedited Safety Reports

In accordance with local regulations, the IND sponsor or designee will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to EIDD-2801. This notification will be in the form of an expedited safety report (ESR) that is to be emailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

8.10. Reporting

Information about all AEs, whether volunteered by the participant, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All AEs experienced by participants will be collected and reported from the first dose of EIDD-2801, throughout the study, and will only be followed for 28 days unless related to the investigational agent.

Participants who have an ongoing AE related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

8.10.1. Routine Adverse Event Reporting

If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, the maximum severity of the AE will be recorded. Adverse events should be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Participants with AEs at study completion should receive post-treatment follow-up as appropriate.

All identified non-serious AEs must be recorded and described on the appropriate Adverse Event Case Report Form (CRF).

8.10.2. Laboratory Test Abnormalities

Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator.

In addition, the following laboratory abnormalities should also be captured on the AE CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the participant to have the investigational product discontinued or interrupted
- Any laboratory abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

8.10.3. Serious Adverse Event Reporting

All SAEs (including deaths) occurring from the first dose of the study drug through the 28 day End-of-Study telephone call will be collected and recorded on the Adverse Event Case Report Form (CRF).

The PI or clinical site personnel should notify of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical site personnel becoming aware of the event. The PI (or designee) will provide the initial notification by sending a completed SAE form which must include the PI's (or designee's) assessment of the relationship of the event to investigational drug and must be signed by the PI. Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to at or via fax.

The SAE Form will collect data surrounding the event (e.g., the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued). The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will also be collected.

SAEs will be reported to each participating site's IRB per institutional guidelines by the PI.

After the initial SAE report, the investigator is required to proactively follow each participant and provide further information regarding the participant's condition.

All AE(s) and SAE(s) will be followed until one of the following conditions is met:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The participant is lost to follow-up
- Death

8.10.3.1. Expedited IND Safety Reports to the FDA

All reporting to the FDA will be completed by the IND sponsor.

7 Calendar-Day Telephone or Fax Report:

The IND sponsor is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be submitted to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:

The IND sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event considering the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

IND Annual Reports:

In accordance with the regulation 21 CFR § 312.33, the IND sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the AEs and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND sponsor.

8.10.4. Pregnancy and Exposure During Breastfeeding

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy in a female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner).

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing a fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported

9. SAFETY OVERSIGHT

9.1. Monitoring Plan

1. All AE and grade 1-3 SAE will be reviewed by the protocol team twice monthly, or more if needed. All grade 4-5 SAEs will be reviewed by the protocol team within 24-48 hours of being received.

2. A safety review committee (SRC), composed of the principal investigator for each study site and the medical monitor, will be established. The Committee will review blinded safety data at regular intervals. If the SRC identifies a potential safety issue, they may ask for additional safety analyses to further assess the issue, in cooperation with the sponsor. Details of SRC composition, responsibilities, and procedures will be provided in a SRC Charter.

Additional details can be found in Section 9.2, in the Data and Safety Monitoring Plan for the study, and in the Study Unblinding Plan.

9.2. Stopping Criteria for the Study

The study enrollment and dosing will be stopped, and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, participant safety is at risk of being compromised:

I. Unexpected death of a dosed participant.

II. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.

III. A trend of unexpected SAEs related to the study product.

IV. Two participants with a Grade 3 or higher lab toxicity for the same parameter associated with the study product.

V. An overall pattern of symptomatic, clinical, or laboratory events that the SRC considers associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.

VI. Any other event(s) which is considered to be a SAE in the good clinical judgment of the responsible physician. This will be appropriately documented.

Upon completion of this review, the SRC will determine if the study enrollment or study dosing should be interrupted or if study enrollment and study dosing may continue according to the protocol. Should the trial not be stopped at this time point, the final analysis would need to account for the number of interim analyses that were conducted. Therefore, we will use the O'Brien and Flemming type spending function to preserve the overall Type 1 error. This will

allow for stopping the trial earlier should the intervention arm be shown to be superior at an interim analysis.

Interim analyses: Interim analyses are planned when 25% and 50% of the final sample size reach Day 14 after initiation of study drug. Blinded data will be reviewed by the principal investigators and the sponsor. Data to be reviewed will include blinded summaries of the primary efficacy endpoint (achievement of undetectable viral RNA by Day 5 in NP swabs) and the primary safety endpoints. For the primary safety endpoints, the cumulative incidence of each type of safety endpoint will be summarized by study arm in addition to the risk difference and 95% confidence interval of the risk difference between study arms. The interim analyses will be used to inform sponsor decisions about whether to continue, amend, or stop the study.

10. ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1. Ethical Standard

The JHU and Ridgeback Biotherapeutics, LP are committed to the integrity and quality of the clinical studies it coordinates and implements. JHU will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all JHU sites participating in this research study.

As the Department of Health and Human Services continues to strengthen procedures for human subjects' protections via new regulations, JHU will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, JHU has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for JHU is FWA00005834.

This assurance commits a research facility to conduct all human subjects' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

10.2. Institutional Review Board

The JHU IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before participant enrollment. The JHU IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

10.3. Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The participant or the participant's legally authorized representative will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the participant for their records. The consent will explain that participants may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the participant in understandable language. Adequate time will be provided to ensure that the participant has time to consider and discuss participation in the protocol. The consent will describe in detail the study interventions/products and risks/benefits associated with participation in the study. The rights and welfare of the participants will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study. Participants with Low English Proficiency or who are Non-English-Speakers will be enrolled with the use of a certified interpreter who will also serve as a consent witness.

10.4. Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the IND Sponsor. The results of the research study may be published, but participants' names or identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with participants' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be coded. Participants' records will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

10.5. Future Use of Stored Specimens

Participants will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the participant will be maintained. There will be no plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy. However, these samples will be taken at the same time as other protocol required samples. No human genetic testing will be performed on the samples.

Samples would not be shared with investigators other than investigators at unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at . Any use of these specimens not specified in the current protocol will be reviewed by the IRB.

10.6. Data Management and Monitoring

10.6.1. Source Documents

The primary source documents for this study will be the participants' medical records. If the investigators maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study. The investigator will retain a copy of source documents. The investigator will permit monitoring and auditing of these data and will allow the IRB and regulatory authorities access to the original source documents. The investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected and entered into the study database/case report form and must be signed and dated by the person recording and/or reviewing the data. All data submitted should be reviewed by the site investigator and signed as required with written or electronic signature, as appropriate. Data entered into the study database will be collected directly from participants during study visits or will be abstracted from participants' medical records. The participants' medical records must record their participation in the clinical trial and what medications (with doses and frequency) or other medical interventions or treatments were administered, as well as any AEs experienced during the trial.

10.6.2. Data Management Plan

Study data will be collected at the study site(s) and entered into the study database. Data entry is to be completed on an ongoing basis during the study.

10.6.3. Data Capture Methods

Sites will collect and enter the minimum necessary study data required by the electronic Case Report Forms (eCRFs) into the study base, which will be contained on the Medidata Rave platform. Medidata Rave has been validated to comply with 21 CFR Part 11 and HIPAA. Study personnel designated on the Delegation of Authority log to enter data will be required to complete training to access the database. Each study site will only have access to data collected at their site, and data captured will be isolated from all other study sites. All actions taken in relation to the database will be tracked via an audit trail. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

10.6.4. Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents.

No study document should be destroyed without prior approval from the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

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Appendix 1. World Health Organization Ordinal Scale for Clinical Improvement of COVID-19 Disease

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Appendix 2. Contraceptive Guidance

Definition of Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

  Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE[a]:
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progesterone-only subdermal contraceptive implant[b] • Intrauterine hormone-releasing system (IUS)[c] • Non-hormonal intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to a medical cause) This is a highly effective contraceptive method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and lifestyle of the participant.
Highly Effective Contraceptive Methods That Are User Dependent[d] (must be used in combination with a barrier method) Combined (estrogen- and progestogen-containing) hormonal contraception – Oral – Intravaginal – Transdermal – Injectable Progestogen-only hormone contraception[b] – Oral – Injectable Barrier methods to be used with hormonal contraceptives above (male condoms are preferred method) • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)

Footnotes:

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

b) If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

c) IUS is a progestin-releasing IUD

d) Failure rate of <1% per year when used consistently and correctly (and not in combination with barrier method). Typical use failure rates are higher than perfect-use failure rates (i.e., when used consistently and correctly).

Note: The following are not acceptable methods of contraception alone or in combination:

– Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

– Male and female condom should not be used together (due to risk of failure with friction).