RIDGEBACKBIO

CLINICAL TRIAL PROTOCOL

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19

Protocol No: EIDD-2801-2003

Protocol Version – 5.0

Date: 15 November 2020

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SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

11/17/2020

Date

Biotherapeutics LP

[redacted]

1/17/2020

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Protocol EIDD-2801-2003

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR part 46); applicable US Food and Drug Administration regulations; standards of the International Council on Harmonisation Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: [redacted] _____
Print/Type

Signed: [redacted] _____ Date: 11/17/2020 _____

SITES PARTICIPATING IN THIS STUDY

EIDD-2801-2003 is a multicenter study that will be initially limited to and conducted at the University of North Carolina Clinical Trials Unit (CTU). Up to 15 additional sites, including Wake Forest University CTU, may be added based on the local incidence of COVID-19.

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GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BID	Twice Daily
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	Coronavirus Disease 2019
CQMP	Clinical Quality Management Plan
CRS	Cytokine Release Syndrome
DAIDS	Division of AIDS
DMT	Data Management Team
DSS	Drug Safety Services (Covance)
EC	Ethics Committee
eCRF	Electronic Case Report Form
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HAE	Human airway epithelial cell culture
HIV	Human Immunodeficiency Virus
HTN	Hypertension
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICU	Intensive Care Unit
ICF	Informed Consent Form
ID	Identification

[redacted]	[redacted]
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IV	Intravenous
MOPS	Manual of Procedures
MERS-CoV	Middle East Respiratory Syndrome coronavirus
m-ITT	Modified Intention-To-Treat
NIH	National Institutes of Health
NP	Nasopharyngeal
NPI	Nonpharmacologic Intervention
OHRP	Office for Human Research Protections
OP	Oropharyngeal
PD	Pharmacodynamic
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetic
[redacted]	[redacted]
PSS	Patient Safety Solutions (Covance)
[redacted]	[redacted]
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SMC	Safety Monitoring Committee
SOE	Schedule of Evaluations
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal

UNC	University of North Carolina
WHO	World Health Organization

SCHEMA

EIDD-2801-2003

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19

DESIGN

This is a Phase IIa, double-blind, placebo-controlled, randomized trial designed to compare the safety, tolerability, and antiviral activity of EIDD-2801 (also known as MK-4482) versus placebo as measured by viral RNA detection in symptomatic adult outpatients with coronavirus disease-2019 (COVID-19).

DURATION

28 days. Treatment will be for 5 days with 23 days of post-treatment follow-up.

SAMPLE SIZE

This study will enroll up to approximately 172 fully evaluable participants in multiple study parts. If participants in a dose group drop out or otherwise have missing or unevaluable primary or key secondary virology endpoint data, additional participants may be enrolled to ensure adequate data at each dose level. The total number of participants to be enrolled will not exceed 204.

Part 1:

- Arm A (EIDD-2801 200 mg): up to approximately 22 participants
- Arm B (placebo): up to approximately 22 participants

Parts 2-4 (Optional):

- Arms C (Part 2), E (Part 3), G (Part 4) (EIDD-2801 up to 800 mg): up to approximately 12 participants per part
- Arms D (Part 2), F (Part 3), H (Part 4) (placebo): up to approximately 4 participants per part

Parts 5-9 (Optional):

- Arms I, K, M, O, Q (EIDD-2801 up to 800 mg): up to approximately 12 participants per part
- Arms J, L, N, P, R (placebo): up to approximately 4 participants per part

The dose of EIDD-2801 evaluated in Part 1 will be 200 mg BID. Doses selected for subsequent study parts may be the same, higher or lower than doses studied in previous Part(s), and will not exceed 800 mg BID. Doses

will be chosen based on emerging virology and safety data from this study and other ongoing clinical studies. Selected doses will be communicated in an official memo/protocol clarification letter. The maximum number of participants enrolled will be 204. Participants who are randomized but do not start study treatment will be replaced. All study part sizes are approximate. Study parts may be combined for randomization purposes if the same dose is planned for more than one part. Study parts enrolling at the same dose level may be enrolled simultaneously.

Sample Treatment Assignment Table (Fully Evaluable Participants)
(doses and order of progression subject to change)

Study Part	Treatment Arm (n)	Placebo Arm (n)	Total Subjects	Projected Dose Level
1	A (22)	B (22)	44	200 mg
2	C (12)	D (4)	16	400 mg
3	E (12)	F (4)	16	400 mg
4	G (12)	H (4)	16	400 mg
5	I (12)	J (4)	16	TBD or 800 mg
6	K (12)	L (4)	16	TBD or 800 mg
7	M (12)	N (4)	16	TBD or 800 mg
8	O (12)	P (4)	16	TBD or 200 mg
9	Q (12)	R (4)	16	TBD or 400 mg
Total:	**118**	**54**	**172**	

POPULATION Symptomatic, outpatient (at baseline), adults (aged ≥18 years) with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection within 7 days of symptom onset.

REGIMEN In Part 1 of the study, participants will be randomized 1:1 into Arms A and B to receive active/placebo study treatment as follows: EIDD-2801 200 mg or placebo orally BID for 5 days. Enrollment for Arms A and B may be considered full when at least 24 and up to approximately 44 participants are enrolled. Enrollment in Part 1 may be interrupted to initiate enrollment in a different study Part, and may resume at a later time point. In subsequent optional study parts, participants will be randomized 3:1 to receive treatment as follows: EIDD-2801 up to 800 mg or placebo orally BID for 5 days.

1. HYPOTHESIS AND STUDY OBJECTIVES

1.1. Hypotheses

1.1.1. EIDD-2801 treatment will decrease the time to clearance of SARS-CoV-2 virus in NP specimens from symptomatic SARS-CoV-2 infected adults compared to placebo.

1.1.2. EIDD-2801 will be safe and well tolerated in persons with symptomatic SARS-CoV-2 infection.

1.2. Primary Objectives

1.2.1. Primary Efficacy Objective To determine if EIDD-2801 reduces the time to viral RNA negativity. Viral RNA negativity will be determined by reverse-transcriptase polymerase chain reaction (RT-PCR) of NP \swabs.

1.2.2. Primary Safety Objective To determine the safety and tolerability of EIDD-2801 including 1) any adverse events (AEs) leading to early discontinuation of treatment, 2) study drug-related discontinuation of treatment, 3) new grade 3 or higher AEs (not already present at baseline), and 4) study drug-related new grade 3 or higher AEs.

1.3. Secondary Objectives

1.3.1. To determine if EIDD-2801 reduces the time (days) to negativity of infectious virus isolation in NP swabs from SARS-CoV-2-infected adults. Infectious virus isolation is determined by isolation in Vero cell line culture.

1.3.2. To compare the incidence of grade 2 or higher AEs and drug-related AEs between treatment arms.

1.3.3. To determine if EIDD-2801 reduces the shedding of SARS-CoV-2 RNA in NP swabs compared to placebo as measured by median change in RNA at Treatment Days 3, 5, 7, 14, and 28 as determined by quantitative RT-PCR.

1.3.4. To determine if EIDD-2801 increases viral RNA mutation rate. RNA mutation rate is measured by Next Generation sequencing.

1.3.5. To determine if EIDD-2801 changes the severity and duration of self-reported symptoms of COVID-19.

1.3.6. To determine if EIDD-2801 treatment reduces the proportion of participants who are hospitalized for COVID-19 related illness by Day 28.

1.3.7. To characterize the PK of EIDD-2801/EIDD-1931 in patients with COVID-19 following administration of study regimen.

1.3.8. To determine the relationship between drug exposure and viral elimination dynamics including time to clearance.

1.4. Exploratory Objectives

1.4.1. To determine if EIDD-2801 will prevent the composite endpoint of hospitalization, oxygen desaturation, oxygen requirement, mechanical ventilation, or death by 28 days after study entry. Hospitalization is defined as ≥24 hours of acute care. Oxygen desaturation will be measured using pulse oximetry. Oxygen requirement will be measured using the World Health Organization (WHO) ordinal scale (see Appendix 1**)**

1.4.2. To determine the comparability between site-collected NP and available OP swabs and available self-collected nasal mid-turbinate swabs for the quantification of SARS-CoV-2 RNA or quantitative culture

1.4.3. To determine comparability between viral RNA detection and virus isolation from site-collected NP swabs.

2. INTRODUCTION

2.1. Background

2.1.1. Public Health Emergency of International Concern

On December 31, 2019, China reported a cluster of cases of severe pneumonia of unknown etiology in the city of Wuhan to the WHO. The China Centers for Disease Control and Prevention (China CDC) rapidly identified a novel betacoronavirus, SARS-CoV-2, as the etiologic agent with approximately 70% genetic homology with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and 50% homology with Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV). In the ensuing 4 months, this virus has infected more than 5 million individuals globally with over 345,000 deaths as of the date of this protocol, leading the WHO to declare the COVID-19 outbreak a Public Health Emergency of International Concern[6].

In the absence of currently approved therapies for SARS-CoV-2 infection and given the rapid spread of this virus with a marked increase in mortality, the identification of an effective therapeutic represents an urgent public health need. As a result, global efforts to identify therapeutic interventions with antiviral or immunomodulatory activity have intensified.

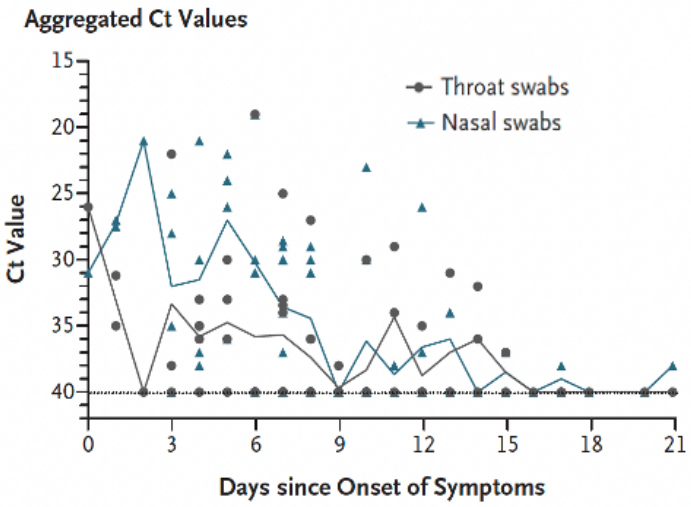

Figure 1: SARS-CoV-2 viral load in throat and nasal swabs [1]

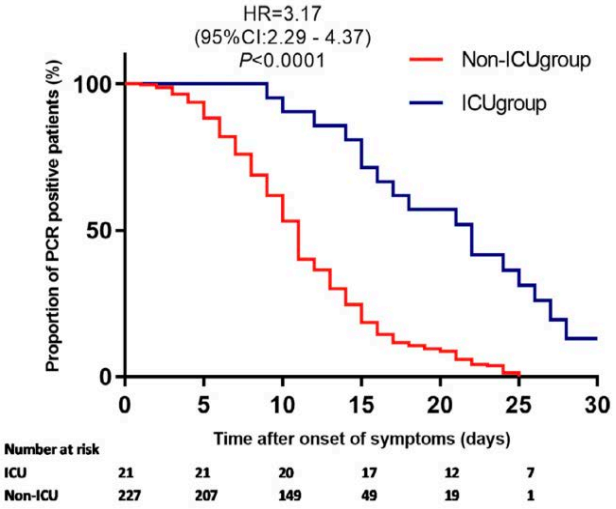

Figure 2: Prolonged viral RNA detection in patients with critical illness

After an incubation period of between 2 and 14 days from exposure, approximately 81% of patients develop uncomplicated illness characterized by variable appearance of non-specific symptoms including fever, non-productive cough, dyspnea and myalgias [1,7-12]. Approximately, 14% of symptomatic patients develop severe illness often defined by a respiratory rate >30 breaths per minute, oxygen saturation ≤93%, a partial pressure of arterial oxygen:percentage of inspired oxygen

(PaO2:FiO2) ratio <300, or greater than 50% lung involvement on chest imaging [7]. An additional 5% of patients become critically ill with respiratory failure, shock and multi-organ dysfunction [7]. Although asymptomatic infection has been described, the relative proportion of patients who never develop symptoms is not known[13,14].

Risk factors for severe disease include older age, male sex, and metabolic syndrome comorbidities including hypertension, diabetes mellitus, and obesity. Markers of a systemic inflammatory response have been reported in association with disease progression and death including D-Dimer, lactate dehydrogenase (LDH) and C-reactive protein (CRP) [2,8-11,15,16]. Additionally, cytokine levels including interleukin (IL)1β, IL1RA, IL7, IL8, IL9, granulocyte-colony stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GMCSF), interferon gamma (IFNγ), inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1α), macrophage inflammatory protein 1 beta (MIP1β), tumor necrosis factor alpha (TNFα), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) levels were increased among patients admitted to the intensive care unit (ICU) compared with non-ICU patients and healthy adults [9]. Though low overall relative to acute respiratory distress syndrome (ARDS) and bacterial sepsis, IL-6 is also increased among non-survivors of COVID-19 [15].

Despite limited data on viral replication dynamics, there is evidence of virus replication in both the upper and lower respiratory tract. Most studies suggest that viral loads are highest in the first week of illness (Figure 1) with long-term viral RNA persistence potentially associated with severity of illness (Figure 2) [1,3,5,16,17]. The median time to viral RNA clearance is approximately 11 days for mild disease and 21 days in patients with severe or critical illness (Figure 2) [2,17]. Increased viral loads in addition to prolonged virus replication in patients with severe illness suggest that viral loads maybe a useful surrogate for assessing severity in COVID-19.

Viral RNA detection is also dependent upon sample type, with evidence of prolonged viral RNA detection in lower respiratory tract samples including saliva and sputum compared with nasopharyngeal swab samples (Figure 1 and Figure 3) [1-3,5,16,17]. Daily sampling of the upper and lower respiratory tract reveal that, in general, viral RNA in OP swabs are elevated in initial samples and already on the decline at the time of presentation whereas sputum samples peak during the first week of symptoms and decline more slowly [5].

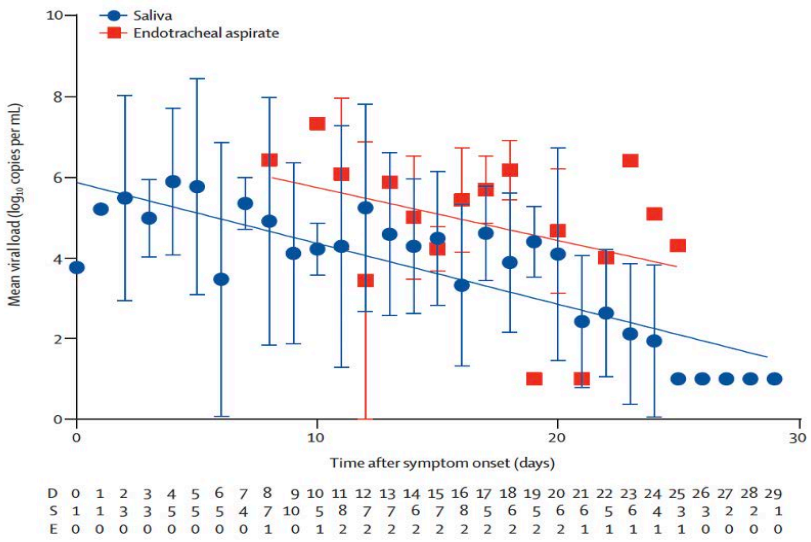

Figure 3: Prolonged viral RNA detection in saliva and endotracheal aspirates [3].

Datapoints denote the mean; error bars indicate SD; slope represents best fit line. The number of patients who provided a sample on each day is shown in the table below the plot. D=days after symptom onset. S=saliva. E=endotracheal aspirate

Less is known about shedding of infectious virus. While infectious virus was readily isolated from clinical samples in a single study, it was again dependent on sample type, viral load, and timing. In the only study to date to evaluate infectious virus kinetics, infectious virus was successfully isolated from 17% of OP swabs and from 83% of sputum samples but only from samples collected within the first week from symptom onset and only in those that contained $>10^6$ viral RNA copies/mL (Figure 4). No infectious virus was isolated beyond Day 8 from symptom onset despite elevated viral loads [5].

The persistence of infectious virus in the upper respiratory tract has important implications for both transmission and infection prevention and control strategies. SARS-CoV-2 is thought to be transmitted primarily through droplet and contact routes during close unprotected contact between an infected and susceptible individual [18]. Although viral RNA has been detected in air samples within airborne isolation rooms, airborne transmission is not believed to be a major driver of transmission based on current evidence [19]. Recent reports indicate that human-to-human transmission in China is largely driven by familial transmission with secondary attack rates of 3-11%[14,18,20]. Among 344 clusters including 1308 of 1836 reported cases in Guangdong, approximately 78-85% occurred within families [18]. Identification of interventions to interrupt household and community transmission could have a profound impact on the pandemic at large as well as slow the surge of patients requiring hospitalization and critical care.

2.2. Rationale

Antiviral therapeutic interventions that reduce infectious virus production could play a key role in decreasing community transmission, decreasing surge on healthcare facilities, and potentially reduce clinical complications of infection. This "treatment as prevention" approach has the potential to reduce the burden of COVID-19 illness and mitigate ongoing transmission. Given the current therapeutic landscape and limitations, there is an urgent need for an orally available direct acting antiviral.

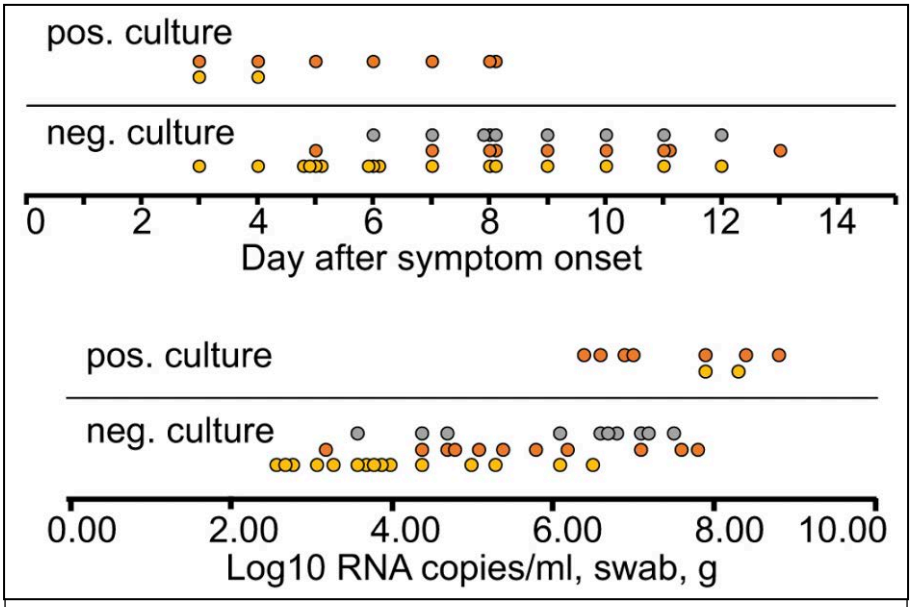

Figure 4: Virus isolation from throat and nasopharyngeal swabs[5]

[redacted] EIDD-2801 is the 5'-isobutyrate prodrug of the broadly active, direct acting antiviral ribonucleoside analogue EIDD-1931, which inhibits replication of multiple viral pathogens from multiple RNA families. Further clinical information is needed to determine safety, tolerability, and antiviral activity in humans.

2.3. Preclinical Data

2.3.1. Mechanism of Action

The primary mechanism of action of EIDD-2801 is inhibition of viral RNA replication by incorporation of the EIDD-1931-5'-monophosphate metabolite into the viral RNA genome resulting in induction of viral error catastrophe. Upon incorporation into nascent chain RNA, EIDD-1931-5'-monophosphate induces increased mutational frequency in the viral genome resulting in the production of non-viable virus. Following oral delivery, EIDD-2801 is rapidly hydrolyzed by circulating esterases to produce high circulating plasma levels of EIDD-1931 which is in turn phosphorylated into a tri-phosphate (EIDD-2601) that can pair with either guanosine or adenosine and can substitute for either CTP or UTP, respectively, resulting in an accumulation of

mutations that increase with each cycle of viral replication [21]. Additionally, the active metabolite, EIDD-1931-5'-triphosphate, may act as a chain terminator and arrest viral replication via a next nucleoside effect. Given this dual mechanism of action, it is anticipated that there will be a high barrier to the development of resistance.

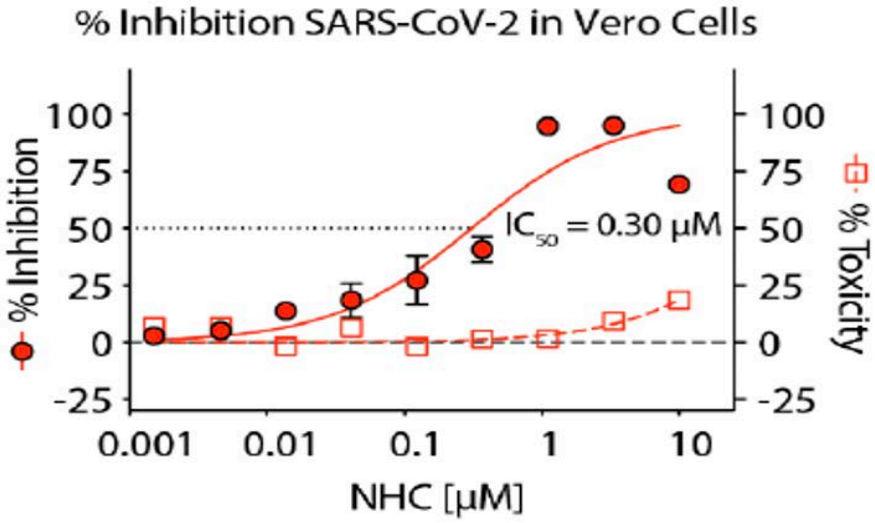

Figure 5: Antiviral activity and cytotoxicity of EIDD-2801 in Vero E6 cells infected with SARS-CoV-2

2.3.2. In Vitro Evidence

Antiviral activity of EIDD-2801 against coronaviruses including MERS-CoV, SARS-CoV, SARS-CoV-2, and related zoonotic group 2b or 2c Bat-CoVs has been demonstrated in a number of different tissue culture cell lines including primary human airway epithelial cell cultures[4]. Using a clinical isolate of SARS-CoV-2, EIDD-1931 exhibited an average half-maximum inhibitory concentration (IC_{50}) of 0.3µM and a 50% cytotoxic concentration (CC_{50}) of >10 µM (Figure 5) [4]. A dose-dependent reduction in infectious virus titers was observed during treatment in a human lung epithelial cell line, Calu-3 cells infected with SARS-CoV-2 with an IC_{50} of 0.09 µM. A dose-dependent reduction in SARS-CoV-2 infectious virus production was also found for EIDD-1931 in primary HAE cell cultures without appreciable alteration of host gene expression at doses up to 100 µM (Figure 6)[4]. Similar results were found for MERS-CoV- and SARS-CoV-infected cell lines and primary HAEs [4].

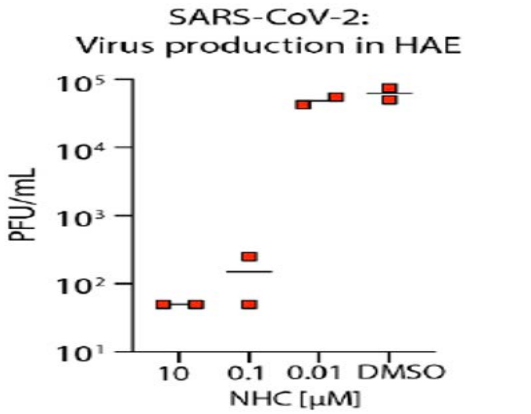

Figure 6: Reduction in infectious SARS-CoV-2 production in primary human airway epithelial cells.

[redacted]

[redacted]

2.4. Evidence in Humans

EIDD-2801 has not been used prophylactically or therapeutically in patients with COVID-19; however, EIDD-2801 has been studied in a single and multiple ascending dose study in healthy volunteers (Study EIDD-2801-1001). Preliminary data from this study showed that doses of 200 mg produce plasma levels of EIDD-1931 that are predicted to show antiviral activity in humans. A brief summary of safety information from Study EIDD-2801-1001 is provided in Section 2.6.

2.5. Potential Risks and Benefits

There remains unmet medical need for the treatment of COVID-19, particularly in outpatients where intravenous administration of antiviral therapy is difficult. Participants in this study will be monitored throughout the 5-day treatment course and follow-up period with surveillance for and reporting of all AEs.

2.5.1. Risks Associated with EIDD-2801

Novel therapies can lead to unexpected, incidental findings that could have a potential effect on the participant's health.

Enrollment in a Phase I study of EIDD-2801 (Study EIDD-2801-1001) in 130 healthy volunteers has completed. No serious AEs were reported and no trends of increased frequency or severity of AEs with higher doses of EIDD-2801 were observed. No clinically significant findings or dose-related trends were observed in clinical laboratory, vital signs, or electrocardiogram (ECG) data.

[redacted] Further details for EIDD-2801-1001 are provided in Section 2.6.

Ongoing surveillance for AEs will be conducted throughout the present study and other ongoing studies, and in the event of confirmation of a potential health effect, the study team will notify participants and will advise appropriate medical follow up when indicated.

EIDD-2801 and EIDD-1931 were shown to be mutagenic (Ames positive) in a bacterial mutagenesis assay with and without metabolic activation. [redacted] Given the anticipated short-duration of treatment for COVID-19 (eg, 5 days), EIDD-2801 is considered to have a benefit/risk profile that supports further clinical development.

2.5.2. Risks of Nasopharyngeal Sampling

This procedure will be nurse-administered on Days 1, 3, 5, 7, 14, and 28. Temporary discomfort is associated with this routine medical diagnostic procedure with no reported risk.

2.5.3. Risks of Self-Nasal Mid-Turbinate Swab Sampling

For participants enrolled at applicable sites only, this optional procedure may be self-administered on Days 1, 3, 5, 7, 14, and 28. No reported risks are associated with this procedure.

2.5.4. Risks of Oropharyngeal Sampling

For participants enrolled at applicable sites only, this optional procedure may be nurse-administered on Days 1, 3, 5, 7, 14, and 28. Temporary discomfort is associated with this routine medical diagnostic procedure with no reported risk.

2.5.5. Risk of Blood Collection

Blood collection may cause pain, bruising, and occasionally a feeling of lightheadedness or fainting. Rarely, it may be associated with an infection at the site of blood drawing.

2.5.6. Risks of Pregnancy and Use in Nursing Women

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 50 days after completion of EIDD-2801 dosing in female participants and for 100 days after completion of EIDD-2801 dosing in female partners of male participants. [redacted]

2.5.7. Risk of Exposure to COVID-19

There is the potential risk for increased transmission of SARS-CoV-2 to study team members. Precautions will be taken to prevent this. Home visits will be carried out by highly trained study nurses equipped with proper personal protective equipment (gown, gloves, N95 respirator, face shield). Wherever possible, single use testing supplies will be used, and other testing equipment will be wiped down with hospital-approved disinfectant between each use. The nurse will perform study procedures with each participant on an individual basis in a separate room. Study participants will be encouraged to use their own devices to complete online questionnaires and symptom

diaries, or through interview with the study nurse, so that tablets are not passed between individuals. Specimens will be stored in individual biohazard bags following the same protocols used in the clinical care setting.

2.5.8. Risks of Breach of Confidentiality

Data gathered on study participants will include their age, sex, medical history, concomitant medications, and symptom status. The study team will also collect home address and contact information in order to carry out study procedures, but this information will not be used as study data (it will not be entered into the study database). In the early phase of the epidemic, a COVID-19 diagnosis may carry significant stigma. The study nurse will use discretion when carrying out home visits, calling ahead and arranging appointment times and using an unmarked vehicle.

2.5.9. Potential Benefits

The study will have generalizable benefits by improving our understanding of whether EIDD-2801 has antiviral effects against SARS-CoV-2 that could make it useful for treatment and/or prevention of COVID-19.

In the absence of an approved therapeutic to reduce progression of illness in COVID-19 and transmission of SARS-CoV-2, new antiviral therapeutics represent an urgent public health need.

[redacted]

2.6. Justification for Dose

In a recent Phase I safety study (Study EIDD-2801-1001) a total of 130 healthy volunteers were enrolled. Sixty-four participants received a single dose of between 50 and 1600 mg EIDD-2801 or placebo; 56 participants received multiple dose of 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.

[redacted] no clinically significant changes in hematological parameters were seen in the Phase 1 study.

In the Phase 1 study EIDD-2801-1001, dose escalations were discontinued before a maximum tolerated dose was reached because plasma exposures that were expected to be efficacious based on scaling from animal models of seasonal and pandemic influenza were exceeded.

[redacted] The 200-mg dose is selected for Part 1 of this study. To allow for variability in PK including intracellular half-life of the EIDD-1931- 5'-triphosphate and to account for uncertainty in scaling assumptions, doses of up to 800 mg are considered appropriate to explore a range of potentially efficacious doses. Based on safety and PK data from a Phase 1 study, doses up to 800 mg BID may be selected for evaluation in subsequent study parts . The subsequent optional study parts may explore different doses, or the same dose used in one part may be repeated in a different Part.

2.7. Justification for the Control Arm

In light of the variability of viral replication kinetics and disease progression in individuals with COVID-19, the inclusion of a control group is essential to evaluate if EIDD-2801 has an antiviral effect. To this end, this trial will include a double-blinded placebo control arm to determine the efficacy, safety, and tolerability of EIDD-2801 in the outpatient setting for individuals with COVID-19.

2.8. Justification for Placebo-Controlled Design

In the absence of efficacy data and in light of potential risks, a placebo-controlled trial will provide the best opportunity to rigorously evaluate the safety, tolerability, and efficacy of EIDD-2801. No approved therapy is available to treat COVID-19 in outpatients.

2.9. Justification for Age Restriction

Children, adolescents, and adults under the age of 18 will not be included in this trial. Initial epidemiologic information indicates that while children and adolescents under the age of 18 are able to be infected, the overwhelming burden of severe disease occurs among adults, particularly older adults. Given the low incidence of disease in children, and in consideration that the Phase I

data for EIDD-2801 are limited to adults, the risk/benefit analysis does not warrant inclusion of this population at this time.

2.10. Justification for Including Women of Childbearing Potential

There is no safety data currently available in pregnant women or those who are breastfeeding. [redacted] pregnant women or those who are nursing will not be eligible for this study. However, in the recently published study of remdesivir, which demonstrated a significant reduction in the duration of illness compared with placebo, the greatest recovery rate ratio occurred in individuals between the ages of 18 and 40. Given the patient population that may benefit the most, there is a now a clear rationale for including women of child-bearing age into this Phase 2 study.

Women of childbearing potential (as defined in Appendix 2) will therefore be eligible for enrollment only if they meet Inclusion Criterion 4.1.10, including the following:

1. Have a negative highly sensitive pregnancy test at Screening
2. Agree to undergo a follow-up pregnancy test on Study Day 28
3. Comply with the contraception guidelines provided in Appendix 2

In addition, male participants must refrain from donating sperm during the study and for 100 days after dosing of the study drug is complete. Male participants with female partners must also comply with the contraception guidelines provided in Appendix 2.

2.11. Justification for Not Performing Urinalysis

This study is being conducted in part at the [redacted] in an outdoor testing facility designed specifically for patients who have COVID-19. This center does not have facilities for urine collection, and therefore, urine cannot be collected at clinic visits.

Review of preliminary, blinded urinalysis data from Phase I study EIDD-2801-1001 has not revealed any safety concerns. Safety data from the ongoing Phase I study and other studies that are initiated will be reviewed by the sponsor on an ongoing basis. If there are any safety signals that suggest that urinalysis testing is needed, this protocol will be reviewed and if warranted, amended to address this issue.

3. STUDY DESIGN

This is a Phase IIa, double-blind, placebo-controlled, randomized trial, designed to compare the safety, tolerability, and antiviral activity of EIDD-2801 versus placebo as measured by viral RNA detection in symptomatic adult outpatients with COVID-19. The study is a multicenter trial.

This study will enroll up to approximately 172 fully evaluable participants in multiple study parts. If participants in a dose group drop out or otherwise have missing or unevaluable primary or key secondary virology endpoint data, additional participants may be enrolled to ensure adequate data at each dose level. The total number of participants to be enrolled will not exceed 204.

In Part 1 of this study, up to approximately 44 participants will be randomized 1:1 to receive EIDD-2801 200 mg BID (Arm A) or placebo (Arm B) orally BID for 5 days. Enrollment in Part 1 may be interrupted to initiate enrollment in a different cohort, and may resume at a later time point. The study may continue to enroll the following optional study parts:

- In Parts 2--4, up to approximately16 participants per part will be randomized 3:1 into Arms C and D (Part 2), Arms E and F (Part 3) and Arms G and H (Part 4) to receive treatment as follows: EIDD-2801 up to 800 mg or placebo orally BID for 5 days.
- In Parts 5--9, up to approximately 16 participants per part will be randomized 3:1 into Arms I and J (Part 5), Arms K and L (Part 6), Arms M and N (Part 7), Arms O and P (Part 8), and Arms Q and R (Part 9) to receive treatment as follows: EIDD-2801 up to 800 mg or placebo orally BID for 5 days.

The dose of EIDD-2801 evaluated in Part 1 will be 200 mg BID. The doses selected for subsequent study parts may be the same, higher or lower than the dose(s) studied in previous study parts, and will not exceed 800 mg BID. Doses will be chosen based on emerging virology and safety data from this and other ongoing studies. Selected doses will be communicated in an official memo/protocol clarification letter. The maximum number of participants enrolled will be 204 .

All study part sizes are approximate. Study parts may be combined for randomization purposes if the same dose is planned for more than one part. Study parts enrolling at the same dose level may be enrolled simultaneously.

Sample Treatment Assignment Table (Fully Evaluable Participants)
(doses and order of progression subject to change)

Study Part	Treatment Arm (n)	Placebo Arm (n)	Total Subjects	Projected Dose Level
1	A (22)	B (22)	44	200 mg
2	C (12)	D (4)	16	400 mg
3	E (12)	F (4)	16	400 mg
4	G (12)	H (4)	16	400 mg
5	I (12)	J (4)	16	TBD or 800 mg
6	K (12)	L (4)	16	TBD or 800 mg
7	M (12)	N (4)	16	TBD or 800 mg
8	O (12)	P (4)	16	TBD or 200 mg
9	Q (12)	R (4)	16	TBD or 400 mg
Total:	**118**	**54**	**172**	

All participants will be followed for 5 days on treatment and an additional 23 days off treatment. Participants who do not start study treatment will be replaced.

In Part 1, randomization will be stratified by time (days) from symptom onset – "early" versus "late" presentation, where "early" and "late" presentation are defined by:

- Early presentation: enrollment (i.e., randomization date and time) 0 to ≤60 hours from symptom onset
- Late presentation: enrollment (i.e., randomization date and time) >60 to ≤168 hours from symptom onset

Randomization will not be stratified in subsequent study parts.

3.1. Recruitment

Participants will be recruited through active outpatient surveillance programs including the [redacted], screening centers at the Wake Forest School of Medicine, local emergency departments, additional study sites, and public health surveillance programs actively conducting outbreak investigations among others including nursing homes. Primary recruitment will begin at UNC, and UNC-affiliated satellite clinics, and will be conducted in partnership with the [redacted] At the time of testing, participants who present to the [redacted] are approached for a global consent to be contacted for research studies. Those who test positive will be approached for enrollment into this study at the time they are notified of their diagnosis. Participants identified in the emergency department will be referred to the study immediately upon SARS-CoV-2 diagnosis by ordering providers and study coordinators who receive test results.

3.2. Study Visits

The informed consent process will be performed in person or remotely in compliance with institutional and regulatory requirements. At Study Entry (Day 1), all consented participants will have an in-person study visit. Blood will be obtained for safety labs, inflammatory markers, immunoglobulins, and pregnancy testing if indicated, and if participants meet all of the inclusion criteria and none of the exclusion criteria, they will be randomized. Participants will provide medical and medication histories and contact information for themselves including their home address and cell phone numbers and that for persons who can be contacted to help locate the study participant in case study staff cannot reach the participant. Participants will be dispensed study treatment and contact numbers for the study staff.

The participant's first symptom(s) associated with COVID-19 and when it/they occurred will be recorded.

Either in-clinic visits or in-home visits will continue on Days 3, 5, 7, 14, and 28.

On Days 3, 7, and 14, study staff will contact participants per the Schedule of Evaluations (SOE), and in-home or in-clinic visits will occur for respiratory sampling including NP swabs, and blood samples will be obtained for safety labs, inflammatory markers, and immunoglobulins. Participants will also be assessed for their symptoms, temperature, oxygen saturation, medication adherence, and major events such as medical visits and hospitalizations. If participants cannot be reached after 2 attempts 24 hours apart, then their alternative contact person(s) will be called.

On Day 5, participants will have an in-clinic visit. Respiratory samples including NP swab, OP swab (at UNC at Chapel Hill only) and self-collected nasal mid-turbinate swab (at UNC at Chapel Hill only) will be collected. Blood will also be obtained for safety labs, inflammatory markers, and immunoglobulins. At sites that are able to process PK samples, single day sparse PK sampling will be collected on Day 5.

On Day 28 (the End-of-Study [EOS] visit), participants will have an in-clinic visit. Blood samples will be obtained for safety labs, pregnancy testing if indicated, inflammatory markers, and immunoglobulins. Respiratory samples including NP swab, OP swab (UNC at Chapel Hill only), and self-collected nasal mid-turbinate swab (UNC at Chapel Hill only) will be collected. At these visits, study staff will record any hospitalizations or outpatient medical visits (including telemedicine visits) that occurred since the last visit.

Participants will be instructed to contact study staff immediately if they seek medical help at any time during the study.

3.3. Isolation Procedures

Given that SARS-CoV-2 is spread through respiratory droplets, each site must develop procedures to protect study staff and participants of other trials from infectious exposure. Each site will have a plan for maximal protection by providing personal protective equipment (PPE), setting up isolation rooms or outside areas, providing special access points or contact with study participants. Each site will develop their own set of procedures for such participant contact.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1. Inclusion Criteria

4.1.1. Able to provide informed consent prior to initiation of any study procedures.

4.1.2. ≥18 years of age at Screening.

4.1.3. Study treatment is expected to begin within ≤168 hours from first symptom onset.

4.1.4. Ability to swallow pills

4.1.5. Documentation of confirmed active SARS-CoV2 infection, as determined by a molecular or non-molecular ("rapid") test conducted at any clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent from a sample collected ≤96 hours prior to study entry.

4.1.6. Experiencing at least one of the following SARS-CoV-2 infection symptoms at the time of enrollment: fever (can be subjective including feeling feverish or having chills) OR signs/symptoms of respiratory illness (including but not limited to upper respiratory congestion, loss of sense of smell or taste, sore throat OR lower respiratory illness – cough, shortness of breath).

4.1.7. Agrees to not participate in another interventional clinical trial for the treatment of SARS-CoV-2 during the study period (28 days) unless hospitalized.

4.1.8. Agrees to not obtain investigational medications outside of the EIDD-2801 study.

4.1.9. Agrees to the sampling detailed in the SOE and to comply with study requirements including contraception requirements.

4.1.10. 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 50 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 or urine) within 24 hours before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 6.2.15.
- 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[22,23], 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.

4.1.11. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 100 days after the last dose of study intervention:

- Refrain from donating sperm

PLUS either:

- 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.

4.2. Exclusion Criteria

4.2.1. Need for hospitalization or immediate medical attention in the clinical opinion of the study investigator.

4.2.2. Hemoglobin <10 g/dL in men and <9 g/dL in women

4.2.3. Platelet count <100,000/ μL or received a platelet transfusion within 5 days prior to enrollment

4.2.4. Is on dialysis or has an estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2

4.2.5. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3x the upper limit of normal (ULN)

4.2.6. History of or current hospitalization for COVID-19. NOTE: Individuals hospitalized and then discharged, even if only hospitalized for 1 day, are excluded.

4.2.7. History of kidney disease as evidenced by estimated creatinine clearance value <30 mL/min.

4.2.8. History of significant liver disease in the opinion of the site investigator or active hepatitis B or active hepatitis C. Human immunodeficiency virus (HIV) that is advanced (CD4 <200/mm^3) and/or on treatment with nucleos(t)ide analogues.

4.2.9. Use of therapeutic interventions with possible anti-SARS-CoV-2 activity within 30 days prior to study entry, e.g., remdesivir, lopinavir/ritonavir fixed dose combination, ribavirin, chloroquine, hydroxychloroquine, and convalescent plasma, or participation in a clinical trial involving any of these drugs whether for treatment or prophylaxis.

4.2.10. Receipt of a SARS-CoV-2 vaccination prior to study entry.

4.2.11. Known allergy/sensitivity or any hypersensitivity to components of EIDD-2801 or its formulation.

4.2.12. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.13. History of recent (within the past 3 months) hemorrhagic cerebrovascular accident (CVA) or major bleed.

4.2.14. Presence of a condition, that in the opinion of the investigator, would place the subject at increased risk from study participation.

4.3. Study Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE) responsible for oversight of the study.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify.

4.3.1. Randomization/Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, a Screening Failure Results form must be completed and keyed into the database. Participants who meet the enrollment criteria will be registered to the study according to standard procedures.

4.4. Co-enrollment Guidelines

For specific questions and approval for co-enrollment in other studies, sites should first contact the protocol team via e-mail.

5. STUDY TREATMENT

5.1. Regimens, Administration, and Duration

Doses of EIDD-2801 and matching placebo will be formed from combinations of [redacted]. In Part 1 of the study, participants will be randomized 1:1 to receive one of the following two regimens:

- ARM A:
  Day 1-5: EIDD-2801 200 mg orally BID for 5 days.
- ARM B:
  Days 1-5: Placebo for EIDD-2801 orally BID for 5 days.

An optional Part 2 may be initiated in which patients will be randomized 3:1 (active:placebo) to receive one of the following two regimens:

- ARM C:
  Day 1-5: EIDD-2801 up to 800 mg orally BID for 5 days.
- ARM D:
  Days 1-5: Placebo for EIDD-2801 orally BID for 5 days.

An optional Part 3 may be initiated in which patients will be randomized 3:1 (active:placebo) to receive one of the following two regimens:

- ARM E:
  Day 1-5: EIDD-2801 up to 800 mg orally BID for 5 days.
- ARM F:
  Days 1-5: Placebo for EIDD-2801 orally BID for 5 days.

An optional Part 4 may be initiated in which patients will be randomized 3:1 (active:placebo) to receive one of the following two regimens:

- ARM G:
  Day 1-5: EIDD-2801 up to 800 mg orally BID for 5 days.
- ARM H:
  Days 1-5: Placebo for EIDD-2801 orally BID for 5 days.

Additional optional Parts 5-9 may be initiated in which patients will be randomized 3:1 (active:placebo) to receive one of the following two regimens:

- ARM I (Part 5), K (Part 6), M (Part 7), O (Part 8), Q (Part 9):
  Day 1-5: EIDD-2801 up to 800 mg orally BID for 5 days.
- ARM J (Part 5), L (Part 6), N (Part 7), P (Part 8), R (Part 9):
  Days 1-5: Placebo for EIDD-2801 orally BID for 5 days.

Each participant will begin study treatment dosing with the first dose on Day 1 and the second dose at least 4 hours later on Day 1. If the first dose on Day 1 is a late evening dose, 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.

5.2. Study Product Formulation and Preparation

[redacted]

5.3. Pharmacy: Product Supply, Distribution, and Accountability

5.3.1. Study Product Acquisition/Distribution

[redacted] will be supplied as [redacted] for oral administration, along with the batch/lot numbers and Certificates of Analysis.

EIDD-2801 and matching placebo [redacted] are supplied by Ridgeback Biotherapeutics.

5.3.2. Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from Ridgeback Biotherapeutics and subsequently dispensed. All unused study products at the sites must be returned to Ridgeback Biotherapeutics (or as otherwise directed by the sponsor) after the study is completed or terminated.

5.4. Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, or Investigator's Brochure to obtain the most current information on drug interactions, contraindications, and precautions.

6. SCHEDULE OF EVENTS

SCHEDULE OF EVENTS	Screening (in person or by phone)	Study Entry / Enrollment		Post-Entry Evaluations					Premature Study Discontin-uation
		Day 1		Day 3	Day 5	Day 7	Day 14	Day 28 (EOS)	
Visit Windows (days)		Pre dose	First Dose			(±1 day)	(±4 days)		
In-Clinic or In-Home Visit				X	X [1]	X		X	X
In-Clinic Visit		X					X		
Informed Consent	X								
Documentation of Positive SARS-CoV-2 Molecular Test[2]	X								
Demographics	X								
Medical history & COVID-19 Symptom Screen	X	X						X	
Vital signs [3]		X		X	X	X	X		X
Review inclusion/exclusion criteria	X	X						X	
Pregnancy Test in Women of Childbearing Potential [4]		X					X		X
Study Kit and Study Diary Dispensed [5]		X							
EIDD-2801 or Placebo BID Daily Days 1-5 [6]			X	X	X			X	
Review of Study Daily Diary[7]				X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X
Study Endpoint Determination				X	X	X	X	X	X
Nasopharyngeal (NP) Swab [8]		X		X	X	X	X	X	X
Oropharyngeal (OP) Swab [9]		X		X	X	X	X	X	X
Self-Collected Nasal Mid-turbinate Swab [9]		X		X	X	X	X	X	X
Safety labs [10]	X	X		X	X	X	X	X	X
Inflammatory Markers		X		X	X	X	X	X	X
Plasma for Immune Responses		X		X	X	X	X	X	X
Plasma for Immunoglobulin Assay		X				X	X		X
Pharmacokinetics (Sparse) [11]					X				
Vital Status Follow-up									X

1. The Day 5 visit will be in-clinic for sites that are able to process PK samples, and may be in-home for other sites.
2. Test to be performed within 96 hours of study entry. Rapid tests are acceptable for confirming infection.
3. Assessment includes measurements of temperature, blood pressure, respiratory rate, heart rate, and oxygen saturation. Height and weight should be recorded and may be obtained by participant's self-report.
4. High sensitivity pregnancy tests are required at Screening (urine or serum) within 24 hours of the first dose of study drug and on Day 28 (serum). 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.
5. Activities will include the collection of secondary contact information.
6. First Dose will be administered in the morning of Day 1, if possible. Dosing is twice daily through Day 5 (inclusive). If the first dose on Day 1 is a late evening dose, 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.
7. Study treatment adherence will be assessed by review of the treatment adherence portion of the study diary and counting returned study drug and containers.
8. The site at which virology testing will be performed (UNC at Chapel Hill) will collect 1 NP swab per timepoint and will divide the sample in preparation for analysis by infectivity versus PCR assay. All other study sites will collect 2 NP swabs (one per nostril) at each timepoint and 1 swab each will be prepared and shipped for analysis by infectivity versus PCR assay.
9. Participants enrolled at the site at which virology testing will be performed (UNC at Chapel Hill) will have OP and nasal mid-turbinate swabs collected at the timepoints indicated. OP and nasal mid-turbinate swabs are not collected at all other study sites.
10. Hematology and chemistry: Results from hematology and chemistry will be evaluated before assessing a participant's eligibility. Lab results obtained within 48 hours of enrollment (i.e., randomization date and time) are acceptable. When screening and enrollment visits are combined, a single blood draw may be performed for both screening and baseline laboratory assessments.
11. At all sites that are able to process PK samples, PK samples will be obtained immediately before the morning dose on Day 5 and at approximately 1 hour and 2 hours after the morning dose, where possible. When possible, participants should fast overnight before their Day 5 visit (i.e. participants should arrive at the Day 5 visit having had no food or drink intake except for water in the previous 8 hours).

6.1. Timing of Evaluations

6.1.1. Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening evaluations to determine eligibility may be completed remotely or in-person. Screening and enrollment (i.e., randomization; Day 1) visits may occur on the same day.

In addition to data being collected on participants who enroll into the study, demographic and available clinical and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the Study database or other applicable site-specific database.

6.1.2. Enrollment and Study Entry

Screening and enrollment visits may be combined whenever possible to ensure the shortest possible time between symptom onset and dosing of study drug. The study enrollment (i.e., randomization; Day 1) visit is an in-person visit as safety labs must be performed prior to initial dosing. Participants must begin study treatment within 168 hours of symptom onset. The first dose of study treatment should be the first of two doses on Day 1.

When screening and enrollment visits are combined, a single blood draw may be performed for both screening and baseline laboratory assessments. Participants must have the NP swab(s) and blood collected prior to receiving the first treatment dose. Optional OP and self-collected nasal mid-turbinate swabs, if performed, should also be collected prior to receiving the first treatment dose.

6.1.3. On-Treatment Evaluations

Participants will undergo an in-clinic or in-home visit on Days 3 and 5 as outlined in the SOE. For sites that are able to process PK samples, Day 5 visits will be in-clinic, as needed.

During these visits, participants will undergo NP swabs, blood collection, and other clinical evaluations as indicated in the SOE. Optional OP and self-collected nasal mid-turbinate swabs may also be collected at applicable study sites.

6.1.4. Post-Treatment Evaluations

Participants will undergo post-treatment evaluations at either in-home or in-clinic study visits on Days 7 and 14 as outlined in the SOE.

6.1.5. End of Study Evaluations

Participants will undergo an in-clinic evaluation on Day 28 for an End of Study visit.

6.1.6. Discontinuation Evaluations

6.1.6.1. Evaluations for Participants Who Do Not Start Study Treatment

Participants who are randomized but do not take the first (confirmed) dose of study treatment do not need to be followed. A study discontinuation electronic case report form (eCRF) must be completed to record this and any evaluations completed for these participants should also be recorded on the Day 1 eCRFs.

6.1.6.2. Premature Treatment Discontinuation Evaluations

Participants who discontinue study treatment early should remain on study and all evaluations should be performed as outlined in the SOE.

6.1.6.3. Premature Study Discontinuation Evaluations

Participants who discontinue study participation should undergo premature study discontinuation evaluations, as outlined in the SOE, within 7 days of study discontinuation. If study discontinuation occurs on or prior to Day 5, all procedures should be performed as described in the SOE for premature study discontinuation evaluations. If study discontinuation occurs on or between Day 5 and Day 28 all evaluations EXCEPT treatment adherence should be performed. If study discontinuation occurs after Day 5, all evaluations including site-collected NP swab(s) and blood collection should be performed.

For participants who prematurely discontinue from the study for reasons other than withdrawal of consent, sites will attempt to obtain information regarding vital status and endpoints per the SOE.

6.2. Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to Section 7.3 for information on the DAIDS AE Grading Table and requirements for reporting of AEs.

6.2.1. Informed Consent

Participants will review and provide informed consent to participate in the study either over the telephone or in person.

6.2.2. Documentation of Positive SARS CoV-2 Infection

Active SARS CoV-2 infection documentation is recorded on the eCRF. If a viral load level is available, it should be recorded as well.

6.2.3. COVID-19 Symptom Screen

Participants will be asked about their first symptoms related to COVID-19 and their current symptoms, to document eligibility. This will include when and what symptoms the participant

noticed having. The date of first symptom onset will be recorded and used to establish the randomization stratum.

6.2.4. Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified for clinical events and other diagnoses regardless of grade within the past 14 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- Hypertension
- Chronic obstructive pulmonary disease
- Obesity (body mass index [BMI] >30)
- "Severe Obesity" (BMI >40)
- Immunosuppressive conditions
- Reactive airway disease, asthma
- Autoimmune disease
- Acquired Immune Deficiency Syndrome (AIDS)-defining conditions
- HIV infection
- Coronary heart disease
- Heart failure
- Myocarditis
- Arrhythmias
- Valvular heart disease
- Stroke
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Pregnancy history
- If known by participant, if they have been diagnosed with an acute viral respiratory infection (influenza, parainfluenza, respiratory syncytial virus, rhinovirus) within the previous 14 days.

A Smoking Status questionnaire will be completed at the Day 1 visit as part of medical history and recorded on the eCRF.

Any allergies to any medications and their formulations must also be documented.

6.2.5. Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history at screening.

Medication Category	Complete History or Timeframe
All prescription drugs	Last 7 days
All over the counter drugs	Last 7 days
Prescription drugs for high blood pressure	Last 3 months
Prescription drugs for diabetes and pre-diabetes	Last 3 months
Prescription drugs for lung disease	Last 3 months
Prescription drugs for heart disease	Last 3 months
Prescription drugs for autoimmune disease	Last 3 months
Cancer chemotherapy	Complete history
Antiretroviral therapy	Last 3 months
Immune-based therapy	Last 3 months
Blinded study treatment	Last 12 months
CoV-related vaccines	Complete history
Alternative therapies	Last 3 months
Dietary supplements	Last 3 months

6.2.6. Clinical Assessments

No physical exams will be conducted.

Clinical investigators will perform a clinical assessment at enrollment including vital signs (temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation). Height and weight should be recorded and may be obtained by participant's self-report. In their clinical judgement, they may identify some participants who are ill enough to warrant further clinical evaluation, which may result in hospitalization. They will then refer these participants for such evaluation. These participants will not start study treatment and will not be included in the analyses. While clinical judgement may not be standard across sites, the blinding process should balance site variation.

Refer to Section 7.2 for AE collection requirements.

6.2.6.1. Concomitant Medications

At entry and post-entry, the following new and discontinued concomitant medications must be recorded:

- High blood pressure medications
- Steroids or other immunosuppressive or immunomodulatory medication
- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Chemotherapy
- Antibiotics, antifungals, and antivirals (including antiretrovirals)
- Hydroxychloroquine or chloroquine or any agent felt to have potential COVID-19 activity
- Inhalers

6.2.6.2. Study Treatment (Intervention) Modifications

Record any modification to treatment, treatment interruption, and permanent discontinuation of treatment, and the reason for the modification, interruption, or discontinuation.

6.2.7. Secondary Contact

At enrollment, secondary contact information for 2 individuals whom the clinical research team can contact if the participant cannot be reached (e.g., spouse, friend, neighbor, etc.) will be collected. Clinical research teams will also request contact information for participants' health care provider(s) and the names of hospitals that the participant is likely to go to if they get sick. Contact information for secondary contacts or health care provider will not be recorded on any eCRF. If participants cannot be reached after 2 attempts 24 hours apart, then their listed secondary contact person(s) or health care provider will be called. At study entry only, the participant's home address will be recorded in site records (it will not be reported on the eCRF).

6.2.8. Study Kit Dispensed

The kit will include:

- Copy of informed consent (if not provided electronically)
- Study Diary (if not completed electronically)
- Study medications
- Pocket/wallet card with site staff contact information
- Instructions on what to do if they have worsening symptoms/become hospitalized

6.2.9. Dispensing of Study Drug, Confirmation of First Dose, and Counseling

Study treatment will be dispensed at study entry. Study staff will confirm the first dose taken by the participant and record this confirmation on an eCRF. Participants who do not start study treatment will be discontinued from the study.

Adherence counseling must be performed prior to the time the first dose of study treatment is taken. This counseling should include review of the timing of the first dose and the timing for the 2 subsequent doses.

6.2.10. Study Diary

Distribution of Study Diary

Participants will be provided a study diary at study entry (either electronic or paper).

Participants will be asked to keep a log of symptoms, temperature (if possible), medications they are taking, presence of feverishness, chills, myalgias, headache, sore throat, loss of sense of smell, loss of sense of taste, cough, shortness of breath, and major events such as urgent visit to an emergency room or clinic (including telemedicine) and hospitalization in their study diary. At study entry, study diary information will be recorded prior to study treatment initiation. Starting on Day 2, participants will be asked to complete the diary in the evening.

Review of Study Diary

The study diary will be reviewed by study staff with each participant at the in-person (in-clinic and in-home) visits described in the SOE and the participant's entries will be recorded in the Participant Study Diary eCRF. If feasible, prior to or during the remote study visits, sites will request that the participant send images of each of their study diary entries to be reviewed at the next study contact.

Participants who report worsening illness from any cause during the trial may be referred to their health care provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, (e.g., hospitalization or death).

Review of Treatment Adherence

The treatment adherence diary will be reviewed by study staff with each participant at the in-person (in-clinic and in-home) visits, as described in the SOE. The participant's answers regarding doses taken will be recorded in the Adherence Assessment eCRF. If any doses are missed, the reason for the missed dose will be recorded.

Collection of Study Diary

The study diary will be reviewed per the SOE.

6.2.11. Study Endpoint Determination

Study endpoints will be collected per the SOE. These will be recorded on the eCRF. Information about AEs, hospitalizations, or death should be keyed on the eCRF within 72 hours of a site becoming aware of an AE, hospitalization, or death.

6.2.12. Vital Status Follow-up

For participants who prematurely discontinue from the study for reasons other than withdrawal of consent, clinical research personnel will attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) from the participant or other sources (such as family members, other designated contacts, or clinic records)

per the SOE. Information about hospitalizations and deaths should be keyed on the eCRF within 72 hours of a site becoming aware of a hospitalization or death.

6.2.13. Virologic Studies

Detailed instructions for preparation and shipment of virologic samples will be provided in a separate document.

Nasopharyngeal (NP) Swab

NP swabs are required to be collected at all sites at the times indicated in the SOE. The site at which virology testing will be performed (UNC at Chapel Hill) will collect 1 NP swab per timepoint and will divide the sample in preparation for analysis by infectivity versus PCR assay. All other study sites will collect 2 NP swabs (1 per nostril) at each timepoint and 1 swab each will be prepared and shipped for analysis by infectivity versus PCR assay.

At study entry (Day 1), the sample should be collected prior to the first dose of study treatment.

Oropharyngeal (OP) Swab (Optional)

Participants enrolled at the site at which virology testing will be performed (UNC at Chapel Hill) will have an OP swab collected per the SOE. At study entry (Day 1), if performed, the sample should be collected prior to the first dose of study treatment. Participants enrolled at other sites will not have OP swabs collected.

Self-collected Nasal Mid-turbinate Swab (Optional)

Participants enrolled at the site at which virology testing will be performed (UNC at Chapel Hill) will have a nasal mid-turbinate swab collected per the SOE. At study entry (Day 1), if performed, the sample should be collected prior to the first dose of study treatment. Participants enrolled at other sites will not have mid-turbinate swabs collected.

Samples collected for viral assessment may be evaluated for the emergence of antiviral resistance at a future date.

6.2.14. Laboratory Evaluations

Laboratory evaluations will be performed on participants prior to study drug administration per SOE. At study entry (Day 1), blood samples should be collected prior to the first dose of study treatment and results will be available for assessment of the participant's eligibility. If the participant has lab study results available from within 48 hours of enrollment (i.e., within 48 hours of randomization date and time), these will be acceptable for baseline values.

Hematology

Per the SOE, participants will have a blood draw for complete blood cell count (CBC) with automated differential and platelet count. These tests will be performed in real-time at the local clinic laboratory.

Chemistry

Per the SOE, participants will have a blood draw for liver function tests (ALT, alkaline phosphatase [ALP], AST, Total Bilirubin, Direct Bilirubin, and Total Protein) and renal function

tests (blood urea nitrogen [BUN], Creatinine, Potassium, Glucose, and Sodium). A creatinine clearance will be recorded. These tests will be performed in real-time at the local clinic laboratory.

Inflammatory Markers

Per the SOE, participants will have a blood draw for LDH, CRP, ferritin and D-dimer. These tests will be performed in real-time at the local clinic laboratory.

Plasma

Per the SOE, blood plasma will be collected and tested for immune responses. Analytes to be tested may include, but may not be limited to, IL8, IL6, TNFα, IFNγ, GMCSF, interferon alpha (IFNα), C-X-C Motif Chemokine Ligand 10 (CXCL10), C-C Motif Chemokine Ligand 2 (CCL2), C-C Motif Chemokine Ligand 3 CCL3, soluble receptor for advanced glycation end products (RAGE), IL-2RApk35, and soluble IL-6Rpk35. Immunoglobulin M (IgM) and immunoglobulin G (IgG) will be tested from samples collected at the times indicated in the SOE.

6.2.15. Pregnancy Testing

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 4.1.
- High sensitivity pregnancy testing should be conducted at screening (serum or urine) within 24 hours of the first dose of study drug and on Day 28 (serum) 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.

6.2.16. Pharmacokinetics

Per the SOE, sparse PK sampling will be collected at sites that are able to obtain and process PK samples. Day 5 blood collection may be used to measure drug levels to assess the relationship between drug exposure and viral elimination dynamics including time to clearance.

When possible, participants should fast overnight before their Day 5 visit (i.e., participants should arrive at the Day 5 visit having had no food or drink intake except for water in the previous 8 hours).

Specifically, blood will be collected for sparse PK measurements at the following timepoints, where possible:

- Just prior to the morning dose on Day 5 (trough)
- Approximately 1-hour post morning dose on Day 5
- Approximately 2-hours post morning dose on Day 5 (if possible)

The timing of the post-dose samples may be adjusted for individual participants to increase the range of timepoints for PK evaluation. No participant will have more than 3 PK samples taken. The approximate time of the 3 doses preceding the PK sampling, the exact time of the dose

immediately preceding the PK sample, the time of the most recent meal, and the exact time of each PK sample collection should be recorded.

If it is determined that sufficient PK samples have been collected to characterize the PK profile in this patient population, PK sample collection may be discontinued by the Sponsor at any time.

7. ADVERSE EVENTS AND STUDY MONITORING

7.1. Definition of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition. The principal investigator (PI) and medical monitor will review all AEs on a weekly basis to determine which are treatment-related AEs.

7.2. Adverse Event Collection Requirements for This Protocol

Post-entry, all AEs must be recorded on the eCRFs within 72 hours if any of the following criteria have been met:

- All Grade ≥2 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade

The PI or clinical site personnel should notify Covance Patient Safety Solutions (PSS) 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 Covance Drug Safety Services (DSS) at SAEIntake@Covance.com 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.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening illness
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect, or
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3. Reporting Requirements for this Study

The PI or clinical site personnel should notify Covance PSS 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 Covance DSS at [redacted] or via fax. The study agents for which expedited reporting are required are:

- EIDD-2801 or Placebo for EIDD-2801

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Additionally, all reported pregnancies from the day of randomization through 50 days (for female participants) or 100 days (for female partners of male participants) after the last dose of study intervention must be reported to the sponsor by the investigator.

7.3.1. Laboratory Test Abnormalities

Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, a 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 diagnosis would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

7.3.2. Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

When changes in severity of an AE occur, the maximum severity for the experience should be noted.

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

7.3.4. Expedited AE Reporting Period

- Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if any pre-existing medical condition increases in severity after starting study treatment, it should be recorded as an AE.
- Although disease progression including hospitalization for COVID-19 will be collected as AEs, SAEs of disease progression will be considered expected for EIDD-2801 in this protocol and will not be reported as SUSARs.

7.3.5. 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 as described in Section 7.3.

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.

7.4. Study Monitoring

7.4.1. Adverse Events

The UNC Safety Monitoring Committee (SMC) will review and assess select expedited adverse events (EAE) reports for potential impact on the study participant safety and protocol conduct as per, guidance documents, and standard operating procedures (SOPs) as applicable. Summary reports of AEs will be shared weekly with the medical monitor(s). SAEs will be reported through the Covance SAE reporting protocol within 24 hours to the medical monitor(s). The EIDD-2801 principal investigator, co-investigators, and Ridgeback medical officer will review all deaths on a weekly basis in a blinded fashion.

7.4.2. Interim Review

The protocol team will monitor the conduct of the study via regular summaries of screening, accrual, study and study treatment discontinuation, and data and specimen completeness. The UNC SMC will monitor safety regularly.

Detailed plans for study monitoring are outlined in a Study Progress, Data, and Safety Monitoring Plan (SPSMP) developed prior to enrollment of the first participant.

8. CLINICAL MANAGEMENT ISSUES

8.1. Toxicity

Criteria for participant management, dose interruptions, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to the study drug. The grading system for drug toxicities is located in the DAIDS AE Grading Table (see Section 7.3.2).

NOTE: The study team must be notified via e-mail within 72 hours regarding toxicities that result in a change in study regimen.

It is possible that some participants will experience transient or prolonged AEs during the study. For any concerning AEs that are felt to require clinical intervention, participants should be instructed to contact their health care provider or seek urgent or emergent care, or 911 should be called, as appropriate.

8.2. Management of Side Effects of EIDD-2801

Only toxicities related to study medications provided through this study will be considered in the toxicity management section. The grading system is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, March 2017: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

8.3. Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue study medications without alteration of the dosage, except as stated in sections below. For participants experiencing Grade 1 or 2 AEs who choose to discontinue all study medications, the site investigator should complete premature discontinuation of study therapy evaluations, contact the study leadership team, and the participant should be encouraged to complete follow-up protocol study evaluations.

NOTE: If participants discontinue study medications due to experiencing Grade 1 or 2 AEs, this should be noted in the eCRF as the reason for discontinuation.

8.4. Grade 3

If the investigator (in consultation with the medical monitor at the investigator's discretion) has evidence that the AE has NOT been caused by study medications, dosing may continue. Participants who develop a Grade 3 AE or toxicity thought to be related to a study medication, except as stated in section below, should have their study medication discontinued. The participant should be reevaluated daily until the AE resolves or returns to baseline. The study leadership team must be notified and the relevant eCRF completed. Participants experiencing Grade 3 AEs requiring permanent discontinuation of all study medications should be followed daily until resolution of the AE and encouraged to complete the premature discontinuation of study therapy and follow-up protocol study evaluations.

8.5. Grade 4

Participants who develop a Grade 4 symptomatic AE or toxicity related to study product, will have the study medication permanently discontinued, except as stated below. Participants experiencing Grade 4 AEs requiring permanent discontinuation of all study medications should be followed daily until resolution of the AE and encouraged to complete the premature discontinuation of study therapy and follow-up protocol study evaluations.

Situations where study product does not need to be discontinued:

- Participants with Grade 3 or 4 asymptomatic creatine kinase (CK) elevation may continue study medication if the investigator has evidence that the CK elevation is not suspected to be related to the study medications.
- Participants with new Grade 3 or 4 AEs that are considered to be COVID-19 related and not study product related may continue study product following discussion with one of the study team leads.

8.6. Pregnancy

The study products may not be given in pregnancy.

8.7. Breastfeeding

The study products may not be given to women who are breastfeeding.

9. CRITERIA FOR DISCONTINUATION

The investigator, in consultation with the Sponsor, may decide to discontinue a subject from dosing or from the study based on their clinical judgement and/or in consultation with the Safety Monitoring Committee.

9.1. Permanent and Premature Treatment Discontinuation

Participants may have study treatment discontinued for reasons including, but not limited to, the following:

- Drug-related toxicity (see Section 8 CLINICAL MANAGEMENT ISSUES).
- Participant experiencing an SAE that is considered at least possibly related to study drug.
- Request by participant to terminate treatment.
- If platelet count drops below 75,000/mm^3 treatment will be discontinued
- NOTE: The reason for treatment discontinuation should be documented (e.g., concern for AE, lack of efficacy, or other reason).
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section (Section 8.1) of the protocol.
- Pregnancy.

9.2. Premature Study Discontinuation

Participants may be discontinued from the study for reasons including, but not limited to, the following:

- Request by the participant to withdraw consent.
- Request of the health care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, FDA, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or sponsor.

In the event that a participant prematurely discontinues from the study, unless they have withdrawn consent, sites will attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) from other sources (such as family members, other designated contacts, or clinic records).

10. STATISTICAL CONSIDERATIONS

10.1. General Design Issues

This is a phase IIa, double-blind, placebo-controlled trial to evaluate the safety, tolerability and antiviral activity of EIDD-2801 as measured by viral RNA detection in symptomatic adult outpatients with COVID-19.

10.2. Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov.

10.3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine if EIDD-2801 reduces the time to viral RNA negativity. Viral RNA negativity will be determined by RT-PCR of NP swabs.	• Qualitative RT-PCR
To determine the safety and tolerability of EIDD-2801 including 1) any adverse events (AEs) leading to early discontinuation of treatment, 2) study drug-related discontinuation of treatment, 3) new grade 3 or higher AE (not already present at baseline), and 4) study drug-related new grade 3 or higher AE.	• All AEs leading to early discontinuation of treatment • Study drug-related discontinuation of treatment • New grade 3 or higher AE • Study drug-related new grade 3 or higher AE

Secondary	
Safety Objective: To compare the incidence of grade 2 or higher AEs and drug-related AEs between treatment arms.	• Grade 2 or higher AEs • Drug-related AEs
Virologic Objectives: • To determine if EIDD-2801 reduces the time (days) to negativity of infectious virus isolation in NP swabs from SARS-CoV-2-infected adults. Infectious virus isolation is determined by isolation in Vero cell line cultures.	• Infectious virus detection in NP swab samples cultured on Vero-cell cultures • Infectious virus detection by microfoci assay of NP swab samples cultured on Vero-cell cultures
• To determine if EIDD-2801 reduces the shedding of SARS-CoV-2 RNA in NP swabs compared to placebo as measured by median change in RNA at Treatment Days 3, 5, 7, 14, and 28 as determined by quantitative RT-PCR.	• Quantitative RT-PCR
• To determine if EIDD-2801 increases viral RNA mutation rate. RNA mutation rate is measured by Next Generation sequencing.	• Comparison of spike and RNA dependent RNA polymerase gene sequences using Next Generation sequencing
Clinical Objectives: • To determine if EIDD-2801 changes the severity and duration of self-reported symptoms of COVID-19	• Patient reported symptoms • Time to improvement of new or worsened symptoms (including feverishness, chills, myalgias, headache, sore throat, loss of sense of smell, loss of sense of taste, cough, and difficulty breathing) as measured by a decrease in <u>all of these symptoms</u> from severe/moderate severity to mild/absent or a decrease in mild severity to absent in symptom diary (Absent or returned to pre-COVID-19 level = 0, Mild =1, Moderate =2, Severe =3).
• To determine if EIDD-2801 treatment reduces the proportion of participants who are hospitalized for COVID-19 related illness by Day 28.	• WHO 9-point ordinal scale (see Appendix 1):

Pharmacokinetic Objective: • To characterize the PK of EIDD-2801/EIDD-1931 in patients with COVID-19 following administration of study regimen • To determine the relationship between drug exposure and viral elimination dynamics including time to clearance.	• Concentrations of EIDD-2801 and EIDD-1931 in blood and levels of viral RNA in respiratory and oral samples
Exploratory	
Exploratory Clinical Objective • To determine if EIDD-2801 will prevent the composite endpoint of hospitalization, oxygen desaturation, oxygen requirement, mechanical ventilation, or death by 28 days after study entry. Hospitalization is defined as ≥24 hours of acute care. Oxygen desaturation will be measured using pulse oximetry. Oxygen requirement will be measured using the WHO ordinal scale (see Appendix 1)	• WHO 9-point ordinal scale (see Appendix 1)
Exploratory Diagnostic Objective • To determine the comparability between site-collected NP swabs and available OP swabs and available self-collected nasal mid-turbinate swabs for the quantification of SARS-CoV-2 RNA or quantitative culture • To determine comparability between RNA detection and virus isolation from site-collected NP swabs	• RT-PCR of site collected NP swabs and available OP swabs • RT-PCR swabs and RT-PCR of NP samples

10.4. Randomization and Stratification

In Part 1 of the study, eligible participants will be randomized using a 1:1 ratio to Arm A or B using permuted blocks. In all subsequent study parts, eligible participants will be randomized using a 3:1 ratio (EIDD-2801:placebo) to Arm C or D (Part 2), Arm E or F (Part 3), Arm G or H (Part 4), Arm I or J (Part 5), Arm K or L (Part 6), Arm M or N (Part 7), Arm O or P (Part 8), or Arm Q or R (Part 9).

In Part 1, randomization will be stratified by "early" versus "late" time from symptom onset, where "early" time from symptom onset is defined by enrollment (i.e., randomization date and time) 0 to ≤60 hours from symptom onset and "late" is enrollment (i.e., randomization date and time) >60 to ≤168 hours from symptom onset. In subsequent study parts, randomization will not be stratified due to lack of availability of subjects in the "early" time from symptom onset.

10.5. Sample Size and Accrual

The proposed total sample size for the study is up to approximately 172 fully evaluable participants. If participants in a dose group drop out or otherwise have missing or unevaluable primary or key secondary virology endpoint data, additional participants may be enrolled to ensure adequate data at each dose level. The total number of participants to be enrolled will not exceed 204.

For Part 1 of the study, the planned sample size is approximately 44 participants who take the first (confirmed) dose of study treatment (approximately 22 each in Arms A and B).

In subsequent, optional study parts, the sample size **for each part** will include approximately 16 participants who take the first (confirmed) dose of study treatment (approximately 12 participants randomized to an active EIDD-2801 arm and 4 randomized to placebo). Participants who are randomized but do not take the first (confirmed) dose of study treatment will not be followed and will be replaced.

This study is designed to evaluate the antiviral activity of EIDD-2801 by estimating the time (days) until elimination of viral RNA detection in NP swabs in people who receive EIDD-2801 compared to those who receive a blinded placebo. Kaplan-Meier estimation will be used with a corresponding exact, stratified log-rank test (for Part 1) and median time (days) until first non-detectable SARS-Cov-2 NP swabs will be estimated in each trial arm.

Power/Sample Size for Part 1:

The distribution of days until SARS-CoV-2 viral RNA is not detectable (i.e., below the limit of quantification in NP swabs) can be compared between the 2 trial arms (drug vs placebo) using an exact log-rank test. At a 0.10 type I error probability and under the assumptions in Figure 8 and the corresponding table below, there is >85% power to detect a difference (Drug - Placebo) of at least 30% if the evaluable sample size is 19 individuals per arm.

Anticipating up to 10% missing data, enrolling n=44 participants total (approximately 22 per arm) in Part 1 will provide 88% power for the primary endpoint. Power was calculated empirically in R version 3.6.2 using 5000 simulated datasets.

- The power to detect a risk difference (RD) (Drug - Placebo) of -30% is 0.88.
- The power to detect a RD (Drug - Placebo) of -40% is 0.98.
- The power to detect a RD (Drug - Placebo) of -50% is >0.99

The table below contains the assumed data for the viral RNA detection simulations. This assumes collection of NP swabs from all enrolled individuals on Study Days 1, 3, 5, 7, 14, and 28.

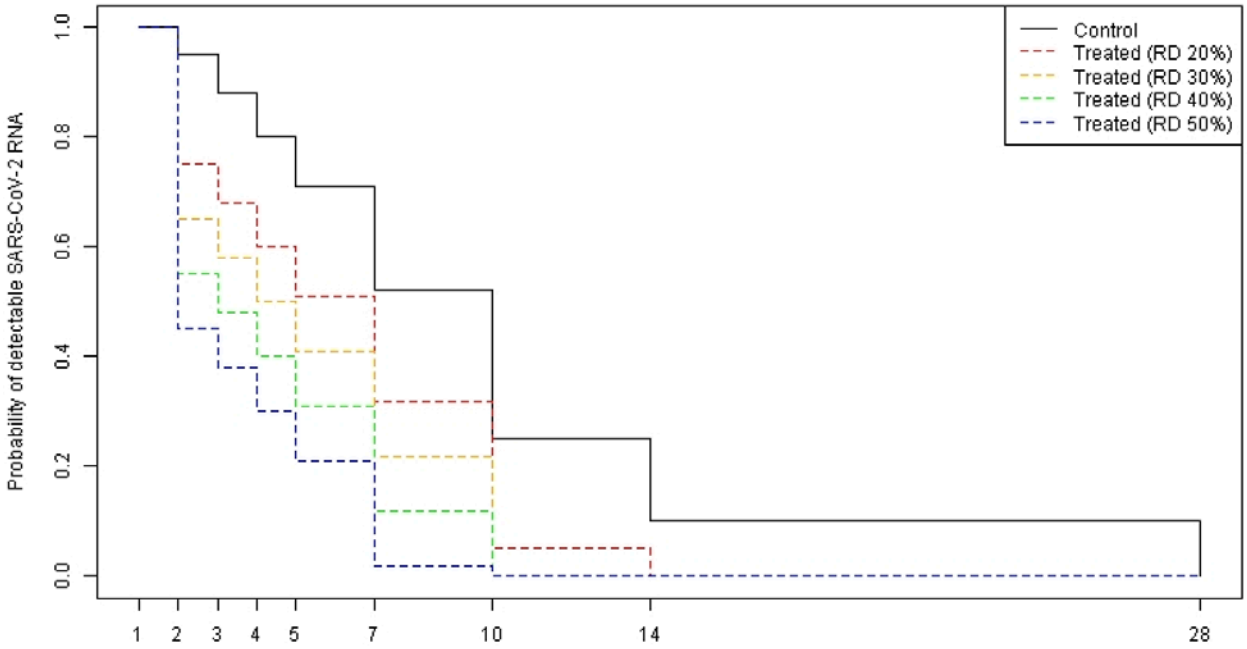

Figure 8. Probability of SARS-CoV-2 viral RNA detection assumed in power/sample size determination

Cumulative probability of viral RNA isolation

Study Day	1	2	3	4	5	7	10	14	28
NP swab	Y	Y	Y	Y	Y	Y	Y	Y	Y
Placebo arm	100%	95%	88%	80%	71%	52%	25%	10%	0%
EIDD-2801 Rx arm (RD -20%)	100%	75%	68%	60%	51%	32%	5%	0%	0%
EIDD-2801 Rx arm (RD -30%)	100%	65%	58%	50%	41%	22%	0%	0%	0%
EIDD-2801 Rx arm (RD -40%)	100%	55%	48%	40%	31%	12%	0%	0%	0%
EIDD-2801 Rx arm (RD -50%)	100%	45%	38%	30%	21%	2%	0%	0%	0%

Assumes treatment starts 3 to 4 days (i.e., 72 to 96 hours) after symptom onset. NP=nasopharyngeal.
*Extrapolated from Chen, J. JI 2020

Abbreviations: D = Day; NP = nasopharyngeal; Rx = treatment; Y = yes.

Power/Sample Size for Parts 2 to 9:

For Parts 2 to 9, no formal statistical hypotheses will be tested. In consideration of analysis of secondary virology endpoints in these dose range finding cohorts, separate power calculations were done for Parts 2 to 9. For Parts 2 to 9, sample size sensitivity was estimated based on the combined study parts to compare the change from baseline in viral RNA between participants treated with EIDD-2801 versus participants treated with placebo. A total 96 participants in the

active group and 32 participants in the placebo group will achieve 83% power to detect a between group difference of at least 0.6 SD in SARS-CoV-2 viral RNA change from baseline with a significance level of 0.05 using a two-sided test.

Participants who receive placebo will be pooled in the final analyses. The between group comparisons assessment of dose and exposure response will be evaluated based on endpoints of time to undetectable SARS-CoV-2 viral RNA and change in viral RNA over time (including viral RNA baseline-normalized AUC through Day 28), and number (%) of subjects with 1, 2 or $\geq$3 $\log_{10}$ viral RNA decline over time.

10.6. Populations for Analyses

Statistical analyses will be performed on the following populations:

- **Modified Intent-to-Treat (mITT)**: All subjects who are randomized into the study and have baseline and at least 1 post baseline viral RNA assessment. Subjects will be analyzed according to the treatment they actually received.
- **Safety:** All subjects who are randomized and take at least 1 dose of study drug. Subjects will be analyzed according to the treatment they actually received.
- **PK:** Subjects in the safety population with at least 1 PK concentration value.
- **Per Protocol (PP):** Subjects in the safety population who had no major protocol deviations and completed the Day 28 follow-up Visit.

10.7. Statistical Analyses

The efficacy, PK, and safety variables and associated analyses are described in this section. Additional details will be described in a statistical analysis plan (SAP) that will be prepared and finalized before database lock. Should the analyses specified in the SAP differ from those described in the protocol, the methodology in the SAP will prevail. General methodology will include descriptive tabular and/or graphical summarizations by treatment group and visit.

Continuous variables will be presented using descriptive statistics: number of observations (n), mean, standard deviation, median, minimum, and maximum values. Categorical values will be summarized with counts and percentages. All collected data will be presented in listings.

10.7.1. Demographic and Other Baseline Characteristics

Descriptive statistical methods will be used to tabulate and summarize demographics and baseline characteristics.

10.7.2. Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analyses

Plasma concentrations of EIDD-2801 and EIDD-1931 will be listed and summarized by treatment and scheduled time point. A PK-pharmacodynamic (PD) model will also be developed to examine the relationship between EIDD-2801/EIDD-1931 PK, viral load reduction, and clinical outcomes. Details of PK and PK-PD analyses will be provided in the SAP.

10.7.3. Part 1 Analyses

Part 1 will be analyzed separately as an a priori powered study. A Statistical Analysis Plan will be developed that describes the analyses to address the study's primary, secondary, and exploratory objectives.

The following provides an outline of the methods for the main comparisons between randomized arms, particularly for the primary outcome measure.

Analyses involving randomized comparisons will include all randomized participants who received the first (confirmed) dose of study treatment, according to a modified intention-to-treat (m-ITT) approach. Participants who do not receive the first (confirmed) dose will be replaced. Unless stated otherwise, the date of randomization will be the time origin for analysis (Day 1). Additional per-protocol analyses may be performed, particularly for virology efficacy endpoints. Missing data are expected to be uncommon (<5 to 10% of participants). Losses to follow-up will be assumed non-informative and complete-case analyses will be conducted.

This is a virology proof-of-principle study, as such a type I error probability of 10% (α=0.10) will be used throughout, with no planned adjustments for multiplicity or primary or secondary endpoints. Throughout, all statistical tests will be two-sided and "exact" statistical procedures that do not rely on large sample assumptions will be applied where computationally feasible.

10.7.3.1. Primary Outcome Measures

Virologic Efficacy: The distribution of days until first non-detectable SARS-CoV-2 viral RNA in NP swabs will be estimated for each randomized arm (drug versus placebo), using Kaplan-Meier methods with a corresponding exact stratified log-rank test (Part 1 only: to account for the "early" versus "late" time from symptom onset randomization strata). "Non detectable" will be defined as a viral load below the limit of quantification (BLOQ). Two consecutive non-detectable viral RNAs in NP swabs (or one negative with no further follow-up) will be required to achieve the event. The date of the first non-detectable will be the event date. Participants who prematurely discontinue the study before achieving non-detectable results will have follow-up for efficacy endpoints censored at the date of last measurement. Losses to follow-up will be assumed non-informative.

Safety and Tolerability: In order to measure the safety and tolerability of EIDD-2801, we will estimate by randomization arm the probability of 1) any AEs leading to early discontinuation of blinded treatment (active or placebo), 2) study drug-related discontinuation of treatment, 3) new grade 3 or higher AE (not already present at baseline), and 4) study drug-related new grade 3 or higher AE. The cumulative probability (i.e., risk) of each safety and each tolerability endpoint (4 endpoints) will be estimated using the Kaplan-Meier approach and stratified log-rank test will be employed for between trial arm comparisons (as outlined for the primary efficacy outcome). Follow-up will be right censored at the date of last known status and event times will be the date of first onset of the given endpoint (e.g., time to first AE leading to early discontinuation of blinded treatment).

The safety and tolerability profile of EIDD-2801 in humans is currently not fully characterized and descriptive participant-level listings of safety and tolerability events will be summarized. We will estimate 28-day risk function of each safety and tolerability endpoint with a corresponding 2-sided 90% confidence interval, with focus on the upper confidence limit for interpretation of results. To inform the design of future larger trials we will estimate the difference in probabilities

(i.e., a risk difference) between randomization arms of each safety and tolerability endpoint with a corresponding 90% confidence interval. A risk ratio may also be estimated for comparison to other studies, although a risk difference is of greater public health relevance.

Endpoints (1) and (2) above may be composited to assess tolerability as any AE leading to early discontinuation of blinded study treatment or any discontinuation of study treatment (active or placebo) deemed related to study drug.

Additionally, we will describe and estimate mortality from any cause or hospitalization during the 28-day period from and including the day of the first (confirmed) dose of study treatment. Hospitalization is defined as requiring at least 24 hours of acute care in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address needs during the COVID-19 pandemic. Evaluation at a hospital or similar facility with less than 24 hours of acute care is not considered a hospitalization. The Kaplan-Meier approach described above will be applied to the endpoint of days until death or first hospitalization and the 28-day risk function will be estimated as described for the primary safety endpoints.

10.7.3.2. Secondary Outcomes

Safety: Occurrence of Grade 2 or higher AEs and drug related AEs will be evaluated using the same approach as outlined for the primary safety analysis in Section 10.7.3.1. We will describe and estimate all-cause mortality and hospitalization during the 28-day period from and including the day of the first (confirmed) dose of study treatment. The Kaplan-Meier approach described above will be applied to the endpoint of days until first hospitalization or death, and the 28-day risk function will be estimated as described for the primary safety endpoints.

Duration of fever, duration of symptoms, and duration of time to self-reported return to usual health will be summarized with descriptive statistics. Participant-specific durations of fever and symptoms will be compared between study arms using a stratified Wilcoxon rank-sum test. The distribution of days until improvement of all new or worsened COVID-19 symptoms will be compared between study arms using Kaplan-Meier methods with a corresponding exact stratified log-rank test (to account for the "early" versus "late" time from symptom onset randomization strata). New or worsened symptoms of COVID-19 may include feverishness, chills, myalgias, headache, sore throat, loss of sense of smell, loss of sense of taste, cough, and difficulty breathing. Improvement in these symptoms is defined as a decrease in all new or worsened symptoms (i.e., from severe/moderate severity to mild/absent/pre-COVID-19 severity, or a decrease in mild severity to absent). Participants who do not have complete symptom diaries due to hospitalization or death will be ranked in these analyses as having poorer outcomes than participants who survived without hospitalization.

Analyses for the additional objectives will be described in the SAP.

Virologic: The distribution of days until first non-detectable SARS-CoV-2 in NP swabs (i.e., infectious virus measurement) will also be estimated for each randomized arm (drug versus placebo), using Kaplan-Meier methods with a corresponding exact stratified log-rank test (to account for the "early" versus "late" time from symptom onset randomization strata). Participants who prematurely discontinue the study before achieving nondetectable results will have follow-up for efficacy endpoints censored at the date of last measurement. Losses to follow-up will be assumed non-informative.

The distribution of days until SARS-CoV-2 is not detectable can be compared between the two trial arms (drug vs. placebo) using an exact stratified log-rank test. At 0.10 (10%) type I error probability and under the assumptions in Figure 9 and the corresponding table below, there is 90% power if the evaluable sample size is 19 individuals per arm in Part 1. In Part 1, anticipating up to 10% missing data, enrolling n=44 participants (approximately 22 per arm) will provide 90% power for the secondary virologic endpoint of time to non-detectable SARS-CoV-2 in NP swabs. Power was calculated empirically in R version 3.6.2 using 5000 simulated datasets.

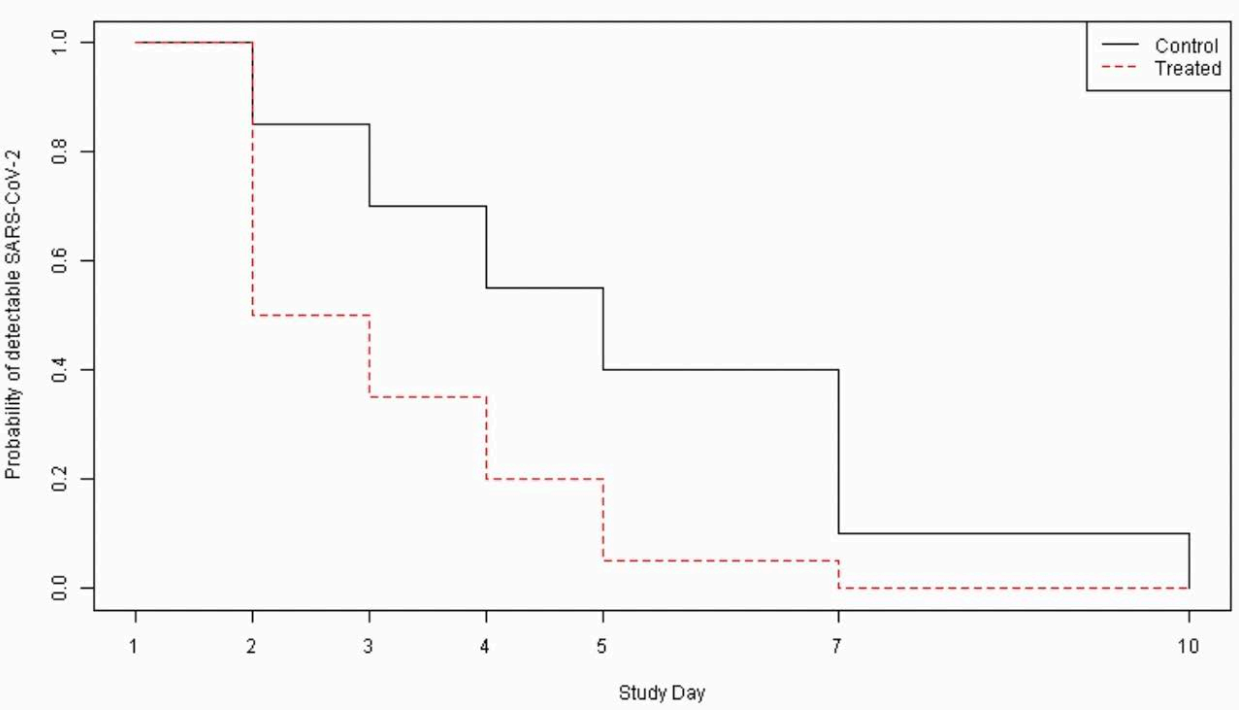

Figure 9: Probability of detectable SARS-CoV-2 assumed in power/sample size determination

*Cumulative probability of infectious virus isolation**

	D1	D2	D3	D4	D5	D7	D10
NP swab	Y	Y	Y	Y	Y	Y	Y
Placebo arm	100%	85%	70%	55%	40%	10%	0%
EIDD-2801 Rx arm	100%	50%	35%	20%	5%	0%	0%

Abbreviations: D = Day; NP = nasopharyngeal; Rx = treatment; Y = yes.
Assumes treatment starts 3 to 4 days (i.e., 72 to 96 hours) after symptom onset. NP=nasopharyngeal.
*Extrapolated from Wolfel, R et al. Nature 2020

Reductions in shedding of SARS-CoV-2 RNA in NP swabs at Treatment Days 3, 5, 7, 14, and 28 will also be compared between arms via stratified Wilcoxon rank-sum tests.

Mutation rate (number of mutations in the viral genome) will be assessed using next generation deep genome sequencing (NGS). Mutation rates will be summarized with descriptive statistics and compared between study arms (drug versus placebo).

10.8. Pooled Analyses

For the final analyses, the demographic, baseline characteristics, and study disposition data will be summarized separately by study part and for the pooled analyses.

Safety and efficacy data will be provided both based on the pooled analyses, as well as per cohort analyses. For the pooled analyses, data across all study parts will be combined. Subjects that received the same dose (i.e., placebo) across study parts will be combined into the same dose group. All analyses will be performed based on the safety population (defined as subjects who received at least 1 dose of randomized study drug as treated) by dose group. Data from the active treatment arms (e.g., Arms A, C, E, G, I, K, M, O, and Q) may be combined for analysis, when appropriate, in comparison with the pooled placebo group. No formal hypothesis tests will be performed for the pooled analyses. An estimation approach will provide the estimated between-group differences and associated 95% confidence intervals. P-values for between-group comparisons may be included as descriptive statistics.

The following provides an outline of the key methods for the efficacy and safety analyses:

Virology Endpoints

The time to response (i.e., time to BLOQ in viral RNA) will be analyzed using Kaplan-Meier methods. The median time to event and associated 95% confidence interval will be provided by dose group. The cumulative probability of BLOQ and associated 95% confidence intervals over time will also be provided by dose group. P-values for between-group comparison will be included as descriptive statistics using a log rank test.

Responder endpoints (i.e., proportion of viral RNA below BLOQ) will be provided descriptively over time by dose group. P-values for between-group comparison will be included as descriptive statistics using a 2-sample binomial test or Fisher's exact test.

Continuous endpoints (actual, change from baseline, percent change from baseline, adjusted AUC on treatment or during study) will be summarized over time by treatment group. The between-group differences and associated 95% confidence intervals will be estimated using an ANCOVA model, where dose group will be included as a fixed effect and baseline and days since infection will be included as covariates. Additional statistical models will be explored and details will be provided in the SAP.

Analyses for the exploratory virologic objectives will be described in the SAP.

Clinical Outcome Analyses

Participant Symptom Diary

Symptom diary data will be listed and individual symptom scores will be summarized by treatment and visit. The worst severity at each visit from the individual symptoms will also be summarized by treatment group.

The time to improvement (defined as symptoms becoming 0=absent or 1=mild; if baseline is mild, then improvement is defined as symptoms becoming absent) in all items and by individual item will be summarized using the Kaplan-Meier method and compared between randomization arms using a log-rank test. The median time to improvement and the cumulative probability of improvement over time with 95% confidence intervals will be provided by treatment group. Additional statistical models will be explored to assess the between group difference. Details will be provided in the SAP.

WHO 9-Point Ordinal Scale and COVID-19 Related Medical Visits

Ordinal Scale Clinical Improvement data will be listed and summarized by treatment. If data permit, the time to hospitalization/death will also be derived and summarized using the Kaplan-Meyer method.

The proportion of participants who require additional medical visits (including telemedicine visits and hospitalization) related to COVID-19 will be summarized by treatment group and compared between active drug versus placebo using a risk difference and corresponding 95% CI.

Safety

All safety data will be provided descriptively by dose group and scheduled time of assessment where appropriate. 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 subjects 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.

Observed values and changes from baseline in laboratory and vital sign test results will be summarized by dose group at each scheduled visit. Laboratory abnormalities will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, if applicable. Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment-emergent. The number and percentage of subjects experiencing treatment-emergent graded laboratory abnormalities will be summarized. Laboratory abnormality shifts from baseline to worst post-baseline assessments will also be summarized for the treatment emergent abnormality.

Additional details will be described in a statistical analysis plan (SAP) and finalized before database lock. Should the analyses specified in the SAP differ from those described in the protocol; the methodology in the SAP will prevail.

10.9. Interim Analysis

No formal interim analysis is planned.

An interim virology data monitoring report may be prepared after approximately the tenth participant in selected study parts (Parts 1 to 9) have data available through study Day 7. Blinded data listings and pooled descriptive interim summaries of viral RNA and infectious virus may be reviewed to verify assumptions made for sizing this proof-of-concept study, to determine whether

to enroll subsequent dose parts and determine doses to be evaluated in subsequent parts. In addition, the sponsor may choose to review pooled, blinded virology data summaries periodically during enrollment.

A sponsor-designated Data Review Group comprised of a limited number of sponsor personnel may also review unblinded virology data from ongoing cohorts if a sufficient number of subjects have been enrolled. Site personnel will remain blinded until the database is locked at the end of the study. These data may be shared with the IND sponsor.

After completion of each study part, unblinded virology data and safety data may be reviewed to determine the dose(s) for the subsequent parts.

10.10. Unblinding

For unblinding requests, including emergency unblinding, refer to [redacted], or other similar site-specific standard operating procedure.

In the event that emergency disclosure of treatment assignment is thought to be required, the site investigator must follow [redacted], or other similar site-specific standard operating procedure.

Unblinding will not occur to allow replacement of participants (see Section 6.2.4).

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 treatment assignment **is unblinded, this information** should only be shared with the physicians responsible for the management of the participant on a need-to-know basis. Treatment assignment should not be shared with others. **This includes not sharing treatment assignment** with the study team.

All site e-mails to the team should be carefully worded to prevent unblinding the team.

Unblinding of all study participants will take place after the last participant has completed the study, all data have been entered into the database, cleaned for primary and secondary outcome measures, and locked. For details, please refer to [redacted].

11. DATA COLLECTION AND MONITORING

11.1. Reporting Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being (ICH E3). The site principal investigator and personnel are responsible for identifying and reporting important deviations. Once important protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the IRB/EC per their guidelines.

For this study, all protocol deviations that meet the definition of important as defined in the MOPS relating to participant safety and confidentiality must be recorded on the study protocol deviation eCRF.

11.2. Records to Be Kept

Electronic case report form screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the SMC. Participants will be identified by the patient identification number and study identification number provided upon randomization.

11.3. Role of Data Management

11.3.1. Instructions concerning entering study data on eCRFs will be provided by the data management team (DMT). Each clinical research site (CRS) is responsible for keying the data in a timely fashion.

11.3.2. It is the responsibility of the DMT to ensure the quality of computerized data for this study. This role extends from protocol development to generation of the final study databases.

11.4. Clinical Site Monitoring and Record Availability

11.4.1. Site monitors, including representatives of the Sponsor, will visit the clinical research sites to review source and study data including the individual participant records, consent records, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.4.2. The site investigator will make study documents (e.g., consent records, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the OHRP,

the sponsor or designee, Western IRB (WIRB) other local, US, and international regulatory entities for confirmation of the study data.

11.4.3. Given the epidemic spread of SARS-CoV-2 and the risk for visiting personnel, the study can be monitored remotely by clinical trial monitors. This will be decided based on the risk environment at the time of monitoring.

12. PARTICIPANTS

12.1. Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. Informed consent will be obtained from the participant either through a signed consent form or through appropriate remote consenting procedures. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the participant's record.

12.2. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB/EC, the FDA, OHRP, other local, US, and international regulatory entities as part of their duties.

12.3. Study Discontinuation

The study may be discontinued at any time by the Sponsor, FDA, IRB/EC, or OHRP as part of their duties to ensure that research participants are protected.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by UNC policies as agreed with Ridgeback Biotherapeutics LP. Any presentation, abstract, or manuscript will be made available for collaboration and review by the Sponsor prior to submission.

14. BIOHAZARD CONTAINMENT

As the transmission of SARS-CoV-2 and other droplet-borne pathogens can occur through contact with persons with active SARS-CoV-2 and infection-contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the clinical research setting and in drawing of blood, collection of respiratory samples, and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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16. APPENDICES

16.1. Appendix 1: 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

Source: World Health Organization web site: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

16.2. 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).