STATISTICAL ANALYSIS PLAN
PHASE IIA

DATE and VERSION OF PLAN:

18-FEB-2021, Version 2.0

BASED ON:

Protocol Version 5.0

STUDY DRUG:

EIDD-2801

PROTOCOL NUMBER:

EIDD-2801-2003

STUDY TITLE:

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

SPONSOR:

Ridgeback Biotherapeutics, LP
3480 Main Highway, Unit 402, Miami, FL 33133

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 2/19/2021 | 10:02:11 AM PST
[redacted]

2/19/2021
Date

[redacted],
Statistician, Pharstat Inc

This document has been reviewed and approved by:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 2/19/2021 | 10:07:27 AM PST
[redacted]

2/19/2021
Date

[redacted]
Chief Medical Officer, Ridgeback Biotherapeutics

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAE	Human airway epithelial cell culture
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
IV	Intravenous
KM	Kaplan-Meier
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
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
SD	Standard Deviation
SMC	Safety Monitoring Committee
ULN	Upper Limit of Normal
UNC	University of North Carolina
WHO	World Health Organization

1. INTRODUCTION

This SAP describes the statistical methods to be used during the analysis and reporting for study EIDD-2801-2003.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database.

This SAP should be read in conjunction with the study protocol and electronic Case Report Form (eCRF). Any further changes to the protocol or eCRF may necessitate updates to the SAP. This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in the SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- Primary Efficacy Objective: To determine if EIDD-2801 reduces the time to viral RNA negativity
- Primary Safety Objective: To determine the safety and tolerability of EIDD-2801

2.1.2. Secondary Objectives

- To compare the incidence of grade 2 or higher AEs and drug-related AEs between treatment arms
- To determine if EIDD-2801 reduces the time (days) to negativity of infectious virus isolation in NP swabs from SARS-CoV-2-infected adults
- 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
- To determine if EIDD-2801 increases viral RNA mutation rate. RNA mutation rate is measured by Next Generation sequencing
- To determine if EIDD-2801 changes the severity and duration of self-reported symptoms of COVID-19

- To determine if EIDD-2801 treatment reduces the proportion of individuals that are hospitalized for COVID-19 related illness by Day 28
- To characterize the pharmacokinetics (PK) of EIDD-2801 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

2.1.3. Exploratory Objectives

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

2.2. Study Endpoints

2.2.1. Primary Endpoint

- The viral RNA negativity determined by reverse-transcriptase polymerase chain reaction (RT-PCR) of NP swabs
- Any adverse events (AEs) leading to early discontinuation of treatment; study drug-related discontinuation of treatment; new Grade 3 or higher AEs (not already present at baseline); study drug-related new Grade 3 or higher AEs and serious AEs

2.2.2. Secondary Endpoint

- Incidence of Grade 2 or higher AEs and drug-related AEs
- Infectious virus detection in NP swab samples cultured on Vero-cell cultures
- Comparison of spike and RNA dependent RNA polymerase gene sequences using Next Generation sequencing
- Patient reported symptoms of COVID-19
- WHO 9-point ordinal scale
- Concentrations of EIDD-2801 and EIDD-1931

2.2.3. Exploratory Endpoints

- RT-PCR of site collected NP swabs and available OP swabs

2.3. Statistical Hypotheses

- 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 For study 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. No hypothesis will be formally tested for study Parts 2-9.
- EIDD-2801 will be safe and well tolerated in persons with symptomatic SARS-CoV-2 infection

The safety and tolerability endpoints will be presented descriptively. No hypotheses for safety and tolerability will be tested.

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, approximately 44 eligible 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, 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, 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.

Participants who do not start study treatment will be replaced. 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.

All participants will be followed for 5 days on treatment and an additional 23 days off treatment. At Study Entry (Day 1), all consented participants will have an in-person study visit at the clinical research center prior to IP administration. Either in-clinic visits or in-home visits will continue on days 3, 5, 7, 14, and 28. Information regarding participant demographics, COVID-19 symptoms, medical and medication histories, and adverse events will be collected at screening. Thereafter, at each study visit, some or all of the following will be collected for each participant: vital signs, study daily diary entries, pregnancy test (where applicable), adverse event information, nasopharyngeal (NP) swab, hematology, chemistry, inflammatory markers, and pharmacokinetics (PK).

In Part 1, randomization will be stratified by time (days) from symptom onset – "early" versus "late" presentation, where "early" and "late" presentations 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. Definition of Study Drugs

[redacted] 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.

3.2. Sample Size Considerations

3.2.1. Sample Size Determination

This study is designed to evaluate the antiviral activity of EIDD-2801 by estimating the time (days) until elimination of viral RNA in NP swabs in people who receive EIDD-2801 compared to those who receive a blinded placebo. Kaplan-Meier (KM) estimation will be used with a corresponding exact log-rank test (for Part 1). The median time (days) until first non-detectable SARS-Cov-2 NP swabs will be estimated in each trial arm. Anticipating up to 10% missing data, enrolling n=44 participants total (approximately 22 per arm) in Part 1 will provide 88% power to detect a risk difference (active – placebo) of -35% for the primary endpoint using an alpha=0.10 type I error rate and with viral RNA measured at Days 1, 3, 5, 7, 14, and 28.

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 type I error rate of alpha=0.05 using a two-sided test.

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.

3.3. Randomization

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.

3.4. Clinical Assessments

The timing of clinical assessments is presented in the
Table 1 below.

Table 1: Schedule of Assessments

SCHEDULE OF EVENTS	Screening (in person or by phone)	Study Entry / Enrollment		Post-Entry Evaluations					Premature Study Discontinuation
		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				
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		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).

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal interim analysis is planned.

Interim virology data monitoring reports may be prepared after approximately the tenth participant in selected study parts has 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 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.

The following unblinded data analyses will be performed after completion of the selected parts. The database will be cleaned and locked for the unblinded analyses.

- Planned unblinded analysis 1: after Parts 1-6 subjects have completed study

4.2. Final Analysis

Any data values requiring investigation or correction will be identified while programming the datasets and Tables, Figures, and Listings (TFLs). The final statistical analysis will be conducted when the last subject has completed the study and will be based on the locked database.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Tables and listings will be prepared in accordance with the current International Conference on Harmonization (ICH) Guidelines. Version 9.3 or higher of the SAS® system will be used to analyze the data as well as to generate tables, figures, and listings.

All analyses will be performed separately for the following:

1. Pooled Parts 1-9
2. Part 1 Only
3. Pooled Parts 2-9

In the pooled analyses, subjects who received the same dose across study parts will be pooled together for safety and efficacy analyses. All subjects who received active EIDD-2801 across doses will be combined as an additional group in the analyses. Data listings will be sorted by dose level, study part, subject, and assessment time.

General Summary Table and Individual Subject Data Listing Considerations:

Summary tables and listings will be prepared according to ICH Guideline E3 and will include a 'footer' providing explanatory notes that indicate:

- Date of output generation.
- SAS program name
- Any other output specific details that require further elaboration

If there are multiple assessments collected on the same scheduled time, the last assessment will be used. Deviations from the analyses planned in the SAP will be identified in the final clinical study report.

5.1. Data Management

Data handling and transfer will take place as described in the Data Management Plan (DMP) for the study.

SDTM datasets will be created based on the raw eCRF and laboratory data and adhere to CDISC SDTM Implementation Guide 3.2. Analysis datasets will be generated using (SAS®) version 9.3 or later software and adhere to ADaM Implementation Guide 1.1 structure.

5.2. Data Presentation Conventions

Unless otherwise stated, continuous data will be summarized with the following descriptive statistics: number of non-missing observations (n), arithmetic mean, standard deviation (SD), median, minimum (min), maximum (max), and for PK parameters only, geometric mean, SD and geometric CV% for continuous variables. Categorical variables are summarized using counts and percentages. All reported p-values will be 2-sided.

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.

- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.

5.3. Analysis Populations

All populations will be defined after database lock when the relevant data are available.

5.3.1. Intent-to-Treat (ITT)

ITT (Randomized) population will include all subjects who are randomized. Subjects will be analyzed according to the treatment they were assigned.

5.3.2. Modified Intent-to-Treat (mITT)

mITT population will include all subjects who are randomized into the study and have at least 1 post baseline viral RNA assessment. Subjects will be analyzed according to the treatment they actually received.

5.3.3. Safety Population

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. All the safety analyses will be performed using the safety population. The patient diary and clinical outcome (Ordinal Scale Clinical Improvement, medial visit) data will also be analyzed using the safety population.

5.3.4. Per Protocol (PP)

Per protocol population will include subjects in the safety population who have no important protocol deviations leading to exclusion from the PP population and have completed the Day 28 follow-up Visit.

5.3.5. Pharmacokinetic Population

All subjects in the Safety Population with at least one plasma PK concentrations of EIDD-2801/EIDD-1931.

5.3.6. Subgroups

If data permit, efficacy analyses will be performed by the following subgroups:

- Number of risk factors for severe COVID-19: 0, 1-2 or >2
- Age ≥65 or <65
- Presence or absence of SARS-CoV-2 antibodies
- Positive Infectivity at baseline (based on infectious virus isolation determined by isolation in Vero cell line culture)

The risk factors for severe COVID-19 are:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
  cardiovascular disease, OR
  hypertension, OR
  chronic obstructive pulmonary disease/other chronic respiratory disease

Additional COVID risk factors (i.e., cancer, pregnancy etc.), demographic and baseline characteristics may be explored as subgroups or as covariates for between treatment comparisons.

5.4. Baseline Definition

The baseline is defined as the last assessment prior to the first dose of study medication (i.e., measured at Day 1 pre-dose or at the screening visit).

5.5. Derived and Transformed Data

5.5.1. Study Day

If the date of interest occurs on or after the first dose date then study day will be calculated as:

- (date of interest – date of first dose) + 1.

If the date of interest occurs prior to the first dose date then study day will be calculated as:

- (date of interest – date of first dose).

There is no study day 0

5.5.2. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

5.5.3. Derived Endpoints

- **SARS-CoV-2 RNA**

Efficacy Endpoint of SARS-CoV-2 RNA will be converted to $\log_{10}$ scale. Listings will include the values in $\log_{10}$ scale and in the original scale. For SARS-CoV-2 RNA values reported as below the limit of detection/quantification (the lower limit of quantification is 1018 copies/mL), 1017 copies/mL will be used in the analyses.

SARS-COV-2 RNA below the limit of detection/quantification will be considered as undetectable (negative) in the analyses.

- **SARS-CoV-2 RNA Rate of Decline**

The individual rate of SARS-CoV-2 RNA decline will be derived as Average Area under the Curve minus Baseline (AAUCMB, i.e., the average daily viral load value minus baseline) for the five time intervals of: D1-D3, D1-D5, D1-D7, D1-D14 and D1-D28 using the following formulas:

$$\text{AAUC} = \frac{\sum_{i=1}^{n-1}\left(t_{i+1}-t_i\right)\left(\frac{x_{i+1}+x_i}{2}\right)}{\left(t_n-t_1\right)} = \frac{\text{AUC}}{\left(t_n-t_1\right)}, \text{ and}$$

AAUCMB=AAUC – Baseline (x at time i=1)

where, x_i is the data value at the i^{th} time point and t_i is the time value at the i^{th} time point.

- **Time to non-detectable SARS-CoV-2 viral RNA in NP swabs based on PCR**

Two consecutive undetectable 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 undetectable result will be the event date. If the subject only has undetectable viral RNA at the last on study assessment, it will be counted as event at the time of the last assessment. Subjects not achieving the event and who complete the study follow-up will be censored at the last viral RNA assessment. Subjects not achieving the event and dropped out before Day 28 will be censored at Day 28.

Time to un-detectable = Date of Event (Censored) – date of first dose+1

- **Time to negativity of infectious virus isolation in NP swabs based on infectious virus isolation determined by isolation in Vero cell line culture**

This endpoint will be derived similarly to time to undetectable viral RNAs in NP swabs based on PCR. Infectious virus will be measured at Days 1, 3, 5, and 7 and additional details will be provided in the CSR.

- **Time to COVID Symptom Resolution:**

Time to COVID Symptom Resolution will be derived based on subject overall assessment of COVID symptoms with resolution defined as 3 consecutive assessments in a resolved state. For subjects with mild, no symptoms or no diary data at the baseline, the time to resolution is defined as the first time where subject overall assessment is no symptoms for 3 consecutive assessments . For subjects with moderate or higher severity at the baseline, the time to resolution is defined as the first time where subject overall assessment is mild or no symptoms for 3 consecutive assessments. Subjects who completed study and have reached the resolved state on the last 2 assessments will be considered as resolved on the day prior to the last assessment. Subjects who completed study and have reached the resolved state on the last assessment will be considered as resolved on the date of the last assessment.

Subjects not achieving symptom resolution and completing the study will be censored at date of last COVID symptom diary. Subjects not achieving the event and dropped out before Day 28 will be censored at Day 28. Subjects who do not achieve the event and do not complete the day 28 diary due to hospitalization will be censored at day 28.

Subject diary data collected within 28 days of first dose will be included in the derivation of the time to COVID symptom resolution endpoint.

Time to resolution (days) = Date of resolution (Censored) – date of first dose+1

- **Time to patient reported general physical health of 3 or 4 (Very Good or Excellent)**

This endpoint will be derived similarly to the time to symptom resolution.

- **Time to patient reported returned to the (Pre-COVID) health**

This endpoint will be derived similarly to the time to symptom resolution.

- **Time to resolution of upper respiratory tract symptoms (based on the worst severity of the 5 symptoms measured: Cough, Shortness of breath, Sore throat, Nasal obstruction and Nasal discharge)**

This endpoint will be derived similarly to the time to symptom resolution.

- **Time to resolution of common COVID symptoms (based on the worst severity of the 13 symptoms measured: Cough, Shortness of breath, Feeling feverish, Muscle aches, Diarrhea, Vomiting, Nausea, Headache, Sore throat, Nasal obstruction, Nasal discharge, Fatigue and Chills)**

This endpoint will be derived similarly to the time to symptom resolution.

- **Time to resolution of common COVID symptoms (based on the worst severity of the 12 symptoms measured: Cough, Shortness of breath, Feeling feverish, Muscle aches, Diarrhea, Vomiting, Nausea, Headache, Sore throat, Nasal obstruction, Nasal discharge and Chills)**

This endpoint will be derived similarly to the time to symptom resolution.

- **Time to resolution of Cough**

This endpoint will be derived similarly to the time to symptom resolution.

- **COVID related medical visit**

A subject is considered to have a COVID related medical visit if the subject meets any of the following:

1. Hospitalized based on the Hospitalization CRF or any outpatient medical visit (including telemedicine visits)
2. Answered "Yes" to the Diary question 'Sought urgent medical care at an emergency room or clinic'
3. Answered "Yes" to the Diary question "Been hospitalized for at least 24 consecutive hours"

5.6. Missing Data and Outliers

For subjects who prematurely discontinue the study, all available data will be included in the analyses. The planned safety and efficacy analyses will be based on the reported data.
An investigation will be made concerning the sensitivity of the results if extreme outliers are detected within the data.

Missing data will not be imputed. However, for adverse events with missing onset dates, treatment emergent flags will be assigned based on the imputation below:

Missing Adverse Event (AE) Onset Date

When a missing or partial onset date has been recorded, the following algorithm will be performed, designed to conservatively assign AEs as treatment emergent when the AE end date is not before the date of first dose.

- If the onset date is entirely missing, then the AE will be assigned as treatment emergent.

- If the year of onset only is provided and the year is the same as the year of first dose of any study drug, then this event would be treatment-emergent. If the year of onset only is

provided and the year is not the same as the year of first dose, then the onset date will be imputed as the 1st of January of that year to determine if the event is treatment emergent.

- If the month and year of onset are provided, and the month and year are equal to the month/year of first dose of any study drug, then this event would be treatment-emergent. In all other cases, the 1st day of the provided month/year of onset will imputed for the onset date to determine treatment emergent. Only if the provided month/year of onset is prior to the month/year of first dose would an event **not** be considered treatment-emergent.

AEs with end date prior to the date of first dose will not be considered treatment-emergent.

AEs with missing severity will be excluded from the by severity summaries. TEAEs with missing relationship to study drug will be considered to be probably related to study drug in the summaries.

Missing Data for SARS-COV-2 RNA Undetectable (Negative) Endpoint

Subjects with missing SARS-COV-2 RNA at a visit(s) will be imputed based on the available non missing SAS-COV-2 RNA data described in the table below:

Visit Before	Visit After	Imputation of Undetectable SAS-COV-2 RNA
BLQ/BLD	BLQ or BLD	Negative
>BLQ	BLQ or BLD	Positive
BLQ/BLD or missing	>BLQ	Positive[1]
Missing	BLQ or BLD	Missing
any value	Missing	Missing

BLD=below the limit of detection. BLQ=below the limit of quantification.
[1] Subjects with missing baseline and reported the first post baseline value as >BLQ, the baseline will be imputed as >BLQ (Positive).

Missing Data for SARS-COV-2 Infectious Virus

Subjects with missing infectivity data will be imputed based rules in the table below:

Visit Before	Visit After	Imputed Infectivity Result
Negative	Negative	Negative
Positive	Positive	Positive
Negative or missing	Positive	Positive[1]
Missing	Negative	Missing
any value	Missing	Missing

[1] Subjects with missing baseline and reported the first post baseline value of Positive, the baseline will be imputed as Positive.

6. TREATMENT COMPARISONS

6.1. Data Display Treatment

Data display treatment descriptors with actual treatment description will be defined as shown below:

Study Part	Treatment Description	Treatment Display Code
Part 1	Part1:EIDD-2801 200 mg BID	A
	Part 1: Placebo	B
Parts 2/3/4/5/6/7/8/9	Parts 2-9:EIDD-2801 200, 400, or 800 mg BID	C/E/G/I/K/M/O/Q
	Parts 2-9: Placebo	D/F/H/J/L/N/P/R
Pooled Treatment	EIDD-2801 200 mg BID	1
	EIDD-2801 400 mg BID	2
	EIDD-2801 800 mg BID	3
	Placebo	9

7. STUDY POPULATION

7.1. Subject Disposition

A summary table will be generated by study part and treatment to provide the following:

- Number of subjects Randomized (ITT)
- Number of subject randomized and not treated
- Number and percentage (based on ITT) of subjects in the Safety population
- Number and percentage (based on Safety) of subjects in the mITT population
- Number and percentage (based on Safety) of subjects in the PK population
- Number and percentage (based on Safety) of subjects in the PP population
- Number and percentage of subjects in the safety population who completed the study
- Number and percentage of subjects in the safety population who completed the Treatment
- Number and percentage of subjects in the safety population who discontinued the study
- Reason for discontinuation of study

A subject listing noting treatment and study duration and reason for withdrawal from the study will be provided. Randomization details will be provided in the listing.
A separate table will be provided by pooled treatment group to provide the following:

- Number of subjects in the Safety population
- Number and percentage of subjects in the mITT population
- Number and percentage of subjects in the PK population
- Number and percentage of subjects in the PP population
- Number and percentage of subjects in the safety population who completed the study
- Number and percentage of subjects in the safety population who completed the Treatment
- Number and percentage of subjects in the safety population who discontinued the study

- Reason for discontinuation of study

For subjects excluded from PP population, reasons for exclusion will be listed.

7.2. Protocol Deviations

Protocol deviations will be summarized and listed. All important protocol deviations, potentially leading to exclusion from the PP population, will be reviewed prior to database lock and unblinding. The reason for exclusion from PP will be documented and approved before unblinding.

7.3. Demographic and Baseline Characteristics

Demographic (age, sex, race, and ethnicity) and baseline characteristics (height, weight, and body mass index [BMI], vital signs, Smoking Status (current Smoker, ex-smoker or Non-smoker), Days from Symptom Onset, D-dimer, CRP levels, WBC absolute neutrophils count and absolute lymphocyte count) will be summarized and listed.

The baseline viral RNA, baseline patient reported symptom will be summarized and listed.

Demographic and baseline characteristics will be summarized for the ITT population by study part and treatment, and separately for the safety population for the pooled analyses.

7.4. Medical History

Medical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23. Medical history will be summarized by the number and percentage of subjects within each SOC and PT.

Ongoing medical conditions that are at increased risk for severe illness from COVID-19 will be reviewed and summarized separately.

7.5. Prior and Concomitant Medications

Medications used prior to the first dosing date of study drug will be recorded as prior medications. Medications used on or after the first dosing date of study drug and during the study will be recorded as concomitant medications.

Non-study medications will be coded to the medicinal product name using the World Health Organization Drug Dictionary (WHO-DD Version March 2017).

Prior and concomitant medications will be summarized using Anatomical Therapeutic Chemical (ATC) Level 2 and Level 4 coded terms.

8. SAFETY ANALYSES

The safety data including AEs, clinical laboratory data, and vital signs will be summarized using descriptive statistics and listed individually for each subject.

8.1. Extent of Exposure

Exposure duration in number of days will be summarized. The exposure duration is derived as (the date of last dose – the date of first dose+1).

The number and percentage of subjects with number of doses received in the following categories will be summarized for the Safety population:

- ≥1 and <5 doses
- ≥5 and ≤9 doses
- 10 Doses

Dosing records will be listed. A separate listing will be provided for subjects who did not complete the treatment (receiving all 10 doses) with reasons for each dose missed.

8.2. Adverse Events

Adverse events will be coded using MedDRA® (Medical Dictionary for Regulatory Activities) Version 23. Any events reported after the initiation of study treatment and up to 14 days after the last dose of study treatment are defined as treatment-emergent AEs (TEAEs). AEs started more than 14 days after the last dose of study treatment will be considered post treatment and will be summarized separately

Adverse event summaries will summarize only TEAEs. Adverse events will be categorized by TEAE, serious TEAE (SAE), death, and discontinuation. These categories will be further summarized by the causal relationship to study drug (Related and Possible related will be grouped together as Related; AEs Reported as Unlikely and Not Related will be grouped together as Not Related).

The Investigator will provide an assessment of the intensity of each AE. Intensity will be assessed in terms of severity (mild, moderate, severe, potentially life-threatening or death). Subjects will be counted once and summarized under their highest severity within a SOC and PT.

The following TEAE summary tables will be prepared:

- Overall Summary of TEAEs (Any TEAE, TEAE Related to study drug, Grade 2 or higher TEAE, Grade 3 or higher TEAE, Drug related TEAEs, Drug related Grade 3 or higher

TEAE, TEAEs leading to study drug discontinuation, Drug related TEAEs leading to study drug discontinuation, Serious TEAE, TEAE leading to death)

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by maximum severity SOC, and PT
- Summary of Grade 2 or higher TEAEs by SOC and PT
- Summary of Grade 3 or higher TEAEs by SOC and PT
- Summary of Drug Related Grade 3 or higher TEAEs by SOC and PT
- Summary of Drug Related TEAEs by SOC, and PT
- Summary of TEAEs resulting in discontinuation from study drug by SOC and PT
- Summary of Drug Related TEAEs resulting in discontinuation from study drug by SOC and PT
- Summary of Serious TEAEs by SOC and PT
- Summary of Drug Related Serious TEAEs by SOC and PT
- Summary of Post Treatment AEs by SOC and PT

8.3. Pregnancies (as applicable)

If any female subjects become pregnant during the study, a listing will be provided.

8.4. Clinical Laboratory Evaluations

Individual data listings of laboratory results will be presented by study part, treatment, subject, and time point. Values outside of the laboratory's reference range (i.e., those with high or low values) and lab toxicity grade will be included in the laboratory listings.

Quantitative values and change from baseline in quantitative values will be summarized by planned nominal time and treatment for each quantitative lab. For Laboratory data reported with "<" or ">" symbols, data will be presented in listings with their inequality symbols; however, for tabulation of summary statistics, the number associated with the inequality sign will be used for analysis.

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.

A summary of treatment emergent Grade 3 and Grade 4 laboratory abnormalities by treatment will also be provided.

Clinical Important LAB Findings

- Platelets less than 50K
- lipase >3xULN

Liver Function Test

Liver Function tests (Alkaline Phosphatase, ALT, AST, Total or Direct Bilirubin and GGT) will be summarized separately. Evaluation of drug-induced serious hepatotoxicity (eDISH) with log-log plots of peak post-baseline TB (x ULN) vs. peak post-baseline AST /ALT (x ULN) will be provided by treatment group.

The number and (%) of subjects meeting the following criteria will be summarized by treatment group based on the liver function tests including the following:

- ALT ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin≥2×ULN
- ALT or AST >3xULN and Bilirubin >2xULN

8.5. Other Safety Measures

8.5.1. Vital Signs

Vital sign assessments will be performed at the time points specified in Table 1. Vital sign results will be listed subject, and time point. Vital signs will be summarized using descriptive statistics (n, mean, SD, median, min, and max) over time in terms of absolute values and changes from baseline at each scheduled time point for the safety analysis set.

8.5.2. Inflammatory Markers

Lab tests collected for inflammatory markers and immune responses will be summarized and listed.

9. EFFICACY ANALYSES

9.1. Efficacy Analyses

SARS-CoV-2 RNA

The actual and change from baseline in SARS-CoV-2 RNA (log 10) will be summarized by treatment and visit in tabular and graphic format using descriptive statistics for each specimen type. Individual SARS-CoV-2 RNA over time will be plotted by treatment.

Treatment comparisons between each active dose group and placebo group in SARS-CoV-2 RNA change from baseline will be analyzed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation and an unstructured covariance matrix. This model corrects for dropout and accounts for the fact that measurements taken on the same subject over time tend to be correlated, by using all available information on subjects within the same covariate set to come up with an estimate of the treatment effect for a dropout free population. The statistical model will be fitted with terms for treatment group, visit, treatment by visit interaction, baseline SARS-CoV-2 RNA and baseline SARS-CoV-2 RNA by Visit interaction. The estimated treatment difference for "Active – Placebo" at each visit will be displayed in the summary of statistical analysis together with the 95% confidence interval and the associated p-value. Least Squares Means for each visit will also be presented with the standard error. Least Squares Means and estimated treatment differences for each visit and the associated 95% confidence interval will be displayed graphically.

Sensitivity analyses will be conducted using an Analysis of Covariance (ANCOVA) model with terms for treatment group and baseline SARS-CoV-2 RNA by each study visit. The estimated treatment difference for "Active – Placebo" at each visit will be displayed in the summary of statistical analysis together with the 95% confidence interval and the associated p-value. Least Squares Means for each visit will also be presented with the standard error. If parametric assumptions are violated, non-parametric tests (e.g., extended Mantel-Haenszel test) may be utilized to provide a p-value for sensitivity analysis.

The number and percent of subjects with SARS-CoV-2 RNA of ≤LLOQ, or SARS-CoV-2 RNA reduction of ≥1, 2, or 3 $\log_{10}$ from baseline will be presented for each treatment group by visit. P-values for between-group comparison may be included as descriptive statistics using a 2 sample binomial test.

Time to response un-detectable Viral RNA will be summarized using Kaplan-Meier method. The median time to response and the cumulative probability of response by visit along with the 95% confidence intervals will be provided by treatment group.

The baseline adjusted average area under curve (AAUCMB) through Day 3, Day 5, Day 7, Day 14 and Day 28 will be derived and summarized by treatment group. Between groups comparisons will be performed using an ANCOVA model with terms for treatment group and baseline SARS-CoV-2 RNA. The estimated treatment difference for "Active – Placebo" at each visit will be displayed in the summary of statistical analysis together with the 95% confidence

interval and the associated p-value. Least Squares Means for each visit will also be presented with the standard error.

The number and percent of subjects with negative infectious virus isolation based on qPCR assay will be summarized for each treatment group by visit. P-values for between-group comparison may be included as descriptive statistics using a 2 sample binomial test.

Time to negativity of infectious virus isolation will be summarized using Kaplan-Meier method. The median time to response and the cumulative probability of response by visit along with the 95% confidence intervals will be provided by treatment group.

9.2. RNA Sequencing

Comparison of RNA dependent RNA polymerase gene sequences will be provided using Next Generation sequencing, amino acid mutations and nucleotide changes based on the detection of changes that occur at >=1% will be flagged by subject and visit.
Treatment emergent mutations are defined as mutations that are not present at baseline. The number and percent of subjects with treatment emergent mutation at each amino acid position will be summarized by treatment group. The data will be presented separately based on the detection of changes occurring at >=1%, >=3% or >=10%. The between treatment group comparisons will be performed using a 2 sample test based on the average number of treatment emergent mutations.

Treatment emergent nucleotide changes are defined as nucleotide changes that are not present at baseline. The number and percent of subjects with treatment emergent nucleotide change at each amino acid position will be summarized by treatment group. The data will be presented separately based on the detection of changes occurring at >=1%, >=3% or >=10%. The between treatment group comparisons will be performed using a 2 sample test based on the average number of treatment emergent nucleotide changes.

The results of mutation analysis of SARS-CoV-2 nucleotide sequences compared to the reference SAS-CoV-2 Virus will be summarized by treatment and study visit. The results of mutation analysis of the post baseline vs. the baseline SARS-CoV-2 nucleotide sequences will be summarized by treatment. The data will be presented separately based on the detection of changes occurring at >=1%, >=3% or >=10%.

9.3. Participant Symptom Diary

Patient diary will be listed and individual symptom scores will be summarized by treatment and visit. The worst severity of all individual symptoms will be summarized by treatment and visit.

The following time to response endpoints will be derived and summarized using KM method

- Time to COVID Symptom Resolution (Overall)
- Time to patient reported general physical health of 3 or 4 (Very Good or Excellent)

- Time to patient reported returned to the (Pre-COVID) health
- Time to resolution of upper respiratory tract symptoms
- Time to resolution of common symptoms (based on the 13 or 12 symptoms)
- Time to resolution of cough

If the data warrants, the resolution or duration of individual symptoms may also be derived and summarized.

9.4. Ordinal Scale Clinical Improvement

Ordinal Scale Clinical Improvement data will be listed and summarized as a continuous score by treatment and visit. If the data permits, the time to hospitalization/death will be derived and summarized using KM method.

9.5. COVID Related Medical Visit

The number and percent of subjects with a COVID medical visit will be presented for each treatment group.

The number and percent of subjects hospitalized during the study will also be summarized by treatment group.

9.6. Exploratory Analyses

- 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 is defined as oxygen saturation ≤93%, measured using pulse oximetry. Oxygen requirement will be measured using the World Health Organization (WHO) ordinal scale

The number and percent of subjects meeting the endpoint criteria during the 28 days will be summarized by treatment.

- Comparability between viral RNA non-negativity (i.e., above the limit of quantification) and virus isolation non-negativity from site collected NP swabs

The viral RNA qualitative results (below or above the limit of quantification) determined by RT-PCR and the qualitative results determined (Positive or Negative) by infectious virus detection cell cultures will be presented in a cross tabulation table. Cohen's kappa statistic will be estimated for the assessment of the between assay agreement.

10. CLINICAL PHARMACOLOGY DATA ANALYSES

10.1. Pharmacokinetic Analyses

Sparse blood sampling will be collected on Day 5, at prior to the morning dose, and where possible at approximately 1 and 2 hours after the morning dose. Plasma EIDD-2801/EIDD-1931 concentrations will be determined by validated analytical procedures.

Plasma concentration data will be summarized descriptively by planned time point.

10.2. Pharmacokinetic and Pharmacodynamic Analyses

The response-response relationship between Plasma EIDD-2801/EIDD-1931 trough concentration (pre-dose at day 5) and efficacy endpoint (i.e., change from baseline in SARS-CoV-2 RNA at day 5) will be analyzed using a simple linear model. The paired concentration and efficacy endpoint(s) will be plotted with a fitted regression line superimposed. Additional statistical models will be explored if the data warrant.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Due to lack of availability of subjects in the "early" time from symptom onset stratum, the between group comparison for the time to non-detectable SARS-CoV-2 viral RNA will be performed using an un-stratified log-rank test.

Statistical comparisons of safety endpoints between treatment groups in Part 1 will not be performed. All safety data will be presented descriptively.

11.1. REFERENCES

11.2. DAIDS Adult Toxicity Table

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

12. ATTACHMENTS

12.1. Table of Contents for Data Display Specifications

The TOC will be provided in a separate document.