Enanta Pharmaceuticals, Inc.

EDP 235-101

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effects of EDP 235 in Non-hospitalized Adults with Mild or Moderate COVID-19

09JUN2023

Statistical Analysis Plan

[redacted]

Protocol Version 4.0

DMC Charter Version 1.0

Prepared by:

[redacted]

Approval Signatures

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List of Abbreviations

3CLpro	SARS-CoV-2 3-chymotrypsin–like cysteine protease
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMI	body mass index
BQL	below quantification limit
CI	confidence interval
CM	concomitant medication
COVID-19	coronavirus disease 2019
CV	coefficient of variation
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOFU	end of follow-up
EOS	end-of-study
EOT	end-of-treatment
GM	geometric mean
[redacted]	
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ITT-c	intent-to-treat
IWRS	Interactive Web Response System
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Authorities
NP	nasopharyngeal
PCR	polymerase chain reaction
PE	physical examination
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PKI	pharmacokinetic intensive
PP	per protocol
PRO	patient-reported outcome
QD	once daily
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	safety (for the analysis population)
SAP	statistical analysis plan

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SCR	Screening
SoA	Schedule of Assessments
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TND	target not detected
WHO	World Health Organization

1. Introduction

With millions of confirmed cases and deaths worldwide, COVID-19 continues to represent a significant medical and social burden to the world community. Despite the availability of COVID-19 vaccines, direct acting antiviral agents and monoclonal antibodies for the treatment of COVID-19, there is still a need for highly effective antiviral therapies.

EDP 235 is a highly potent inhibitor of SARS-CoV-2 3CL protease (3CLpro), one of two cysteine proteases that are indispensable for SARS-CoV-2 replication. EDP 235 is a slow -onset, -slow reversible inhibitor of 3CLpro, with an IC_{50} (half-maximal inhibitory concentration) of 5.8 ± 3.7 nM. [redacted] Additional information about EDP 235 is available in the Investigator's Brochure.

This statistical analysis plan (SAP) is based upon Section 11 (Statistical Considerations) of the protocol [redacted] for this Phase 2 clinical study, and is prepared in compliance with International Conference on Harmonization (ICH) E9. Furthermore, this SAP contains definitions for analysis sets, derived variables, and statistical methods and data presentations for the analysis of efficacy and safety endpoints.

1.1. Objectives

1.1.1. Primary Objectives

- To evaluate the safety and tolerability of EDP 235

1.1.2. Secondary Objectives

- To evaluate the effect of EDP 235 on COVID-19 clinical symptoms and outcomes
- To evaluate the effect of EDP 235 on SARS-CoV-2 viral load
- To evaluate the pharmacokinetics of EDP 235

[redacted]

2. Investigational Plan

2.1. Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, parallel group, multi-site study in non-hospitalized adult subjects who test positive for SARS-CoV-2 and have COVID-19 symptom onset within 5 days of randomization and who are not at high risk for progression to severe COVID-19. Subjects can be vaccinated or unvaccinated for COVID-19. Subjects with prior COVID-19 infection <90 days before enrollment and/or who received a COVID-19 vaccine dose <90 days before enrollment are excluded from trial participation.

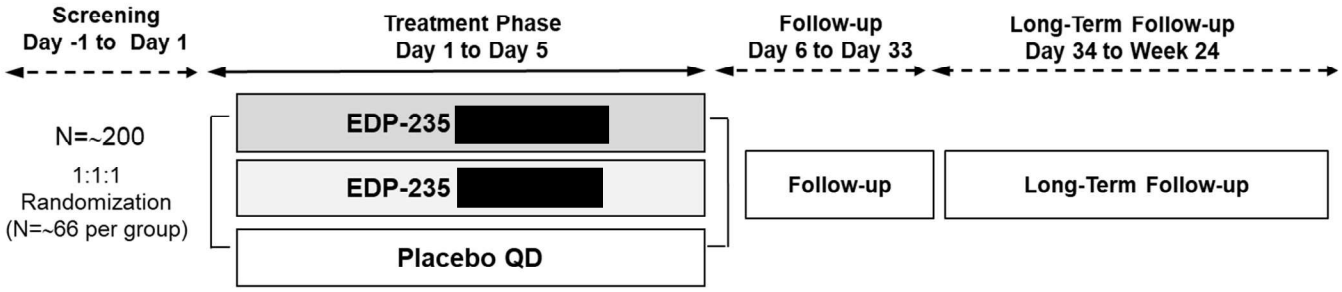
Subjects will be randomized in a 1:1:1 ratio to receive either EDP 235 [redacted], EDP 235 [redacted], or placebo orally once daily for 5 days. Randomization will be stratified by age (≤50 years or 51 to 64 years) and by the duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days).

The study includes 4 periods:

- Screening period will occur from Day -1 to Day 1. Screening should be completed as soon as possible, and the subject will be randomized within 24 hours of signing the ICF. A subject will be considered enrolled at the time of randomization.
- Treatment period will begin with the first dose of study treatment on Day 1 and will conclude with the end-of-treatment (EOT) visit on Day 5.
- Follow-up period will begin following the last dose of study treatment and will conclude at the end of follow-up (EOFU) visit on Day 33 (28 days after the last dose of study treatment).
- Long-term follow-up period (LTFU) will begin at Day 34 and concludes at the end-of-study (EOS) visit at Week 24.

An overview of the study design is shown in **Figure 1**. Study site visits and assessments are detailed in the Schedule of Study Procedures (Appendix 14.1).

Figure 1: Study Design

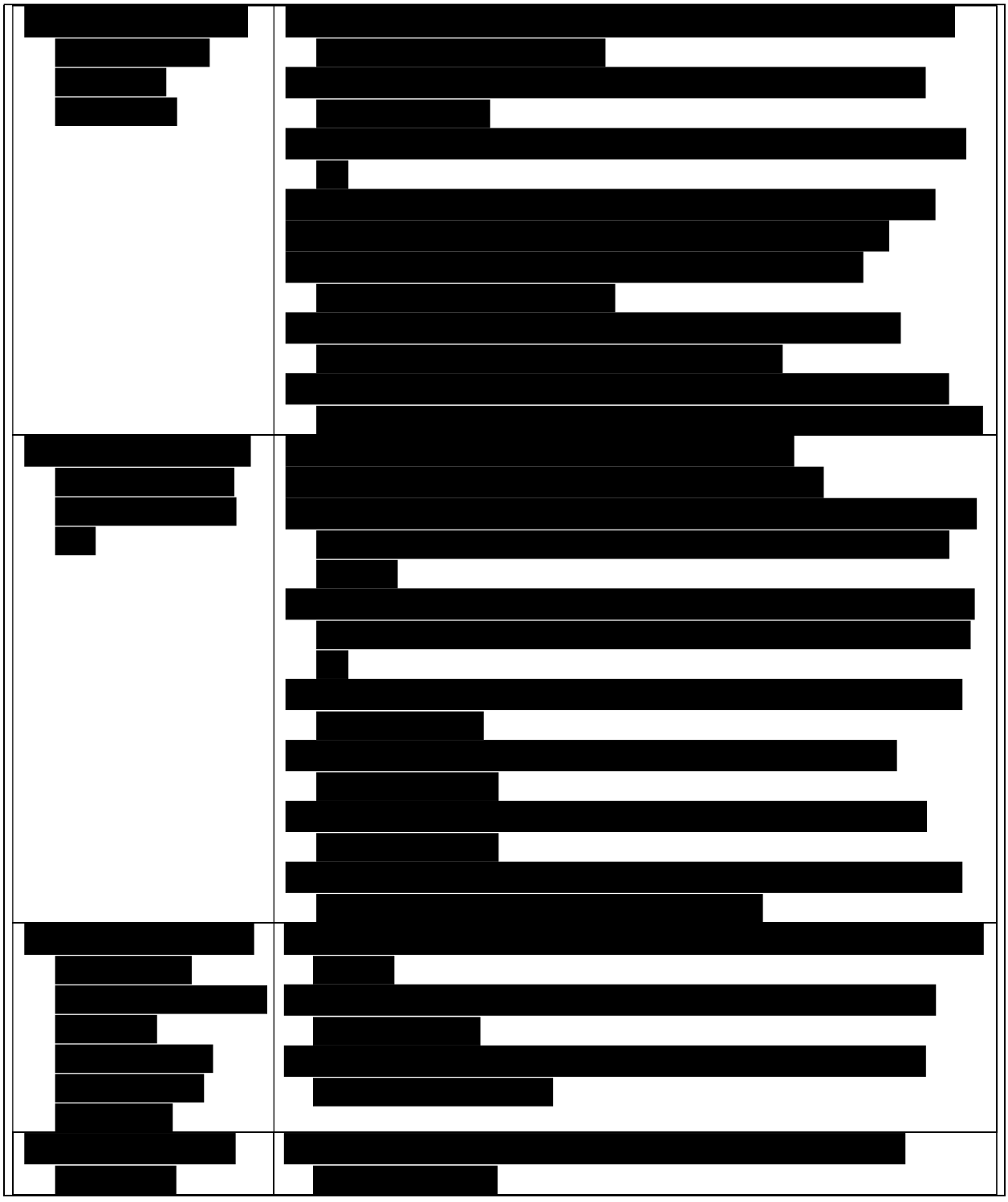


2.2. Study Endpoints

The study's primary, secondary, and exploratory objectives and their associated endpoints are displayed in **Table 1**.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the safety and tolerability of EDP 235	**Primary Endpoint** • Safety and tolerability of EDP 235 compared to placebo as assessed by, but not limited to, adverse events (AEs), clinical laboratory results, and vital signs through Day 33
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of EDP 235 on COVID-19 clinical symptoms and outcomes	• Time to improvement of targeted COVID-19 signs/symptoms using the COVID-19 Symptom Diary through Day 33 • Proportion of subjects with targeted COVID-19 signs/symptom improvement using the COVID-19 Symptom Diary through Day 33 • Change from baseline in targeted COVID-19 signs/symptom score using the COVID-19 Symptom Diary through Day 33 • Proportion of subjects with medically attended visits for COVID-19 through Day 33 • Proportion of subjects requiring hospitalization (defined as ≥24 hours of acute care) for COVID-19 through Day 33 • Proportion of subjects who require hospitalization and mechanical ventilation (invasive and non-invasive) through Day 33 • Proportion of subjects with any of the following COVID-19 related events or all-cause mortality through Day 33 o complications based on the investigator's assessment o medically attended visits o hospitalizations o intensive care unit (ICU) admissions o requirement for supplemental oxygen or increased in supplemental oxygen requirement o requirement for mechanical ventilation (invasive and non-invasive)
• To evaluate the effect of EDP 235 on SARS-CoV-2 viral load	• Change from baseline in SARS-CoV-2 RNA viral load through Day 33 • Change from baseline in infectious SARS-CoV-2 viral load through Day 33 • AUC of SARS-CoV-2 RNA viral load through Day 33 • Proportion of subjects with SARS-CoV-2 RNA viral load target not detected (TND) over time through Day 33 • Time to SARS-CoV-2 RNA TND through Day 33
• To evaluate the pharmacokinetics of EDP 235	• Plasma concentrations of EDP 235
[redacted]	[redacted]



2.3. Treatments

EDP 235 is a highly potent inhibitor of SARS-CoV-2 3CL protease (3CLpro), one of two cysteine proteases that are indispensable for SARS-CoV-2 replication. EDP 235 is a slow -onset, -slow reversible inhibitor of 3CLpro, with an IC_{50} (half-maximal inhibitory

concentration) of 5.8 ± 3.7 nM. Oral EDP 235 treatment in repeat dose, general nonclinical toxicity studies at up to 14 days of once-daily dosing across species was well-tolerated.

The EDP 235 doses selected for this study are [redacted] once daily (QD), administered with food, orally for 5 days. These doses were selected based on all relevant available nonclinical and clinical data, including repeat-dose toxicology studies, in vitro pharmacology studies with EDP 235, and clinical safety and PK data from the first-in-human phase 1 study (EDP 235-001). The selected doses are expected to provide exposures in the anticipated therapeutic range.

Following randomization on Day 1, subjects will receive the first dose of EDP 235 or placebo orally while at the study site. After the first dose, subjects will be instructed to take or be administered the study treatment orally on each of the 5 subsequent days, at approximately the same time every day (±1 hour). Study treatment will be administered with food. The total dose administered once daily will be either:

- EDP 235 [redacted] orally QD
- EDP 235 [redacted] orally QD
- Placebo, orally QD

2.4. Dose Adjustment/Modifications

Dose modifications are not permitted for subjects in this study.

3. General Statistical Considerations

Continuous variables will be summarized using n, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum values. The precision for continuous variables will be based on the precision of the data itself. The mean, median, 25th percentile, and 75th percentile will be presented to one more significant figure than the original results; the SD will be presented to two more significant figures than the original results; the minimum and maximum will be presented to the same level of precision as the original results.

Categorical variables will be summarized using frequency counts and percentages. Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

When **count data** are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations as needed to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in the treatment group within the analysis set of interest, unless otherwise specified.

Baseline, unless otherwise specified, will be defined as the last non-missing measurement collected prior to dosing on the same date as the first dose of study treatment; if it is not available, the first measurement up to 2 hours post first dose of study treatment will be used. For

subjects who are randomized, but not treated, the baseline will be defined as the last non-missing measurement on or before the date of randomization. For height, weight and body mass index baseline will be defined as the last non-missing measurement collected on or before the date of the first dose of study treatment (without consideration of time). .

Study Day 1 is the calendar day that the first dose of the study treatment is administered. Subsequent study days are calculated as the date of assessment/event – date of the first dose + 1. If a subject is not treated, the date of randomization is used to define study day rather than the date of first dose. For assessments or events that occur before the first dose date, study day is calculated as the date of interest minus the first dose date.

Unscheduled visits measurements will be included in the analysis as follows:

- Derivation of baseline and worst post-baseline measurements.
- Individual subject data listings as appropriate.

Unscheduled visits will not be included in the by-visit summary or analyses.

No additional analysis visit windowing will be done other than what is specified for Baseline and worst post-baseline above.

When there are multiple values within an analysis visit for laboratory assessments,, the worst value (and the latest value if applicable) will be used in the analysis. For graded labs, worst is defined as the highest grade and if there is more than one record of the same grade for a given analysis visit, the latest value will be selected for analysis. For non-graded labs, worst is defined as the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold. If a subject has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen.

For all other assessments, if there are multiple values within an analysis visit the latest record will be selected for analysis.

All diary data will be summarized based on the actual day.

Time-to-event variables are defined from the date of first dose.

3.1. Incomplete and Missing Data

Imputation rules for missing dates of prior/concomitant medications, including COVID-19 vaccinations and prohibited medications, and procedures are provided in Appendix 14.5.

Imputation rules for missing AE data are provided in Appendix 14.5.

Data that are continuous in nature but are reported in the form $<x$, $>x$, $\leq x$, *or* $\geq x$ (where x is considered as the limit of quantitation) will be set to limit of quantitation value with the following exceptions:

- Efficacy endpoint data will be imputed as detailed in Appendix 14.5.
- PK concentrations data will be imputed as detailed in Appendix 14.5.

- Other incomplete/missing data will not be imputed, unless specified otherwise.

All analyses will be conducted using SAS Version 9.4 or higher. Unless otherwise stated, a two-sided test will be used at a significance level (alpha) of 0.05 for all analyses. Two-sided 95% confidence intervals (CI) will be provided when appropriate.

Summary Tables and Figures will be presented by treatment group and will be labelled as follows:

- "EDP 235 [redacted]"
- "EDP 235 [redacted]"
- "Placebo"

All subject data will be presented in individual subject data listings. Dates will be shown in subject listings as they have been recorded. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by subject number, date/time and visit. The treatment group (randomized) as well as subject's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects randomized.

When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no records for this table/listing."). For analyses where convergence or the analysis cannot be performed, "NC" (not calculable) will be presented in summary tables.

For the reporting of this study both CDISC SDTM (SDTM Implementation Guide version 3.3 or later) and ADaM (ADaM Implementation Guide version 1.3 or later) standards will be applied.

[redacted]

3.3. Randomization, Stratification, and Blinding

Subjects who have completed screening assessments and are eligible for participation in the study will be randomized to blinded treatment before the first dose of study treatment (Day 1) in a 1:1:1 ratio to receive either EDP 235 [redacted], EDP 235 [redacted], or placebo orally once daily for 5 days. Randomization will be stratified by age (≤50 years or 51 to 64 years) and the duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days).

The study will be double-blinded, meaning that the subjects, investigators, and site staff will be blinded to treatment assignment until the completion of the study. During the study, investigators, site personnel, and blinded contract research organization/Sponsor staff will not have access to results for individual subjects that could impact clinician assessments, including results for SARS-CoV-2 viral load, respiratory pathogen panel testing, certain biomarkers, and PK.

The unblinding method will use the IWRS process which will allow the investigator to have immediate access to the unblinding system. Unblinding of individual subject treatment by the investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In situations where the urgency of the case requires immediate action, investigators should use their best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding. In emergency situations, the decision to unblind resides solely with the investigator.

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the [redacted] Medical Monitor should be notified within 24 hours of unblinding of the treatment and should inform the Sponsor's Medical Monitor.

3.4. Analysis Populations

3.4.1 Randomized Population

The Randomized Population includes all subjects who are randomized.

3.4.2. Safety (SAF)

The Safety Population includes all subjects in the Randomized Population who receive at least one dose of the study treatment. Subjects will be analyzed in the treatment group that corresponds to the study treatment received during the study.

3.4.3. Intent-to-Treat-c (ITT-c)

The Intent-to-Treat (ITT-c) Population includes all subjects in the SAF Population with their SARS-CoV-2 status confirmed by central RT-PCR viral load at baseline ≥ lower limit of quantification (LLOQ) and with at least one post-baseline primary efficacy measurement. Subjects will be analyzed as randomized.

The reasons for exclusion from the ITT-c population will be summarized by treatment group using the Safety population.

3.4.4. Per Protocol (PP)

The Per Protocol (PP) Population includes all subjects in the ITT-c Population who do not have any protocol deviations that may unduly influence the primary efficacy outcomes as assessed by the sponsor prior to unblinding (Section 4.2) and do not meet any of the criteria shown below.

1. Compliance rate <80% (Section 6.4.1. Extent of Treatment Exposure and Compliance)
2. Do not complete Day 33 Visit (discontinuation from study prior to Day 33 or incomplete follow-up at the time of analysis)

The reasons for exclusion from the PP Population will be summarized by treatment group and listed using the ITT-c Population.

Subjects will be analyzed in the treatment group that corresponds to the study treatment received during the study.

3.4.5. Pharmacokinetic (PK) Population

The Pharmacokinetic (PK) Population includes all subjects in the Safety Population receiving active study treatment and having at least one measurable plasma concentration of study treatment at any timepoint.

3.4.6. Intensive Pharmacokinetic (IPK) Subset Population

The Intensive PK Subset Population includes subjects in the PK population participating in the intensive PK sampling.

3.4.7. Safety Long-Term Follow-Up (SAF LTFU) Population

The Safety Long-Term Follow-Up Population includes all subjects in the Randomized Population who receive at least one dose of the study treatment and consented to be a part of the long-term follow-up. Subjects will be analyzed in the treatment group that corresponds to the study treatment received during the study.

3.4.8. Intent-to-Treat-c Long-Term Follow-Up (ITT-c LTFU) Population

The Intent-to-Treat Long-Term Follow-Up Population includes all subjects in the SAF LTFU who have met the ITT-c criteria and have any Week 12 or Week 24 assessment completed.

4. Subject Disposition

4.1. Disposition

A subject will be considered to have completed the study after his/her attendance at the last planned study visit (Day 33 ± 1 day), or the last unscheduled visit (if any occur), as applicable. For each subject his or her study completion status (Yes/No) is recorded on the End of Study CRF.

The number of subjects randomized and in the SAF, ITT-c, PP, PK and IPK populations will be summarized using frequencies and percentages. All percentages will be based on the number of subjects randomized.

Subject disposition will be summarized by treatment group and overall, for all subjects who are randomized. A disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were randomized, subjects who completed study treatment per protocol, subjects who discontinued study treatment early, subjects who completed the study, subjects who discontinued from the study early. All percentages will be based on the number of subjects randomized. The reasons for discontinuation of study treatment and study participation will also be summarized in this table.

The reason for discontinuation of study treatment or study participation may include any of the following:

- Adverse event
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by subject
- Physician decision
- Death
- Other reason

Subject disposition data will also be presented in listings, including a listing by analysis population.

Screen failures were not included in the study database and will not be included in any SDTM or ADaM datasets. If required, a listing of screen failures from all screened subjects, including the inclusion or exclusion criteria that were not met, may be provided from vendor IRT data.

A separate listing of subjects that were randomized, treated and then found to meet exclusion or fail to meet inclusion criteria will be provided including the inclusion or exclusion criteria.

4.2. Protocol Deviations

All protocol deviations (both significant and non-significant) will be entered and tracked in [redacted] Clinical Trial Management System (CTMS) by the study team throughout the conduct of the study in accordance with [redacted] Study Deviation Rules Document. A significant deviation is any deviation that may affect primary efficacy analyses, safety assessments, the safety or mental integrity of a subject, or the scientific value of the trial.

Data will be reviewed by the study team prior to unblinding and closure of the database to ensure all significant deviations and those leading to exclusion from analysis are captured and properly categorized. Particularly, deviations leading to exclusion from the PP population will also be determined by the study team and flagged in the final CTMS Deviation Data file.

Significant protocol deviations will be summarized by treatment group and overall. Separate listings will be provided for significant and non-significant protocol deviations. Summaries will be conducted on the randomized population.

5. Demographics and Baseline Characteristics

5.1. Demographics and Baseline Clinical Characteristics

A summary of demographics and baseline information will be presented by treatment group and overall, for all subjects in the SAF, ITT-c and PP populations.

For the SAF LTFU and ITT-c LTFU, a summary will be presented by treatment group and separately for reinfection status at Week 12 and Week 24 [positive, negative, and overall (including missing)] Section 8.3.21 and 8.3.21.

Demographics and baseline clinical characteristics include:

- Age
- Sex
- Race (if available)
- Ethnicity (if available)
- Childbearing potential (for female subjects only)
- Post-menopausal (for female subjects only)
- Duration of COVID-19 symptoms
- Cigarette Smoking history
- COVID-19 vaccine history
- Weight (kilograms)
- Height (centimeters)
- Body mass index (calculated as (body weight in kilograms) / (height in centimeters / 100)^2).

Subject demographic and baseline clinical characteristics will also be presented in a listing for all subjects in the SAF, ITT-c and PP population.

5.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or higher. The number and percentage of subjects with any relevant medical history will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of subjects in the SAF population.

Subject medical history data including specific details, will also be presented in a listing.

5.3. Baseline Disease Characteristics

The following baseline disease characteristics will be presented by treatment group and overall and stratified by age group and duration of baseline COVID-19 symptoms (≤3 days or >3 days and ≤5 days) for all subjects in the SAF, ITT-c and PP populations. Additionally, baseline disease characteristics will be listed for all subjects in the SAF population.

- SARS-CoV-2 RNA viral load
- Infectious SARS-CoV-2 viral load
- SARS-CoV-2 RNAemia
- SARS-CoV-2 serostatus
- Respiratory pathogen test
- SARS-CoV-2 variant
- COVID-19 symptom diary total score

- COVID-19 symptom diary severity

SARS-CoV-2 RNA viral load, Infectious SARS-CoV-2 viral load and SARS-CoV-2 RNAemia will also be summarized as positive, negative and missing where either a numeric or "POS" result is considered positive and TND is considered negative.

Baseline SARS-CoV-2 serostatus will be based on Day 1 SARS-CoV-2 anti-nucleocapsid and anti-spike IgG, and IgM antibodies. If at least one qualitative result is positive or IgM > 1.0, the serostatus will be considered positive. In order to be considered negative, all four results must be non-missing, all qualitative results must be negative and IgM equal to "<1.0".

A description of how symptoms are scored from the COVID-19 Symptom Diary is in Appendix 14.2. The total symptom score and the following severity categories will be presented:

- Only mild symptoms at Day 1
- 1 moderate and no severe symptoms
- 2 or more moderate symptoms and no severe symptoms
- 1 or more severe symptom(s) and no moderate symptoms
- 1 or more severe symptom(s) and 1 or more moderate symptom(s)

6. Treatments and Medications

6.1. Prior and Concomitant Medications

Any medication or therapy taken within one month of signing the ICF and during the study throughout the end of the study will be collected on the CRF. All medications will be coded using the World Health Organization Anatomical Therapeutic Chemical (ATC) Level 2 Classification and World Health Organization preferred term from the WHO Global Drug Dictionary version September 2022 B3 or later.

Prior medications are defined as those medications with a start date prior to the date of first dose of study treatment. Concomitant medications are defined as any medications with a start date on or after the date of first dose of study treatment or any medications with a start date prior to the date of first dose and a stop date after the date of first dose. Furthermore, a medication could be labeled as both a prior and concomitant medication if it was started prior to the first dose of study treatment and continued after the first dose of study treatment.

The number and percentages of subjects with at least one prior medication will be summarized by treatment group and overall. The number and percentages of all prior medications will be summarized by treatment group and overall and listed by Anatomical Therapeutic Chemical (ATC) level 2 and preferred term. All summaries will be performed using the SAF population.

The number and percentages of subjects with at least one concomitant medication will be summarized by treatment group and overall. The number and percentages of all concomitant medications will be summarized by treatment group and overall and listed by Anatomical Therapeutic Chemical (ATC) level 2 and preferred term. All summaries will be performed using

the SAF population. Additionally, prior and concomitant medications will be summarized for the long-term follow-up period using the Safety Long-Term Follow-Up population.

Prior and concomitant medications, including prohibited medication, will also be presented in a listing. Details for imputing missing or partial start and/or stop dates of medications are described in Appendix 14.5.

6.2. COVID-19 Vaccination History

COVID-19 vaccination history includes whether a subject has been vaccinated, the type of vaccination, and the date and dose of the vaccination. COVID-19 vaccination history will be summarized overall and by treatment group in a table and presented in a listing.

6.3. Prior and Concomitant Therapies

Prior and concomitant therapies include surgical interventions, procedures, COVID-19 related oxygen supplementation, or other non-medication treatments. All reported therapies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or higher and classified by system organ class (SOC) and preferred term (PT).

Prior therapies are defined as those therapies with a start date prior to the date of first dose of study treatment. Concomitant therapies are defined as any therapies with a start date on or after the date of first dose of study treatment or any therapies with a start date prior to the date of first dose and a stop date after the date of first dose. Furthermore, a therapy could be labeled as both a prior and concomitant therapy if it was started prior to the first dose of study treatment and continued after the first dose of study treatment.

Concomitant therapies will be summarized by treatment group and overall based on the reported categories, as appliable, and by SOC and PT. Both prior and concomitant therapies will be presented in one listing. Additionally, prior and concomitant therapies will be summarized for the long-term follow-up period using the Safety Long-Term Follow-Up population. Additional details for supplemental oxygen use will be presented in a separate listing. Details for imputing missing or partial start and/or stop dates of medications are described in Appendix 14.5.

6.4. Study Treatments

6.4.1. Extent of Treatment Exposure and Compliance

Duration of study treatment in days will be calculated as: last dose date – first dose date + 1 day, regardless of study treatment interruption (i.e., missed dose). Study treatment exposure (total study treatment administered in mg) will be summarized by treatment group and overall using the safety population.

The study treatment compliance will be calculated as: 100 * (total number of days compliant / number of days of treatment planned per protocol), where a day of compliance is defined as taking one capsule per bottle on consecutive days for Days 1 to 5.

Study treatment compliance will be summarized for all subjects in the SAF population with descriptive statistics by treatment group and overall. Additionally, the number and percentages of subjects who completed treatment per protocol and in each compliance category (<80%, ≥80% to ≤100%) will be also presented by treatment group and overall.

A summary of each subject's exposure and compliance will also be presented in a listing.

7. Safety Analysis

The primary objective of the study is to evaluate the safety and tolerability of EDP 235 compared to placebo as assessed by, but not limited to, adverse events, clinical laboratory results, and vital signs. All safety analyses will be conducted on the safety population. Safety data, including treatment emergent adverse events (TEAEs), serious adverse events (SAEs), vital sign measurements, and laboratory values, will be summarized separately by treatment group.

7.1. Adverse Events

Adverse events will be summarized by the MedDRA version 25.0 or higher using SOC and PT by treatment group and all summary table percentages will be calculated out of the number of subjects in the Safety population. All events of SARS-CoV-2 reinfection will be considered adverse events. Additionally, adverse events will be summarized for the long-term follow-up period using the Safety Long-Term Follow-Up population and will not include any treatment discontinuation summaries.

All AEs will be presented in a data listing.

7.1.1. Treatment-Emergent Adverse Events

AEs that occur or worsen on or after the date and time of first dose of study treatment through Day 33 are considered Treatment-Emergent Adverse Events (TEAEs) and will be used for safety analyses.

7.1.2. Incidence of Adverse Events

An overview of TEAEs will be presented overall and by treatment, including the number and percentage of subjects with any:

- TEAEs
- Related TEAEs
- Grade 3 or higher TEAEs
- Maximum severity TEAE (Mild, Moderate, Severe, Life-Threatening, Death)
- TEAEs leading to study treatment discontinuation
- TEAE's leading to study discontinuation
- TEAEs leading to death
- Treatment emergent SAEs
- Related treatment emergent SAEs

All TEAEs will also be presented in a summary table by SOC and PT through end of study participation. A subject may have more than 1 TEAE for an SOC or PT. A subject with 2 or more TEAEs within the same level of summarization will be counted only once in that level. The summary of TEAEs will be presented in descending order from the SOC with the highest total incidence to the SOC to the lowest total incidence. If the total incidence for any 2 or more SOCs are equal, the SOCs will be presented in alphabetical order. The PTs within each SOC will be presented in alphabetical order.

7.1.3. Relationship of Adverse Events to Study Treatment

A summary of TEAEs by relationship to study treatment will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study treatment. The possible relationships are Not Related, Unlikely, Possibly, and Related. In the TEAE relationship table, if a subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. Not Related and Unlikely Related are considered to be unrelated to the study treatment while Possibly and Related are considered to be related to the study treatment.

All TEAEs will be presented in a summary table for each treatment group and total by SOC, PT, and relationship to study treatment. If a subject has 2 or more TEAEs in the same SOC (or with the same PT) with a different relationship to study treatment, then the subject will be counted under Related. If the relationship information is missing, the TEAE will be considered related in the summary but will be presented as missing in the data listings.

7.1.4. Severity of Adverse Event

Adverse events will be evaluated and documented using the National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 dated July 2017:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. TEAEs that are missing severity will be presented in tables as severe but all TEAEs will be presented in the data listing with a non-imputed severity.

7.1.5. Serious Adverse Events

All treatment-emergent SAEs will be presented in a summary table by treatment group and total by SOC and PT. Treatment-emergent SAEs will also be presented by relationship to the study treatment, SOC and PT for each treatment group and total. All treatment-emergent SAEs will be presented in a listing. Additionally, serious adverse events will be summarized for the long-term follow-up period using the Safety Long-Term Follow-Up population and will not include any treatment discontinuation summaries.

7.1.6. Adverse Events Leading to Treatment Discontinuation

All TEAEs leading to treatment discontinuation will be presented in a table by SOC and PT and in a data listing.

7.1.7. Adverse Events Leading to Study Discontinuation

All TEAEs leading to study discontinuation will be presented in a table by SOC and PT and a data listing.

7.1.8. Proportion of Subjects with Adverse Events through Week 24

The proportion of subjects with adverse events through Week 24 will be summarized for each treatment group and will be analyzed using the same CMH methods as described in Section 8.

7.1.9. Proportion of Subjects with Serious Adverse Events through Week 24

The proportion of subjects with serious adverse events through Week 24 will be summarized for each treatment group and will be analyzed using the same CMH methods as described in Section 8.

7.2. Clinical Laboratory Evaluations

Central laboratory values will be used for analysis and results will be graded using the National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 dated July 2017.

Laboratory values and change from baseline will be summarized overall and by treatment group for scheduled visits. Shift tables by scheduled visit and worst post-baseline will also be generated by reference range and grade as follows :

Additionally, results will be summarized according to any value greater than the high limit, 2x upper limit of normal (ULN) or 3x ULN and any value less than the lower limit, 2x lower limit of normal (LLN) or 3x LLN (i.e 1/2 of LLN or 1/3 of LLN).

All laboratory data will be included in the data listings. Test values greater than the high limit, 2x ULN, 3x ULN, less than the lower limit, 2x LLN and 3x LLN.

7.2.1. Pregnancy Tests and Follicle-Stimulating Hormone Test

For female subjects only, all pregnancy and follicle-stimulating hormone test results will be presented in a listing.

7.3. Vital Sign Measurements

Vital sign observed, change from baseline and pulse oximetry measurements will be summarized by treatment by visits.

7.4. Electrocardiogram

All Electrocardiogram (ECG) results will be summarized by treatment group and visit in the Safety population and a listing will be presented of all results with abnormalities flagged.

8. Efficacy Analysis

Unless otherwise specified, efficacy analyses will be performed using ITT-c population and the following methods will be implemented:

For time to event endpoints time and date will be used and 24 hours will be considered as a day. Descriptive statistics using the Kaplan-Meier method will include the median, 25th and 75th percentile, and 95% CIs (log-negative-log transformation). Additionally, the cumulative event rate (SE) will be summarized by treatment group and presented graphically over time. For between group comparisons, Cox Proportional Hazards models (tie handling will be addressed first using the exact method then with Efron's method if the exact method does not converge) will include treatment group, randomization stratification factors of age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤ 3 days or >3 days and ≤5 days), and the baseline value of the endpoint. The hazard ratios with associated 95% CIs (Wald) and p-values (analysis of maximum likelihood estimates) comparing EDP 235 [redacted] versus Placebo, and EDP 235 [redacted] versus Placebo will be reported. Model assumptions will be checked via a log-negative-log plot and/or Schoenfeld residuals as appropriate. Subjects who do not achieve the specified endpoint will be censored with time imputed as treatment start time as follows:

<u>COVID-19 diary:</u>

- Subjects who have not been followed through the Day 33 visit (discontinuation from study or incomplete follow-up at the time of analysis) or completed Day 33 diary will be censored at Day 33.

<u>Other time to event endpoints:</u>

- Subjects who discontinued from the study will be censored at Day 33.
- Subjects who have completed the Day 33 visit will be censored at Day 33 Visit Date.

For treatment comparisons of change from baseline endpoints, analysis of covariance (ANCOVA) models will include treatment group, randomization stratification factors of age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤ 3 days or >3 days and ≤5 days) and baseline value of the endpoint as the covariate. The least-squares means, SE, and 95% CIs will be presented for individual groups and the difference between groups. The p-value for

the difference between groups will also be presented. In addition, a two-sample t-test will be used to compare change from baseline between treatment without covariate adjustment (unadjusted mean difference). The p-value for the difference between groups will also be presented under the pooled test (equal variances assumption). Line graphs for both the adjusted and unadjusted means with corresponding 95% CIs will also be generated for secondary efficacy endpoints.

Proportional endpoints will be summarized by treatment group. A 2x2x2x2x2 Cochran-Mantel-Haenszel (CMH) test will be used to test the association treatment group (EDP 235 [redacted] versus Placebo) and the endpoint analyzed while taking into account randomization stratification factors of age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤ 3 days or >3 days and ≤5 days). In addition to the p-value, the risk differences and associated 95% CIs will be reported (using the cmh commonriskdiff (test=mh) option in SAS PROC FREQ). A similar 2x2x2x2x2 Cochran-Mantel-Haenszel (CMH) test will be used for EDP 235 [redacted] versus Placebo. There is no planned multiplicity control for the analysis of efficacy endpoints.

In addition to the summaries noted above, all data will be presented in listings. If the two EDP 235 treatment groups exhibit similar efficacy, a comparison may be done between the combined EDP 235 treatment groups and placebo.

8.1. Primary Efficacy Endpoints

The primary efficacy endpoints are as follows:

- Time to improvement of targeted COVID-19 signs/symptoms using the COVID-19 Symptom Diary through Day 33
- Time to SARS-CoV-2 RNA Viral Load TND Assessed by RT-qPCR

8.1.1. Primary Analyses

8.1.1.1. Time to Improvement of Targeted COVID-19 Signs/Symptoms using the COVID-19 Symptom Diary through Day 33

Improvement of targeted COVID-19 signs/symptoms is defined by the following the event occurring on the first of 2 consecutive days or on Day 33 when the following criteria are met:

- All symptoms scored as mild, moderate or severe at baseline are scored as mild or absent
- All symptoms scored as absent at baseline are scored as absent

Time to improvement of targeted COVID-19 signs/symptoms through Day 33 will be summarized graphically using Kaplan-Meier plots and analyzed by the Cox proportional hazard model as described in Section 8.

8.1.1.2. Time to SARS-CoV-2 RNA Viral Load TND Assessed by RT-qPCR through Day 33

Time to SARS-CoV-2 RNA to TND is defined as the time between the date of the first dose to the first date of achieving viral load TND.

Time to SARS-CoV-2 RNA TND will be analyzed as described in Section 8.

8.1.2. Sensitivity Analyses

The primary analyses above will be conducted on the PP population as a sensitivity analyses.

8.1.3. Subgroup Analyses

Subgroup analyses for the primary efficacy endpoints may be considered for the following baseline variables, if there are enough subjects in the subgroups to support the planned analyses:

- Sex (female vs male)
- Age (≤50 years of age vs 51 to 64 years of age)
- SARS-CoV-2 Vaccination Status (not vaccinated vs vaccinated)
- Duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days)

The analysis for the selected primary efficacy endpoints will be analyzed as described in Section 8 with the addition of a subgroup-by-treatment interaction included in the model and only the p-value of the interaction term will be reported.

8.2. Secondary Efficacy Endpoints

8.2.1. Proportion of Subjects with Targeted COVID-19 Signs/Symptom Improvement using the COVID-19 Symptom Diary through Day 33

The proportion of subjects demonstrating targeted COVID-19 signs/symptoms improvement through Day 33 will be summarized overall and by treatment group and CMH methods applied as described in Section 8.

8.2.2. Change from Baseline in Targeted COVID-19 Signs/Symptom Total Score using the COVID-19 Symptom Diary through Day 33

Change from baseline in targeted COVID-19 signs/symptoms will be summarized for the total mean score and analyzed using the methods described in Section 8.

Additionally, the 14 individual symptom scores will be summarized descriptively by study visit for each treatment group.

8.2.3. Proportion of Subjects with Medically Attended Visits for COVID-19 Through Day 33

The proportion of subjects with medically attended visits for COVID-19 through Day 33 will be summarized by treatment group and will be analyzed using the same CMH methods as described in Section 8.

8.2.4. Proportion of Subjects Requiring Hospitalization (Defined as ≥24 Hours of Acute Care) for COVID-19 Through Day 33

The proportion of subjects requiring hospitalization for COVID-19 through Day 33 will be summarized by treatment group by treatment group and will be analyzed using the same CMH methods as described in Section 8.

8.2.5. Proportion of Subjects who Require Hospitalization and Mechanical Ventilation (Invasive and Non-Invasive) Through Day 33

The proportion of subjects who require hospitalization and mechanical ventilation through Day 33 will be summarized by treatment group and will be analyzed using the same CMH methods as described in Section 8.

8.2.6. Proportion of Subjects with COVID-19 Related Events or All-Cause Mortality Through Day 33

COVID-19 related events include complications based on the investigator's assessment, medically attended visits, hospitalizations, intensive care unit (ICU) admissions, requirement for supplemental oxygen or increased in supplemental oxygen requirement, requirement for mechanical ventilation (invasive and non-invasive) or all-cause mortality. The proportion of subjects with COVID-19 related events or all-cause mortality through Day 33 will be summarized by treatment group and will be analyzed using the same CMH methods as described in Section 8.

8.2.7. Change from Baseline in SARS-CoV-2 RNA Viral Load Assessed by RT-qPCR Through Day 33

The antiviral activity of EDP 235 on viral kinetics will be measured using SARS-CoV-2 RNA viral load assessed by RT-qPCR of NP swab samples on Days 1, 3, 5, 9, 14, and 33. Change from baseline values for SARS-CoV-2 RNA viral load will be summarized using the methods described in Section 8.

8.2.8. Change from Baseline in Infectious SARS-CoV-2 Viral Load Assessed by Cell Culture Infectivity Assay Through Day 33

The infectious SARS-CoV-2 viral load will be measured using a SARS-CoV-2 cell culture infectivity assay of NP swab samples on Days 1, 3, 5, 9, 14 and 33. Change from baseline values for infectious SARS-CoV-2 viral load will be summarized using the methods described in Section 8.

8.2.9. AUC of SARS-CoV-2 RNA Viral Load Assessed by RT-qPCR Through Day 33

The area under the curves (AUC) from Day 1 through Day 33 will be calculated for SARS-CoV-2 viral load data using actual sampling times via non-compartmental analysis using Phoenix® WinNonlin® Version 8.3.4 or higher according to the linear trapezoidal with linear interpolation

method. AUCs will be derived for Days 1-5, Days 1-14, and Days 1-33. Additionally, the AUC from Day 1 through Day 5, the AUC from Day 1 through Day 14, and the AUC from Day 1 through Day 33 will be standardized for 5, 14 and 33 days by multiplying 5, 14, $33/t_{last}$ where t_{last} is the actual time in days of the last available assessment. No AUC will be calculated if there are less than 3 results available.

The observed value from Day 1 predose sample will be used as baseline assessment for SARS-CoV-2 viral load. For the baseline viral load (Day 1), time is set as 0. For each assessment post first dose, the actual time in days is computed as difference between the date/time of the assessment and the date/time of the first dose.

The 3 standardized AUCs from Day 1 through Day 5, Day 1 through Day 14, and Day 1 through Day 33 will be compared an analysis of covariance (ANCOVA) model using the methods described in Section 8. In addition, a two-sample t-test will be used to compare viral load standardized AUCs between treatment groups without covariate adjustment (unadjusted mean difference).

8.2.10. Proportion of Subjects with SARS-CoV-2 RNA Viral Load TND Assessed by RT-qPCR Over Time Through Day 33

The proportion of subjects with SARS-CoV-2 RNA viral load TND will be summarized by visit and through Day 33 for each treatment group and will be analyzed using the same CMH methods as described in Section 8.

[redacted]

8.3.4. AUC of SARS-CoV-2 RNAemia Viral Load Through Day 33

The area under the curve (AUC) from Day 1 through Day 33 will be calculated for SARS-CoV-2 RNAemia viral load data using actual sampling times via non-compartmental analysis using Phoenix® WinNonlin® Version 8.3.4 or higher according to the linear trapezoidal with linear interpolation. AUCs will be derived for Days 1-14 and Days 1-33. Additionally, the AUC from Day 1 through Day 14 and the AUC from Day 1 through Day 33 will be standardized for 14 and 33 days by multiplying 14, $33/t_{last}$ where t_{last} is the actual time in days of the last available assessment. No AUC values will be calculated if there are less than 3 results available. The same methods used in Section 8.2.9 will be applied.

8.3.5. Time to SARS-CoV-2 RNAemia TND Through Day 33

Time to SARS-CoV-2 RNAemia to TND is defined as per Section 8.1.1.2 and will be summarized and analyzed as described in Section 8.

8.3.6. Change from Baseline in SARS-CoV-2 Nucleocapsid Antigenemia Through Day 33

Change from baseline of SARS-CoV-2 nucleocapsid antigenemia will be summarized as described in Section 8.

8.3.7. Proportion of Subjects with Positive SARS-CoV-2 Serostatus at Day 33

The proportion of subjects with positive SARS-CoV-2 serostatus will be defined the same as baseline SARS-CoV-2 serostatus (Section 5.3) and summarized for each treatment group and will be analyzed using the same CMH methods as described for the primary endpoint in Section 8.

[redacted]

[redacted]

[redacted]

9. Pharmacokinetics

9.1. All Pharmacokinetic Subjects

On Day 1, one postdose plasma PK sample will be taken at least 1 hour after dosing or right before the subject leaves the site, whichever is later. On Day 3 and Day 5, one predose plasma PK sample will be collected at the same approximate time as the nasopharyngeal swab

collection. Time and date of collection will be recorded on the Plasma PK Sample Collection eCRF.

For subjects included in the PK population, the concentration data for EDP 235 will be summarized by study day, collection time relative to dose and by treatment group. Only Day 1 postdose, and Day 3 and Day 5 predose concentration data will be summarized for the PK population. Concentrations <LLOQ will be treated as zero for the computation of descriptive statistics. If more than 50% of subjects have concentration values <LLOQ, descriptive statistics will not be presented except for maximum and BQL (below quantification limit) will be displayed for mean and minimum, respectively. The number of observations, arithmetic mean, standard deviation (SD), % coefficient of variation (%CV), median, minimum, maximum, geometric mean, and %CV of the geometric mean (%GCV) will be summarized.

Mean (+/-standard error) and individual PK concentration over Study Day (Days 1, 3, and 5) by treatment group will be plotted on linear and semi-log scale.

Individual concentration data will be presented in listings.

9.2. Intensive PK Subset Subjects

A small subset of subjects will be enrolled into an intensive PK sampling group. Approximately 30 subjects will be enrolled in this subset (10 from each of EDP 235 [redacted] and [redacted]). These subjects will have PK collections on Day 1 at 1, 2, 4, and 8 hours postdose, Day 3 predose, and Day 5 at predose, and 1, 2, 4, 8 hours postdose. Time and date of collection will be recorded on the Plasma PK Sample Collection eCRF.

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings.

For subjects included in the intensive PK subset Population, plasma concentration data for EDP 235 will be summarized using descriptive statistics as described above using the unique timepoints in the intensive PK subset. PK parameters (C_{max}, t_{max}, C_8, $AUC_{0\text{-}last}$, $AUC_{0\text{-}8}$) will be summarized. Mean (+/-standard error) and individual PK concentration over time (Day 1 and Day 5 to 8-hours postdose and Day 3 predose) by treatment group will be plotted on linear and semi-log scale.

Individual concentration data and PK parameters will be presented in listings.

9.3. PK Analyses

For subjects included in the intensive PK subset Population, plasma PK parameters for EDP 235 will be estimated using non-compartmental methods with WinNonlin® using best fit regression. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. In estimating the PK parameters, BQL values before the first quantifiable point will be set to zero, BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or

quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times, and samples collected outside the allowable window will be included in the PK analysis. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameters. Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, %GCV, median, min, and max) will be used to summarize the calculated PK parameters by treatment group. For t_{max}, only median, min and max will be presented.

Table 2 Plasma PK Parameters for EDP 235 are shown as below.

Table 2

Parameter	Description	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	C_{max} from WNL
t_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	t_{max} from WNL
C_8	Plasma concentration at 8 hours postdose.	From SAS
$AUC_{0\text{-last}}$	The area under the plasma concentration-time curve, from time 0 to the last measurable nonzero concentration, as calculated by the linear up/log down method.	$AUC_{0\text{-last}}$ from WNL
$AUC_{0\text{-}8}$	Area under the concentration-time curve from time 0 to 8 hours postdose.	$AUC_{0\text{-}8}$ from WNL

9.4. PK/PD Analyses

PK/PD will be presented as scatter plots of absolute values and percent change from baseline versus PK concentration on a linear and log scale figures as follows:

- SARS-CoV-2 RNA Viral Load and PK Predose on Day 5
- SARS-CoV-2 RNA Viral Load Change From Baseline and PK Predose on Day 5
- SARS-CoV-2 RNA Viral Load AUC Days 1-5 and PK Predose on Day 5
- SARS-CoV-2 RNA Viral Load AUC Days 1-14 and PK Predose on Day 5
- COVID-19 signs/symptom score using the COVID-19 Symptom Diary and PK Predose on Day 5
- COVID-19 signs/symptom score using the COVID-19 Symptom Diary Change from Baseline and PK Predose on Day 5.

[redacted]

11. Data Monitoring Committee

The DMC will review the safety data from this study throughout the study and all outputs will use the safety population . The DMC will be headed by a DMC Chair and will include one or more physicians with expertise in SARS-CoV-2, consisting of expert(s) independent from the Sponsor. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor and PPD, will be governed by a separate DMC charter.

[redacted]

[redacted]

13. References

CDC. (2001). Data table of BMI-for-age charts. Updated August 23, 2001. Available at: https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm

CDC. (2021). SARS-CoV-2 variant classifications and definitions. Updated December 1, 2021. Available at https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html

Matthews JN, Altman DG, Campbell MJ, et al. Analysis of serial measurements in medical research. BMJ. 1990; 300(6719): 230-5.

United States Food and Drug Administration Guidance Document. International Conference on Harmonization E6 Good Clinical Practice. May 1996.

United States Food and Drug Administration Guidance Document. International Conference on Harmonization E3 Structure and Content of Clinical Study Reports. July 1996.

United States Food and Drug Administration Guidance Document. International Conference on Harmonization E9 Statistical Principles for Clinical Trials. September 1998.

14. Appendices

14.1. Schedule of Study Procedures

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth,
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	H=home visit by trained health care provider)
Eligibility															
Informed consent form	X												X*		Informed consent must be obtained before conducting any study specific assessments. *Participants who completed the study at the EOFU (Day 33) visit will be asked to participate in the long-term follow-up. If the participant agrees to participate, informed consent must be obtained for the long-term follow-up. Protocol Section 12.1.3 AEs, concomitant medications and therapies, and medically attended visits should be captured in the eCRF retrospectively for subjects who re-enter the study; data will be collected starting the next day after the participant completes the EOFU visit.
Inclusion/exclusion review	X	X													Protocol Section 4.1 and Protocol Section 4.2
SARS-CoV-2 diagnostic test	X														The SARS-CoV-2 diagnostic test should be a PCR or rapid antigen test approved for use in the country; PCR test is preferred. A test is required at Screening if a positive result from a SARS-CoV-2 diagnostic test performed as part of clinical care within 24 hours prior to randomization is not available. If an NP swab is collected for the SARS-CoV-2 diagnostic test, one swab from the left nostril will be collected. Protocol Section 8.1.1
Demographics	X														Protocol Section 8.1.2

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth,
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	H=home visit by trained health care provider)
Medical, smoking and COVID-19 disease history	X														Protocol Section 8.1.2
Prior medications and therapies	X														Section 8.1.3
Physical examination (PE)	X														Full PE at Screening. Subsequent PEs performed at the discretion of investigator will be targeted to new signs and symptoms, including specific assessments for any changes from previous status. Protocol Section 8.1.4
Weight, height, BMI	X														BMI=weight (kg)/height (m)^2. Protocol Section 8.1.5
Vital signs	X	X[d]		X		X		X		X		X[g]			Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, body temperature, and pulse oximetry. Vital signs will be measured after the participant has been supine for at least 5 minutes. If screening and randomization occur on different calendar days, vital signs should be repeated on D1 for baseline values. Protocol Section 8.3.1
Pregnancy test	X	X[d]										X			For female participants of childbearing potential. Urine test will be performed at Screening. On D1 and Day 33 (EOFU), blood will be collected for serum pregnancy test to be performed by central laboratory. The screening urine pregnancy test results will be used to qualify participants at study entry. Protocol Section 8.1.6
Randomization and Study Drug															

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth,
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	H=home visit by trained health care provider)
Randomization		X													Protocol Section 6.4
Dispense study drug and study supplies		X													Study supplies may include an electronic device to record COVID-19 Symptom Diary and other PRO assessments. Protocol Section 8.1.7
Study drug dosing		X*	X	X*	X	X*									*Study drug (EDP-235 or placebo) administered at approximately the same time every day (+ 1 hour) at the clinic on clinic visit days (D1, D3, and D5). If this is not possible, the participant should take the medication at home before the visit. Self-administered dosing date and time of study drug will be recorded in source based on participant recall. Protocol Section 6.1
Study drug accountability				X		X*						X*			Study drug accountability by capsule count will be completed by study staff. Protocol Section 6.2 and Protocol Section 6.3 * If a participant discontinues treatment before completing 5 days of dosing but remains in the study, the participant should return study drug for accountability at the EOT visit. If a participant withdraws from the study before day 5, the participant should return study drug for accountability at the EOFU visit.

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth,
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	H=home visit by trained health care provider)
Study Assessments															
Clinical laboratory assessments (chemistry, hematology, coagulation)		X[d]*		X		X		X		X		X[g]			*Blood samples for select laboratory assessments should be taken from all randomized subjects and sent to the local laboratory for these identified tests (noted with superscript "a" in Protocol Table 1), which should be assayed and reported in an expedited manner. Review of laboratory results is not required prior to randomization or dosing. In parallel, hematology, chemistry, and coagulation panels should be sent to the central laboratory with the other Day 1 samples. From D1 through D5, samples should be collected predose. See Protocol Section 1.4 for the list of laboratory assessments.
Follicle stimulating hormone		X[d]													Follicle-stimulating hormone should be tested in selected postmenopausal females. Protocol Section 8.1.6
12-lead ECG (resting)		X[d]				X				X		X[g]			Protocol Section 8.3.2
COVID-19 Symptom Diary	X	X[d]	X	X	X	X	X	X	X	X	X	X			The COVID-19 Symptom Diary will be completed by participants during Screening to determine eligibility and after randomization, predose on Day 1 as a baseline measurement. If Screening and Day 1 occur on the same calendar day, the Screening Diary entry will be used as the baseline measurement and a separate Day 1 Diary will not be collected. In addition, the diary will be completed once daily at the same time each day ±2 hours. Protocol Section 8.2.2
Global Impression Questions		X[d]	X	X	X	X	X	X	X	X	X	X	X	X[h]	Global impression questions include Return to Usual Health, Return to Usual Activities, PGI-C and PGI-S questions, which will be answered every day from D 1 to D33 after the COVID-19

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth,
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	H=home visit by trained health care provider)
															symptom diary is completed. Protocol Section 8.7.2.1
EQ-5D-5L		X[d]				X				X		X	X	X[h]	Protocol Section 8.7.2.2
NP swabs collection		X[d]		X		X		X		X		X	X	X	NP swab samples will be collected predose by a study nurse or other trained healthcare professional (HCP) at the clinic or the participant's home. Two NP swabs, one from the right nostril (primary and first to be collected) and one from the left nostril (back-up) will be collected at each visit. Protocol Section 8.2.1
SARS-CoV-2 serology sample collection		X[d]										X			Serology tests are SARS-CoV-2 anti-spike and anti-nucleocapsid IgG and IgM antibodies. Protocol Section 8.7.1
[redacted]															
Study staff review of COVID-19 Symptom Diary and other PRO questionnaires		Continuous from baseline through Day 33													Protocol Section 8.1.7
Assess ICU admissions, hospitalizations, and medically attended visits		Continuous from randomization through end of study participation													Medically attended visits include any unscheduled interactions with healthcare professionals other than study staff or designees that are not for routine health maintenance. Protocol Section 8.2.3
Adverse events		Continuous from signing of ICF through end of study participation[i]													Protocol Section 8.4
Concomitant medications and therapies		Continuous from signing of ICF through end of study participation													Concomitant medications and therapies will include the use of supplemental oxygen, increased

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth,
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	H=home visit by trained health care provider)
															use per PI judgment and mechanical ventilation. Protocol Section 8.1.3
PK sample collection		X+		X		X+*						X*			On D1, collect one postdose plasma PK sample at least 1 hr after dosing or right before the participant leaves the site, whichever is later. On D3 and D5, collect one plasma PK sample predose at the same approximate time as the NP swab collection. If the participant takes the study drug before the study site visit, a PK sample should be taken at the same approximate time as the NP swab collection. + On D1 and D5, intensive PK sampling will be conducted in a subset of participants. Additional PK samples will be drawn at 1, 2, 4, and 8 hours postdose. See Protocol Table 4 for time windows for intensive PK sampling. * If a participant discontinues treatment before D5 and remains in the study, a PK sample should be taken at the approximate time as the NP swab at the EOT Visit. If the subject discontinues treatment before D5 and does NOT remain in the study, a PK sample should be taken at the approximate time as the NP swab at the EOFU visit (Protocol Section 8.5).

Abbreviations: BMI=body mass index; D=day; ECG=electrocardiogram; EOFU=end of follow-up; EOS=end-of-study; EOT=end-of-treatment; ICF=informed consent form; LT=long-term follow-up; NP=nasopharyngeal; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK=pharmacokinetic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SCR=screening

[a] During the Follow-up period (Day 6 through Day 33), if the participant has symptom recurrence or symptom worsening , an unscheduled visit should be done within 2 days of patient reported symptom recurrence or worsening.. At the unscheduled visit, NP swabs will be collected in addition to clinical assessments deemed necessary by the Investigator.

[b] Screening assessments should occur within 24 hours of randomization.

[c] D1 assessments are to be done only in randomized participants. Randomization, predose baseline measurements, and dosing must occur on the same calendar date.

[d] These assessments should be done predose as baseline measurements

[e] Participants who discontinue treatment before completing 5 days of dosing should return to the study site within 24 hours of their last dose to complete EOT procedures and proceed to complete all follow up assessments 4, 9 and 28 days (EOFU visit) after their last dose of study drug. Participants who discontinue the study before Day 33 (EOFU) should return to the study site within 24 hours and no more than 48 hours later to complete the EOFU procedures.

[f] Visits may be completed at the study site or by study site personnel via a home visit, if feasible.

[g] These assessments are only required for participants who discontinued the study before Day 5 (ie, do not have an EOT visit before discontinuing the study) or participants who discontinued the study after Day 5 and before Day 14. These participants should have an EOFU visit with additional assessments as indicated.

[h] For the Week 12 and Week 24 assessments, paper questionnaires may be used for the Global Impression Questions and EQ-5D-5L and transcribed into the eCRF.

[i] At Week 12 and Week 24, study staff will contact each participant to ask if they have COVID-19 signs and symptoms and record that information into the AE eCRF.

14.2. COVID-19 Symptom Diary Scoring

Symptoms	Response Options and Scoring
What was the severity of your [insert symptoms] at its worst over the past 24 hours?	None = 0 Mild = 1 Moderate = 2 Severe = 3
1. Stuffy or runny nose	
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you vomit (throw up) in the last 24 hours?	I did not vomit at all =0/none 1 to 2 times = 1/mild 3 to 4 times = 2/moderate 5 or more times = 3/severe
12. How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	I did not have diarrhea at all = 0/none 1 to 2 times =1/mild 3 to 4 times = 2/moderate 5 or more times = 3/severe
13. Rate your sense of smell in the last 24 hours	My sense of smell is THE SAME AS usual = 0/none My sense of smell is LESS THAN usual = 1/mild I have NO sense of smell = 2/moderate
14. Rate your sense of taste in the last 24 hours	My sense of taste is THE SAME AS usual = 0/none My sense of taste is LESS THAN usual = 1/mild I have NO sense of taste = 2/moderate

14.3. Global Impressions Questions

Return to Usual Health	In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No

Return to Usual Activities	In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No
Patient Global Impression of Change (PGI-C)	In the past 24 hours, what best describes the overall change in your COVID-19-related symptoms? Much better, A little better, No change, A little worse, Much worse
Patient Global Impression of Severity (PGI-S)	In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst? None, Mild, Moderate, or Severe

14.4. EQ-5D-5L

Mobility	No problems; Slight problems; Moderate problems; Severe problems; Extreme problems
Self-care	No problems; Slight problems; Moderate problems; Severe problems; Extreme problems
Usual Activities	No problems; Slight problems; Moderate problems; Severe problems; Extreme problems
Pain/Comfort	No problems; Slight problems; Moderate problems; Severe problems; Extreme problems
Anxiety/Depression	No problems; Slight problems; Moderate problems; Severe problems; Extreme problems
EQ-5D-5L Index	Derived per EQ-5D-5L User Guide [redacted] Updated September 2019 Weights used: For US sites: https://euroqol.org/wp-content/uploads/2020/12/US_valueset_SAS.txt For Romania sites: https://euroqol.org/wp-content/uploads/2023/04/Romania_EQ5D5L_valueset_SPSS.txt
EQ VAS	Analogue scale: 0 (The worse health you can imagine) to 100 (The best health you can imagine)

14.5. Imputation Rules

Imputation rules for missing or partial AE start/end dates and times are defined as:

- If Time (start or end) of any AE is missing and corresponding date is also not missing, then impute as 23:59.
- Only Day of AE start date is missing:
    - If the AE start year and month are the same as that for the first dose date, then:
        - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date.
    - Otherwise, impute the AE start day as the first day of the month.
- If Day and Month of AE start date are missing:
    - If AE start year = first dose year, then:
        - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date.
    - Otherwise, impute the AE start MONTH as January and the DAY as 1.
- If Year of AE start date is missing:
    - If the year of AE start is missing or AE start date is completely missing, then query site and leave as missing.
- For missing and partial adverse event end dates, imputation will be performed as follows:
    - If only the day of the month is missing, the last day of the month will be used to replace the missing day.
    - If the day and month are missing or a date is completely missing, it will be considered as missing.

Imputation rules for missing or partial medication/therapy start/stop dates are defined below:

- If only Day of start date is missing:
    - If the start year and month are the same as that for the first dose date, then:
        - If the full (or partial) end date is NOT before the first dose date or end date is missing, then impute the start day as the day of first dose date.
    - Otherwise, impute the start day as 1.
- If Day and Month of start date are missing:
    - If start year = first dose year, then:
        - If the full (or partial) end date is NOT before the first dose date or end date is missing, then impute the start Month and Day as the Month and Day of first dose date.
    - Otherwise, impute the start MONTH as January and the DAY as 1.

- If Year of start date is missing:
    - If the year of start is missing or start date is completely missing, then query site and leave as missing.
- For missing and partial end dates, imputation will be performed as follows:
    - If only the day of the month is missing, the last day of the month will be used to replace the missing day.
    - If the day and month are missing or a date is completely missing, it will be considered as missing.

Imputation rules for SARS-CoV-2 viral load and SARS-CoV-2 nucleocapsid antigenemia data:

- SARS-CoV-2 RNA and RNAemia viral load values reported as TND will be imputed with 1 copy/mL (i.e., 0 $\log_{10}$ copies/mL)
- Infectious SARS-CoV-2 viral load values reported as TND will be imputed with 1 TCID50/mL(ie, 0 log10 TCID50/mL).
- SARS-CoV-2 nucleocapsid antigenemia reported as TND will be imputed as 1 fg/mL.
- Numeric values <LLOQ will be set to the LLOQ.
- Numeric values >ULOQ will be set to the ULOQ.
- Values reported as "POS" will be imputed as half of the LLOQ.
- Imputed values will be used in tables and listings will present actual data.

Imputation rules for PK concentrations

- Serum concentrations that are <LLOQ will be treated as zero for PK analyses, except for <LLOQ values observed between 2 quantifiable concentrations and <LLOQ values that occur after the first quantifiable point, which will be set to missing. If consecutive <LLOQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after <LLOQ concentrations will be treated as missing. Missing concentrations will be treated as missing in the PK parameter calculations.

Imputation rules for all other data:

- No other imputations will occur for any data not previously mentioned.