STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2a Study in Participants with Early Stage COVID-19 to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation
Name of Test Drug:	Remdesivir
Study Number:	GS-US-553-9020
Protocol Version (Date):	Amendment 3: 13 January 2021
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area-under-the-curve
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
DAVG	Time-weighted average change from baseline
DOB	date of birth
FAS	Full Analysis Set
FEV_1	forced expiratory volume in the first second of expiration
FLU-PRO©	InFLUenza Patient-Reported Outcome
Hb	Hemoglobin
HLT	high-level term
HLGT	high-level group term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IXRS	interactive voice or web response system
LLT	lower-level term
LOQ	limit of quantitation
MAVs	medically attended visits
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
PCR	polymerase chain reaction
PK	pharmacokinetics
PT	preferred term
PTM	Placebo to match
Q1, Q3	first quartile, third quartile
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
RT-qPCR	quantitative reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan

SARS	severe acute respiratory syndrome
SE	standard error
SD	standard deviation
SOC	system organ class
SpO_2	oxygen saturation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve
Vz/F	apparent volume of distribution of the drug

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-553-9020. This SAP is based on the study Protocol Amendment 3 dated 13 January 2021 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made to the SAP after the finalization will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is:

- To characterize the impact of inhaled RDV on SARS-CoV-2 viral load in participants with early stage COVID-19

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of inhaled Remdesivir for Injection formulation in participants with early stage COVID-19
- To evaluate the PK of inhaled Remdesivir for Injection formulation and its metabolites in participants with early stage COVID-19 in Parts A and B
- To characterize and evaluate disease progression from baseline
- To characterize the efficacy, safety, and tolerability of Remdesivir for Inhalation Solution formulation administered with a mouthpiece in Part C of the study

CCI [redacted]

1.2. Study Endpoints

The primary endpoint of this study is:

- Time weighted average change in SARS-CoV-2 viral load which is defined as AUC of viral load change divided by time between baseline through Day 7

The secondary endpoints of this study are:

- Proportion of participants with treatment-emergent AEs (TEAEs) and laboratory abnormalities
- Proportion of participants with TEAEs leading to study treatment discontinuation
- Composite of all-cause medically attended visits (MAVs) (medical visits attended in person by the participant and a health care professional) or death by Day 28
- Composite of COVID-19 related medically attended visits (MAVs) (medical visits attended in person by the participant and a health care professional) or death by Day 28
- Proportion of participants hospitalized by Day 28
- Characterization of the plasma concentrations of inhaled RDV and its metabolites including $AUC_{0\text{-}24h}$, AUC_{last}, $CL_{ss/F}$, $t_{1/2}$, $V_{z/F}$, C_{max}, T_{max}, C_{last}, T_{last}, AUC_{tau}, λ_z, and C_{tau} (Parts A and B only)
- Change in SARS-CoV-2 viral load from baseline to Day 5
- Change in SARS-CoV-2 viral load from baseline to Day 7
- Change in SARS-CoV-2 viral load from baseline to Day 14 (Parts A and B only)
- Time to negative SARS-CoV-2 polymerase chain reaction (PCR)
- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19 adapted InFLUenza Patient-Reported Outcome (FLU-PRO©) questionnaire

CCI [redacted]

1.3. Study Design

This is a randomized, blinded, placebo-controlled, multicenter study to evaluate the safety, efficacy, and PK of inhaled RDV in participants with early stage COVID-19. The study will be conducted in 3 parts (Parts A, B, and C).

Parts A and B

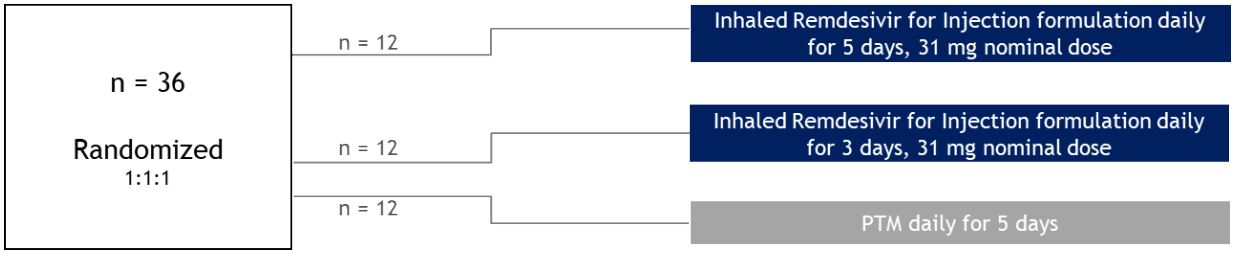
In Part A, approximately 36 eligible participants will be randomized in a 1:1:1 ratio to receive 1 of the following 3 study treatments administered via facemask:

Treatment Group 1: 31 mg inhaled Remdesivir for Injection formulation daily for 5 days

Treatment Group 2: 31 mg inhaled Remdesivir for Injection formulation daily for 3 days followed by PTM daily for 2 days

Treatment Group 3: PTM daily for 5 days

Part A



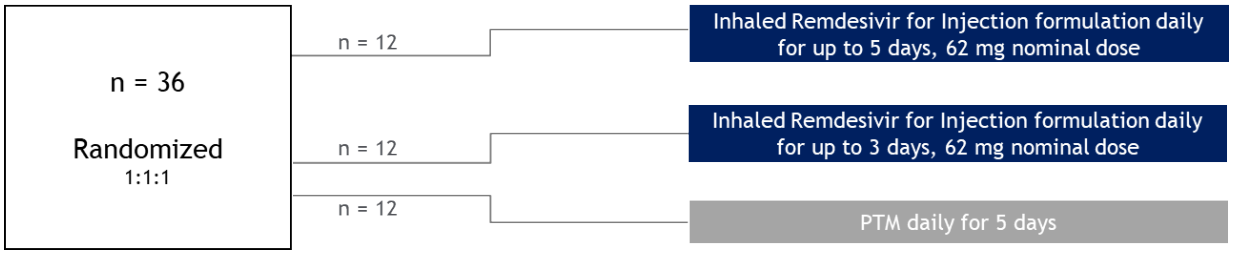
In Part B, if supported by Phase 1a data in healthy volunteers, an additional 36 eligible participants may be randomized in a 1:1:1 ratio to receive 1 of the following 3 study treatments administered via facemask:

Treatment Group 4: 62 mg inhaled Remdesivir for Injection formulation daily for up to 5 days

Treatment Group 5: 62 mg inhaled Remdesivir for Injection formulation daily for up to 3 days followed by PTM through Day 5

Treatment Group 6: PTM daily for 5 days

Part B



In Parts A and B, at in-clinic screening, after the participant has provided informed consent, assessments will include but are not limited to the following: demographic and baseline characteristics, medical history, and concomitant medications will be documented. Body weight and height will be measured. A urine pregnancy test will be performed for women of childbearing potential. Vital signs including heart rate, temperature, blood pressure, respiration rate and SpO_2 will be recorded. A complete physical examination will be performed.

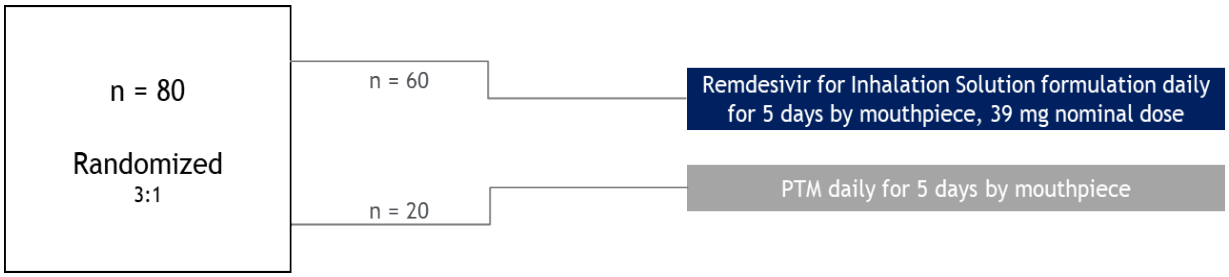
Participants with PCR-confirmed COVID-19 who enroll in the study will return to clinic daily on Days 1 through 5 for study treatment administration and clinical assessments. Participants will return to clinic on Days 7 and 14 for follow-up clinical assessment and undergo a Day 28 follow-up which may be completed by telephone.

Part C

Part C of the study will include an expanded safety and efficacy assessment of an additional 80 participants. Participants in Part C will be enrolled after review of preliminary safety data from Parts A and B through at least Day 7. Approximately 80 eligible participants will be randomized in a 3:1 ratio to receive 1 of the following 2 study treatments administered via mouthpiece:

Treatment Group 7: 39 mg Remdesivir for Inhalation Solution formulation once daily for 5 days

Treatment Group 8: PTM daily for 5 days



At screening, after the participant has provided informed consent, assessments will include but are not limited to the following: demographic and baseline characteristics, medical history, and concomitant medications will be documented. Body weight and height will be measured. A urine pregnancy test will be performed for women of childbearing potential. Vital signs including heart rate, temperature, blood pressure, respiration rate and SpO_2 will be recorded. A complete physical examination will be performed.

In Part C, participants with nucleic acid testing, direct antigen testing, or PCR-confirmed COVID-19 who enroll in the study will be administered Remdesivir for Inhalation Solution formulation or PTM on Days 1 through 5. Clinical assessments may be conducted at home with the assistance of home nursing on Days 1, 3, 5, and 7. Participants will undergo Days 14 and 28 telephone contact follow-ups.

Additional details regarding study assessment can be found in Appendix 1.

1.4. Sample Size and Power

The sample size in this study is determined based on practical considerations and past experience with similar types of studies. No sample size or power calculation was performed. A sample size up to approximately 152 participants (72 participants for Part A and Part B; 80 participants for Part C) should provide a suitable assessment of the descriptive efficacy, PK, and safety profiles in this population.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

No interim analysis is planned.

2.2. Final Analysis

The unblinded final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by study part and participant identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants included will be summarized in the disposition table by treatment group as described in Section 4.

A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Randomized Analysis Set

The all Randomized Analysis Set includes all participants who are randomized into the study.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all participants who (1) are randomized into the study, and (2) have received at least 1 dose of study treatment. Participants will be grouped according to the treatment to which they were randomized. This is the primary analysis set for MAVs and FLU-PRO questionnaire analyses.

3.1.3. Modified Full Analysis Set

The modified Full Analysis Set (mFAS) includes all participants who (1) are randomized into the study, (2) have received at least 1 dose of study treatment, and (3) have positive SARS-CoV-2 viral load at baseline (result of 'No SARS-CoV-2 detected' is considered as negative). The mFAS is defined separately for SARS-CoV-2 viral load from nasopharyngeal swab sample (Nasopharyngeal mFAS), oropharyngeal swab samples (Oropharyngeal mFAS), and saliva samples (Saliva mFAS). Participants will be grouped according to the treatment to which they were randomized. The mFAS is the primary analysis set for SARS-CoV-2 viral load analyses.

3.1.4. Safety Analysis Set

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which includes all participants who (1) are randomized into the study and (2) have received at least 1 dose of study treatment. Participants will be grouped according to the actual treatment received.

3.1.5. Pharmacokinetic Analysis Set

The PK Analysis Set is defined separately for each analyte and includes all participants who (1) are randomized into the study, (2) have received at least 1 dose of RDV, (3) have at least 1 nonmissing postdose PK concentration datum reported by the PK laboratory. Participants will be grouped according to the actual treatment received.

3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set, FAS, or mFAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. For the PK Analysis Set, participants will be grouped according to the actual treatment received.

The analysis of time-weighted average change from baseline through day 7 (DAVG7) in SARS-CoV-2 viral load based on the mFAS, and time to COVID-19-related MAVs or all-cause death by Day 28 based on the FAS may also be grouped according to the following:

- 5 RDV treatments (31 mg for 3 days vs. 31 mg for 5 days vs. 62 mg for 3 days vs. 62 mg for 5 days vs. 39 mg for 5 days) vs. pooled PTM (Parts A, B, and C)

- Pooled all RDV treatments (31 mg for 3 days, 31 mg for 5 days, 62 mg for 3 days, 62 mg for 5 days, and 39 mg for 5 days) vs. pooled PTM (Parts A, B, and C)

- Pooled 31 mg RDV (31 mg for 3 days and 31 mg for 5 days) vs. pooled 62 mg RDV (62 mg for 3 days and 62 mg for 5 days) vs. 39 mg RDV for 5 days vs. pooled PTM (Parts A, B, and C)

3.3. Strata and Covariates

For the primary efficacy endpoint, the baseline value of the SARS-CoV-2 viral load will be included as a covariate in the efficacy analysis model.

This study does not use a stratified randomization schedule when enrolling participants.

3.4. Examination of Participant Subgroups

The primary efficacy endpoint will be examined using the following subgroups:

- Age: < 60 years and ≥ 60 years
- Sex at birth: male and female
- Race: (a) Asian, (b) Black, (c)White, and (d) other (all races other than Asian, Black and White including Not Permitted)
- Baseline SARS-CoV-2 viral load (log_{10} copies/ml): < median and ≥ median

If there is an imbalance between treatment groups in the presumed prognostic baseline characteristics that are not prespecified, subgroupings based on these imbalanced baseline characteristics may also be explored for analysis of efficacy endpoints.

3.5. Multiple Comparisons

No prespecified multiplicity adjustments are planned for confidence intervals or statistical tests.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

In this study, a missing pre-treatment laboratory result would be treated as normal (i.e., no toxicity grade) for the laboratory abnormality summary. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

SARS-CoV-2 viral load results that are below LOQ but have a positive signal will be reported as "< 2228cp/mL SARS-CoV-2 detected" (nasopharyngeal/oropharyngeal swabs) or "<1390cp/mL SARS-CoV-2 detected" (saliva) and those that are below LOD and negative will be reported as "No SARS-CoV-2 detected". The data will be imputed as follows:

- A value of 1114 copies/ml (1/2 of the LOQ of 2228 copies/ml) will be used to calculate descriptive statistics if the datum is reported as "< 2228cp/mL SARS-CoV-2 detected" from nasopharyngeal/oropharyngeal swab sample.

- A value of 746.5 copies/ml (1/2 of the LOD of 1493 copies/ml) will be used to calculate descriptive statistics if the datum is reported as "No SARS-CoV-2 detected" from nasopharyngeal/oropharyngeal swab sample.

- A value of 695 copies/ml (1/2 of the LOQ of 1390 copies/ml) will be used to calculate descriptive statistics if the datum is reported as "< 1390cp/mL SARS-CoV-2 detected" from saliva sample.

- A value of 501 copies/ml (1/2 of the LOD of 1002 copies/ml) will be used to calculate descriptive statistics if the datum is reported as "No SARS-CoV-2 detected" from saliva sample.

Any SARS-CoV-2 viral load samples collected on or after the participants are receiving additional COVID-19 treatments (see Appendix 2) will be excluded from the viral load analysis.

Patients with negative viral load at baseline are not included in the viral load analysis.

Base 10 logarithm transformation will be used for analyzing SARS-CoV-2 viral load.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing concentrations. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. For intensive PK concentration, values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purpose. For predose or postdose timepoint of sparse PK and single anytime PK, values that are BLQ will be treated as one-half the value of the LLOQ for summary purpose.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ."

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day 1 is defined as the first dosing date of study drug.

Study Days are calculated relative to Study Day 1 and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, **Study Day 1/ First Dose Date** is the day of first dose of study drug administration, as recorded on the Study Drug Administration eCRF form.

Last Dose Date is defined as the maximum, nonmissing, nonzero dose end date of treatment recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF.

Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, FLU-PRO questionnaire collection date, and the laboratory visit dates, including the 28-day follow-up visit date, and the death date (if applicable, only for participants who prematurely discontinued study according to the Study Completion eCRF).

Baseline value is defined as the last value obtained on or prior to the first dose date (and time, if available) unless otherwise specified (see Section 3.8.3).

3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for vital signs and SpO_2 are provided in Table 3-1 (Parts A and B) and Table 3-2 (Part C).

Table 3-1. Analysis Visit Windows for Vital Signs, and SpO_2 in Parts A and B

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (pre dose)*
Day 1	1	1 (post dose)	1
Day 2	2	2	2
Day 3	3	3	3
Day 4	4	4	4
Day 5	5	5	6
Day 7	7	7	9
Day 14	14	10	21
Post Day 14	28	22	(None)

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time.

Table 3-2. Analysis Visit Windows for Vital Signs and SpO_2 in Part C

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (pre dose)*
Day 1	1	1 (post dose)	1
Day 3	3	2	4
Day 5	5	5	6
Day 7	7	7	13
Post Day 7	14	14	(None)

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time.

The analysis windows for SARS-CoV-2 viral load are provided in Table 3-3 (Parts A and B) and Table 3-4 (Part C).

Table 3-3. Analysis Visit Windows for SARS-CoV-2 Viral Load in Parts A and B

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (pre dose)*
Day 2	2	1 (post dose)	2
Day 3	3	3	3
Day 4	4	4	4
Day 5	5	5	6
Day 7	7	7	9
Day 14	14	10	21
Post Day 14	28	22	(None)

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time.

Table 3-4. Analysis Visit Windows for SARS-CoV-2 Viral Load in Part C

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (pre dose)*
Day 3	3	1 (post dose)	4
Day 5	5	5	6
Day 7	7	7	9
Post Day 7	14	10	(None)

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time.

The analysis windows for hematology, coagulation, and chemistry laboratory tests are provided in Table 3-5 (Parts A and B) and Table 3-6 (Part C).

Table 3-5. Analysis Visit Windows for Hematology, Coagulation, and Chemistry Laboratory Tests in Parts A and B

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (pre dose)*
Day 3	3	1 (post dose)	4
Day 5	5	5	6
Day 7	7	7	9
Day 14	14	10	21
Post Day 14**	28	22	(None)

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time
** Post Day 14 laboratory values will be considered for treatment-emergent laboratory presentations only.

Table 3-6. Analysis Visit Windows for Hematology, Coagulation, and Chemistry Laboratory Tests in Part C

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (pre dose) *
Day 3	3	1 (post dose)	4
Day 5	5	5	6
Day 7	7	5	13
Post Day 7**	14	14	(None)

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time.
** Post Day 7 laboratory values will be considered for treatment-emergent laboratory presentations only.

FEV_1 will be performed daily during treatment days; therefore, windows are not assigned and results will be summarized for each study day. Participants will complete the adapted FLU-PRO Questionnaire daily from Day 1 through Day 14; therefore, windows are not assigned and results will be summarized for each study day.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window or study day. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window or study day.

If multiple valid, nonmissing measurements exist in an analysis window or study day, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date (and time, if available) of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.

  — For FLU-PRO data, if there are multiple records on Day 1, the baseline value will be selected as follows:

    ■ The record closest to the dosing day will be selected.

    ■ If there are more than 1 records on the selected day with different times, the least severe score will be selected as baseline. If there are multiple records with same severity, the measurement with the lowest severity at later time will be selected.

- For postbaseline values (other than PCR negative confirmation and PCR for DAVG):

  — The record closest to the nominal day for that visit will be selected with the exception of viral load in which the latest record will be selected.

- If there are 2 records that are equidistant from the nominal day, the later day will be selected.
- If there is more than 1 record on the selected day, values will be selected for analysis as follows:
  - For viral load, if there is more than 1 record on the selected day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the geometric mean value (copies/mL) will be taken.
  - For FLU-PRO questionnaire response, the worst severity will be taken if there is more than 1 record on the selected day. If the severity is the same, the latest record will be selected.
  - For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

- For postbaseline values of PCR negative confirmation (separately by sample types):
  - Use all available data to derive negative confirmation except if there are multiple records on the same day, worst value will be used for negative confirmation for that day
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.

- For postbaseline values PCR for DAVG calculation:
  - All values from different days within an analysis window will be used for DAVG calculation.
  - If there is more than 1 record on a study day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the geometric mean value (copies/mL) will be taken.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of participant enrollment will be provided by treatment group and overall for each investigator site by study part using the Safety Analysis Set. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A summary of participant disposition will be provided by treatment group and overall by study part for all screened participants. This summary will present the number of participants screened, screen failure participants who were not enrolled, participants who met all eligibility criteria but were not randomized, participants randomized, participants randomized but never treated, and participants in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- Modified Full Analysis Set for each sample type
- PK Analysis Set for each analyte

In addition, the number and percentage of the participants in the following categories will be summarized:

- Completed randomized treatment as recorded on the Study Drug Completion form
- Prematurely discontinuing study drug prior to completion of dosing with summary of reasons for discontinuing study drug as recorded on the Study Drug Completion form
- Completed study
- Prematurely discontinuing study

The denominator for the percentages of participants in each category will be the number of participants in the Safety Analysis Set.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure

Number of doses received will be summarized as continuous and categorical variables by treatment groups including placebo group for the Safety Analysis Set. Exposure data will be listed.

4.3. Protocol Deviations

A listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations and the total number of important protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the FAS. A by-participant listing will be provided for those participants with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (i.e., age, sex at birth, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by part and treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic and baseline characteristics data will be provided for the Safety Analysis Set.

In addition, age groups (< 60 vs ≥ 60 years), and race groups (Asian, Black, White, and other) will be summarized by treatment group and overall.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data and row mean scores for ordinal data [age group]) will be used. For continuous data, the Kruskal-Wallis test will be used to compare the 3 treatment groups, and the Wilcoxon rank sum test will be used to compare the 2 treatment groups.

A by-participant demographic listing will be provided by study part and participant ID number in ascending order.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall for each part using descriptive statistics:

- Duration of symptoms prior to first dose of study drug
- Duration from SARS-CoV-2 PCR/NAAT/antigen testing confirmation to first dose of study drug
- Baseline alanine aminotransferase (ALT)
- Baseline aspartate aminotransferase (AST)
- Baseline respiration rate
- Baseline SARS-CoV-2 viral Load (as a continuous variable, and a categorical variable with categories of < median and ≥ median) for each sample type collected

The summary of these baseline characteristics will be provided for the Safety Analysis Set. For categorical data, the Cochran-Mantel-Haenszel (CMH) test (i.e. general association) will be used. For continuous data, the Kruskal-Wallis test will be used to compare the 3 treatment groups, and the Wilcoxon rank sum test will be used to compare the 2 treatment groups.

A by-participant listing of other baseline characteristics will be provided by study part and participant ID number in ascending order.

5.3. Additional Baseline Characteristics

Symptoms for each domain will be summarized as categories 0-4 from FLU-PRO for participants in Part C. The Cochran-Mantel-Haenszel (CMH) test (i.e. row mean scores for ordinal data) will be used to compare the 2 treatment groups.

5.4. Medical History

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is considered to be preexisting and should be documented as medical history. General medical history data will be collected at screening. It will be coded using the MedDRA Version 23.1. A summary table will present the percentages of participants reporting each medical history preferred term, sorted first in alphabetical order by system organ class (SOC) and then by preferred term (PT) in descending order of total frequency within SOC.

A by-participant listing of medical history will be provided by participant ID number in ascending order.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The viral load assay for the primary analysis is: 2019-nCoV Real-Time RT-PCR Viral Load assay (v2). The assay is based on CDC's qualitative 2019-nCoV EUA Assay using primers targeting SARS-CoV-2 nucleocapsid (N) gene.

6.1.1. Definition of the Primary Efficacy Endpoint

The primary endpoint of the study is time-weighted average change from baseline to Study Day 7 ($DAVG_7$) in SARS-CoV-2 viral load (log_{10} copies/mL). The $DAVG_7$ in SARS-CoV-2 viral load is defined as the time-weighted average between the first postbaseline value through the last available value up to Study Day 7 minus the baseline value in SARS-CoV-2 viral load. $DAVG_7$ is calculated using the trapezoidal rule and the area-under-the-curve (AUC) concept as follows:

$$DAVG_7 = \frac{AUC_{t_1-t_7}}{(t_7 - t_1)} - Y_0$$

The AUC between t_1 and t_n in a time (i.e., study day) versus SARS-CoV-2 viral load plot is calculated as follows:

$$AUC_{t_1-t_n} = \sum_{i=1 \; to \; (n-1)} \frac{1}{2}(Y_i + Y_{i+1}) \times (t_{i+1} - t_i)$$

Where Y_i is the SARS-CoV-2 viral load at time t_i, t_1 is the first postbaseline time, and Y_0 is the baseline SARS-CoV-2 viral load.

For participant with SARS-CoV-2 viral load data only available up to Day x ($x < 7$), the $DAVG_7$ is defined as $DAVG_7 = \frac{AUC_{t_1-t_x}}{(t_x - t_1)} - Y_0$

If there is no post-baseline data, then the participant will be excluded from the analysis. If there is one post-baseline data value Y_i, $DAVG_7 = Y_i - Y_0$.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: The RDV groups are not different from the PTM groups in virologic response with respect to $DAVG_7$ in SARS-CoV-2 viral load.

Alternative hypothesis: The RDV groups are different from the PTM groups in virologic response with respect to $DAVG_7$ in SARS-CoV-2 viral load.

6.1.3. Analysis of the Primary Efficacy Endpoint

$DAVG_7$ in SARS-CoV-2 viral load will be summarized by treatment group using descriptive statistics in Parts A, B and C. For Part C, $DAVG_7$ in SARS-CoV-2 viral load will be compared between the RDV and PTM groups using analysis of covariance (ANCOVA) with baseline viral load included in the model as a covariate. Due to small sample sized in Parts A and B, no comparison test will be applied.

The following summary tables will be provided by treatment group:

- $DAVG_7$ in SARS-CoV-2 viral load based on nasopharyngeal swab samples
- $DAVG_7$ in SARS-CoV-2 viral load based on oropharyngeal swab samples
- $DAVG_7$ in SARS-CoV-2 viral load based on saliva samples

After checking that the Part A, Part B, and Part C data are poolable with regard to demographic and baseline characteristics, $DAVG_7$ in SARS-CoV-2 viral load will be analyzed by the pooled groups outlined in Section 3.2 and comparison will be done using ANCOVA with baseline viral load as the covariate.

The mFAS will be the primary analysis set for evaluation of $DAVG_7$ in SARS-CoV-2 viral load. A by-participant listing for $DAVG_7$ in SARS-CoV-2 viral load will be provided. Descriptive statistics will be provided for $DAVG_7$ in SARS-CoV-2 viral load by treatment group for each of the subgroups defined in Section 3.4.

6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed in Section 1.2.

6.2.1. Analysis of Secondary Efficacy Endpoints

The FAS will be the primary analysis set for hospitalizations, MAVs and FLU-PRO questionnaire analyses. The mFAS will be the primary analysis set for SARS-CoV-2 viral load analyses.

Composite Endpoint of All-Cause MAVs or All-Cause Death by Day 28

The proportion of participants with all-cause MAVs or all-cause death by Study Day 28 will be estimated using Kaplan-Meier methods by treatment group and compared among 3 treatment groups in Part A and Part B and between the 2 treatment groups in Part C using a log-rank test.

If participants have no event by Study Day 28, participants will be censored at date of earlier of Study Day 28 and last study day. If a participant has a MAV first and then dies, then date of the MAV and status will be used for this participant.

Composite Endpoint of COVID-19 Related MAVs or All-Cause Death by Day 28

The proportion of participants with COVIS-19 related MAVs or all-cause death will be analyzed using the same method as used for composite endpoint of all MAVs or all-cause death by day 28.

In additional, a summary by pooled RDV and Pooled PTM may be provided and compared using CMH method including Part as strata in the model.

Proportion of participants hospitalized by Day 28

The proportion of participants with all-cause hospitalization (ICU, non-ICU, or unknown ward from Hospitalization/MAVs CRF) by Study Day 28 will be estimated using the Kaplan-Meier method and compared among treatment groups using a log-rank test. The time to all-cause hospitalization is defined using the first hospitalization date by Study Day 28, depending on which happens first. If participants have no event by Study Day 28, participants will be censored at date of earlier of Study Day 28 and last study day/death.

Time to Negative SARS-CoV-2 PCR

Negative SARS-CoV-2 PCR based on RT-PCR viral load is defined as:

(1) the results reported as 'No SARS-CoV-2 detected', AND

(2) two consecutive negative results, or negative at last available sample for participants who completed or discontinued from study.

The time to negative SARS-CoV-2 PCR is defined (in days) as the number of days to first confirmed negative:

First date of two consecutive dates achieving negative result – First dose date +1.

Participants without negative SARS-CoV-2 PCR will be censored at last non-missing SARS-CoV-2 viral load date. The Kaplan-Meier product limit method will be used to estimate time to negative SARS-CoV-2 PCR and p-values will be calculated using a log-rank test.

Time to Alleviation of Baseline COVID-19 Symptoms (Part C)

Using the COVID-19-adpated FLU-PRO Plus, the alleviation (mild or absent) of baseline COVID-19 symptoms, i.e. overall alleviation of all symptoms scored 1 or higher at baseline for each participant, is defined as:

(1) symptoms scored as 2 or higher at baseline are scored as 0 or 1 at post-baseline, AND symptoms scored as 1 at baseline are scored as 0 at post-baseline, AND

(2) for two consecutive days.

Time to alleviation of baseline COVID-19 symptoms is defined (in days) as:

First date of the two consecutive dates achieving alleviation – First dose date +1.

If a participant has baseline COVID-19 symptoms and not achieved symptom alleviation at last FLU-PRO assessment or early discontinuation of study, the participant will be censored at the date of last FLU-PRO assessment. The Kaplan-Meier product limit method will be used to estimate and log-rank test will be used to compare time to alleviation (mild or absent) of baseline COVID-19 symptoms by treatment group. The hazard ratio and its 95% CI from Cox model will be provided.

Change in SARS-CoV-2 Viral Load from Baseline

Change in SARS-CoV-2 viral load from baseline at each postbaseline analysis window will be provided for each of nasopharyngeal swab samples, oropharyngeal swab samples and saliva samples. Descriptive statistics will be provided by treatment group for each nasopharyngeal, oropharyngeal and saliva test as follows: (1) Baseline values, (2) Values at each postbaseline analysis window, (3) Change from baseline at each postbaseline analysis window.

Following by-participant listing will be provided by study part, participant ID number and time point in chronological order:

- Hospitalizations/MAVs
- SARS-CoV-2 viral load (log_{10} copies/mL)
- COVID-19-adapted FLU-PRO© questionnaire

CCI [redacted]

[redacted]

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the safety analysis set. All safety data collected on or after the date that study drug was first dispensed through 30 days after last dose will be summarized by treatment group for the Safety Analysis Set, unless specified otherwise. Safety endpoints listed in Section 1.2 include:

- Proportion of participants with treatment-emergent AEs (TEAEs) and laboratory abnormalities
- Proportion of participants with TEAEs leading to study treatment discontinuation

All safety data will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

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

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening) or Grade 5 (death) according to toxicity criteria specified in the document above. The severity grade of events for which the investigator did not record severity will be left as “missing” for data listings.

7.1.3. Relationship of Adverse Events to Study Drug

Study drug-related AEs are those for which the investigator selected “Related” on the AE CRF to the question of “Related to Study Treatment.” Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedure

Study procedure-related AEs are those for which the investigator selected "Yes" on the AE CRF to the question of "Related to Study Procedures." Events for which the investigator did not record relationship to study procedure will be considered as missing. No summary table for relationship of AE to study procedure will be presented.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definition of SAE specified in the study protocol. SAE captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety (GLPS) before data finalization.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.6.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.7. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- Grade 3 or higher treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Grade 3 or higher treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described above, treatment emergent study drug related SAEs and treatment emergent deaths will be provided by treatment group.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all treatment-emergent AEs, treatment-emergent AEs with Grade 3 or higher, treatment-emergent study drug-related AEs, and treatment-emergent study drug-related AEs with Grade 3 or higher will be summarized by PT only, in descending order of total frequency. Preferred terms with the same total frequency will be sorted in alphabetical order. Treatment-emergent AEs and study-drug related treatment-emergent AEs will also be summarized by highest grade.

Data listings will be provided for the following:

- All AEs
- Study-Drug-Related AEs
- AEs with severity of Grade 3 or higher
- SAEs

- Study-Drug-Related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-participant listing for laboratory test results will be provided by study part and participant ID number and visit in chronological order for hematology, coagulation, and serum chemistry separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the DAIDS Grading Scale will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. For glucose, only assessments under fasting status will be summarized.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0, which is not included in the DAIDS table, will be used to includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

Treatment-emergent laboratory abnormalities will be summarized for fasting glucose or nonfasting glucose if their baseline values are observed. Maximum postbaseline grade will be summarized for both fasting glucose and nonfasting glucose with or without baseline assessment.

Abnormalities in coagulation parameters will be graded for international normalized ratio (INR) and aPTT.

For INR, prothrombin time (PT) and aPTT, protocol specified toxicity grading scale depends on the upper limit of normal range (ULN). While the ULN of INR and aPTT depends on whether the participant is taking anticoagulant medication or not (ie, Not taking oral anticoagulant: 0.8 - 1.2; Taking oral anticoagulant: 2.0 – 3.0), this information is not collected by the reference laboratory. As a result, INR and aPTT will be graded by assuming the participant is not taking an oral anticoagulant, which is a conservative approach that may lead to over-reporting of abnormalities for INR and aPTT.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by study part, lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 30 after last dosing date.

A by-participant listing of all treatment-emergent laboratory analyses and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by study part and participant ID number and visit in chronological order.

7.3. Vital Signs, SpO_2, and FEV_1

Descriptive statistics will be provided by treatment group for vital signs (heart rate, blood pressure, and respiration rate), SpO_2, and FEV_1 as follows:

- Baseline value
- Values at each postbaseline time point
- Change from baseline at each postbaseline time point

Two types of baseline will be defined for vital signs. An overall baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Day 1 pre-dose baseline is defined the same as the overall baseline. A pre-dose baseline per day for each of dosing days 2-5 will use the "Predose" record on that day as baseline. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the respective baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

Additionally, for FEV_1, the number and percentage of participants with > 15% reduction in FEV1 at 10 minutes postdose compared with the same day predose FEV1 will be summarized by study day through day 5.

Temperature will not be summarized due to different methods of measuring temperature.

A by-participant listing of body weight, BMI, vital signs (heart rate, temperature, blood pressure, and respiration rate), SpO_2, and FEV_1 will be provided by study part, participant ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the Gilead-modified World Health Organization (WHO) Drug dictionary.

Concomitant medications are defined as medications taken while a participant took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each study part and treatment group. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drug) will be provided in a listing sorted by study part and participant ID number and administration date in chronological order.

7.5. Electrocardiogram Results

ECG was performed at baseline only. A listing for ECG assessment results will be provided by study part and participant ID number.

7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study.

Although not necessarily related to safety, a listing of all comments received during the study on the comments form will be provided by study part, participant ID number, and form for which the comment applied.

7.7. Changes from Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSES

In Part A and B, sparse plasma PK will be collected at Day 1 (end of nebulization, CCI [redacted]) and Day 3 (predose and end of nebulization). CCI [redacted] Descriptive statistics (n, mean, SD, coefficient of variation [%CV], minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI) will be presented for plasma concentration and parameter data. For concentration values BLQ, the number of participants with values of BLQ will be presented.

In study Part C, sparse plasma PK will be collected at Days 3 and 5 (predose). A single anytime PK sample will be collected on Day 7.

The following tables will be provided for Remdesivir, GS-704277 and GS-441524 by visit day and nominal timepoint in Parts A and B. CCI [redacted]

[redacted]

[redacted]

9. REFERENCES

10. SOFTWARE

SAS® Software Version 9.4 SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessments

Appendix Table 1. Study Parts A and B: Study Procedures Table

Schedule of Assessments	Screening	TREATMENT PERIOD					FOLLOW-UP PERIOD		
		Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14 (± 3 days)	Day 28[b] (± 5 days)
Obtain Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Documentation of SARS-CoV-2	X								
ECG[c]		X							
Complete or Symptom-Directed Physical Examination	X	X	X	X	X	X	X	X	
Body Weight	X								
Height	X								
Vital Signs (Heart Rate, Temperature, Blood Pressure), SpO_2	X	X	X	X	X	X	X	X	
Completion of Daily Adapted FLU-PRO© Questionnaire[d]		X	X	X	X	X	X	X	
Chest X-Ray[e]		X							
FEV_1		X	X	X	X	X			
Safety Laboratory Assessments (Hematology, Chemistry, Coagulation)		X		X		X	X	X	
Pregnancy Test (Urine)	X								
Serum FSH Test[f]	X								
Nasopharyngeal and Oropharyngeal Swabs and Saliva Samples for SARS-CoV-2 RT-qPCR Testing and Possible Viral Resistance Testing		X	X	X	X	X	X	X	
Sparse Plasma PK Assessments[g]		X		X					
CCI									

Schedule of Assessments	Screening	TREATMENT PERIOD					FOLLOW-UP PERIOD		
		Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14 (± 3 days)	Day 28[b] (± 5 days)
CCI									
Inhaled Remdesivir for Injection Formulation or PTM Administration[j]		X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; FEV_1 = forced expiratory volume in the first second of expiration; FLU-PRO© = InFLUenza Patient-Reported Outcome; FSH = follicle-stimulating hormone; PCR = polymerase chain reaction; PK = pharmacokinetic(s); RT-qPCR = quantitative reverse transcriptase polymerase chain reaction; RDV = (remdesivir, GS 5734™); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation as measured by pulse oximetry

a If the screening and Day 1 visits occur on the same day, no procedures need to be repeated.
b Day 28 assessments may be completed by telephone.
c ECG will not be required at screening. However, ECG should be performed prior to dosing on Day 1. If subject randomizes and doses on the same day as screening, then ECG will be done at screening.
d Adapted FLU-PRO© questionnaire is to be completed daily (Days 1-14).
e Chest x-ray will be performed at Day 1. If screening visit and Day 1 are the same day, chest x-ray does not need to be repeated if completed as SOC < 2 days before screening.
f Serum FSH test: Childbearing female participants who are not postmenopausal (see Protocol Appendix 5 who do not wish to follow protocol defined contraception will need a serum FSH test (FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)
g Sparse plasma PK will be collected at Day 1 (end of nebulization, CCI) and Day 3 (predose and end of nebulization).
h [redacted]
j Inhaled Remdesivir for Injection formulation will be administered to participants at the site under close supervision. Healthcare professionals administering inhaled Remdesivir for Injection formulation should have the appropriate medication available for immediate use in case of hypersensitivity. The participant should be treated according to the SOC for management of hypersensitivity reaction. After dose administration, monitoring should be done as follows: Approximately 30 minutes post dose administration, participants should be observed, and vital signs should be performed prior to discharge.

Appendix Table 2. Study Part C: Study Procedures Table

		TREATMENT PERIOD					FOLLOW-UP PERIOD		
Schedule of Assessments	**Screening[a]**	**Day 1[b]**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7**	**Day 14[c] (± 3 days)**	**Day 28[c] (± 5 days)**
Obtain Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Documentation of SARS-CoV-2[d]	X								
Complete or Symptom-Directed Physical Examination	X	X		X		X	X		
Body Weight	X								
Height	X								
Vital Signs (Heart Rate, Temperature, Blood Pressure), SpO_2	X	X		X		X	X		
Completion of Daily Adapted FLU-PRO© Questionnaire[e]		X	X	X	X	X	X	X	
FEV_1		X	X	X	X	X			
Safety Laboratory Assessments (Hematology, Chemistry, Coagulation)		X		X		X	X		
Pregnancy Test (Urine)	X								
Serum FSH Test[f]	X								
Nasopharyngeal and Oropharyngeal Swabs and Saliva Samples for SARS-CoV-2 RT-qPCR Testing and Possible Viral Resistance Testing		X		X		X	X		

Schedule of Assessments	Screening[a]	TREATMENT PERIOD					FOLLOW-UP PERIOD		
		Day 1[b]	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14[c] (± 3 days)	Day 28[c] (± 5 days)
Sparse/Single Plasma PK Assessments[g]				X		X	X		
Remdesivir for Inhalation Solution Formulation or PTM Administration[h]		X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; FEV_1 = forced expiratory volume in the first second of expiration; FLU-PRO© = InFLUenza Patient-Reported Outcome; FSH = follicle-stimulating hormone; PCR =polymerase chain reaction; PK = pharmacokinetic(s); RT-qPCR = quantitative reverse transcriptase polymerase chain reaction; RDV = (remdesivir, GS 5734™); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation as measured by pulse oximetry

a Study visits, with the exception of the screening visit, may be performed in-clinic or at the participant's home via home health and/or telehealth, virtually or remotely, as permitted by local and institutional regulations.
b If the screening and Day 1 visits occur on the same day, no procedures need to be repeated.
c Days 14 and 28 assessments may be completed by telephone.
d Documentation of SARS-CoV-2 infection first confirmed by nucleic acid testing or direct antigen testing with sample collected ≤ 4 days prior to randomization
e Adapted FLU-PRO© questionnaire is to be completed daily (Days 1-14).
f Serum FSH test: Childbearing female participants who are not postmenopausal (see Protocol Appendix 5) who do not wish to follow protocol defined contraception will need a serum FSH test (FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)
g Sparse plasma PK will be collected at Days 3 and 5 (predose). A single anytime PK sample will be collected on Day 7 visit.
h Remdesivir for Inhalation Solution formulation may be administered to participants in the participant's home with in-person or telehealth support. For participants with pre-existing pulmonary conditions (ie, COPD or asthma) enrolled in Part C of the study, prescribed inhalers may not be used ≤ 30 minutes prior to Remdesivir for Inhalation Solution formulation administration. Healthcare professionals overseeing Remdesivir for Inhalation Solution formulation therapy remotely will observe the participant for any signs of adverse event. If any adverse event is observed and cannot be managed remotely, appropriate urgent care measures will be implemented. Approximately 30 minutes after dose administration, participants should be observed remotely prior to telehealth support session concluding.

Appendix 2. Programming Specifications

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

   Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

   a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

   b) Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   c) Divide the result in (b) by 12,

   AGE = the integer of the result in (c),

   Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened participants refer to all participants who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same participant is counted only once.

3) Screen failure participants are the participants who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the participant was consented to.

4) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the participant is randomized (ie, participant with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if participant took at least 1 dose of study drug and assigned as blank if the participant was never dosed.

6) In the disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

7) Body mass index (BMI)

   BMI will be calculated only at baseline as follows:

   — BMI = (weight [kg]) / (height [meters]^2)

   Baseline height and weight will be used for this calculation if available.

8) For demographics tables, "Not Permitted", "Unknown", or missing categories will be excluded from percentage for detailed race categories summary (i.e. race categories collected on eCRF). For combined Race category (e.g. Asian, White, Black, Other), "Not Permitted" is included in "Other" and "Other" will be include in the count of percentage.

9) TEAE

Events with Missing Onset Day and/or Month

An event is considered treatment emergent if all of the following 3 criteria are met:

i. The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug, and

ii. The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and

iii. End date is as follows:

The (complete) end date is on or after the first dose date, or

The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or

End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the 3 criteria specified above.

10) The precision in reporting numerical values should be as follows:

Raw measurements will be reported the same as the data captured electronically or on the eCRF for all.

Standard deviation and standard error will be reported to one more significant decimal place than the raw measurement.

Mean, median, minimum, Q1, Q3, and maximum will be reported to the same number of decimal places of the raw measurements.

Exceptions may be considered; for example, if more than 4 significant digits are provided for the measurement.

Precision for derived parameters will be kept as 8 decimals and in listings 2 decimals will be kept.

Precision for derived parameters as follows:

Parameters	Decimal Places
log 10 of SARS-CoV-2 viral load	2
Time-weighted average change in SARS-CoV-2 viral load	2
BMI	2

11) Last dose date is not expected to be missing. However, if last dose date is missing, it will be imputed using the maximum of non-missing, non-zero dose, study drug start and stop dates.

12) Incomplete death dates will be imputed as the maximum of the study drug start dates (lasfdt), study drug end dates (lasldt), clinic visit dates (lvis28dt), laboratory visit dates (llab28dt), including the 28-day follow-up visit date plus 1, ie dthdt = max(lasfdt,lasldt,lvis28dt,llab28dt) + 1.

13) Censoring rules

Time to hospitalization: If a participant prematurely discontinues from the study prior to Day 28 or the hospitalization status is missing, the participant is censored at last study date or day 28 whichever is earlier.

Time to negative SARS-CoV-2 viral load, participants are censored at the last assessment day and participants are required to have at least one postbaseline assessment to be included in the analysis.

Time to alleviation of baseline COVID-19 symptoms:

- For overall baseline symptom alleviation, participants are censored at the last assessment day that at least one of the baseline symptoms were assessed.
- For baseline symptom alleviation for each domain, participants are censored at the last assessment day that at least one of the baseline symptoms within that domain were assessed.

14) For 95% CI of KM%, log-log transformation method is adopted.

15) Hazard ratio for time to alleviation

The following SAS code will be used to compute hazard ratio (HR) and its 95% CI:

```
proc phreg;
class trt01pn;
model days*censor(0) = trt01pn / rl;
run;
```

16) Graded Laboratory Abnormalities Summary

The following labels will be used for laboratory abnormalities and Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Lymphocytes	Decrease	Lymphocytes (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Creatinine Clearance	Decrease	Creatinine Clearance (Decreased)
	Direct Bilirubin	Increase	Direct Bilirubin (Hyperbilirubinemia)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose	Decrease	Serum Glucose (Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	Prothrombin Intl. Normalized Ratio (Increased)
	Activated partial thromboplastin time (aPTT)	Increase	Activated partial thromboplastin time (Increased)
	Prothrombin Time (PT)	Increase	N/A

17) The first Part B participant was screened on Oct 29, 2020 and the first Part C participant was screened on Jan 24, 2021. Screen failure participants of each study part is derived from scrndt,

```
if part='' then do;
  if .< scrndt <29Oct2020 then part='Part A';
    else if scrndt >= 29Oct2020 & scrndt <24Jan2021 then part='Part B';
    else part='Part C';
end;
```

18) SARS-CoV-2 viral load from nasopharyngeal and oropharyngeal swabs and saliva samples were to be collected. SARS-CoV-2 viral load in nasopharyngeal and oropharyngeal swabs and saliva samples will be analyzed separately.

   a) For numeric SARS-CoV2 summary (e.g, mean viral load, change from baseline etc.), "Inconclusive" SARs-CoV2 result is set to missing.

   b) For categorical SARS-CoV2 summary, 3 categories will be included, i.e. Positive, Inconclusive, and Negative.

      i) Positive = any numeric result or "<LLOQ SARS-CoV2 detected" - LLOQ could vary by sample type

      ii) Negative = "No SARS-CoV2 detected"

      iii) Inconclusive = "Inconclusive"

   c) For Negative SARS-CoV2 confirmation, "Inconclusive" SARs-CoV2 result will not be considered as missing thus a "Negative" followed by a "Inconclusive" is NOT confirmed.

   d) 2 negative results from the same day do not equal confirmation.

   e) If last PCR sample is negative for participants completed the study or for participant withdrawn early from the study, then one negative PCR of last sample is considered as confirmed negative.

   f) Categorical SARS-CoV2 and SARS-CoV2 negative summary will be separated out by sample type. There will be no combined positive or negative category using 2 or more sample types.

19) SAS code for ANCOVA analysis of DAVG:

```
ods output ParameterEstimates=out1 LSMeans=out2 LSMeanCL=out3
LSMeanDiffCL=out4;

proc glm data=dat1 plots=none;
  class trt01pn;
  model DAVG = trt01pn base / solution;
  lsmeans trt01pn / stderr cl pdiff;
run;
ods output close; quit;
```

20) Symptom scores in the FLU-PRO questionnaire raw data start from 1 to n (total number of responses in a question), while in the FLU-PRO user manual, symptom scores start from 0. In the analysis dataset, symptom scores will be re-mapped to match the scoring in the FLU-PRO user manual for proper calculation of total score and domain score.

21) FLU-PRO Total and Domain Score:

The presence and severity of influenza signs and symptoms are assessed across 7 body systems affected by influenza: Nose (4 items), Throat (3 items), Eyes (3 items), Chest/Respiratory (7 items), Gastrointestinal (4 items), Body/Systemic (11 items), and Sense (2 items). For 29 of the items, the severity scale is as follows: 0 ("Not at all), 1 ("A little bit"), 2 ("Somewhat"), 3 ("Quite a bit"), and 4 ("Very much"). For 5 items, severity is assessed in terms of frequency, i.e., vomiting or diarrhea (0 times, 1 time, 2 times, 3 times, or 4 or more times); with frequency of sneezing, coughing, and coughed up mucus or phlegm evaluated on a scale from 0 ("Never") to 4 ("Always"). For 2 items, severity is assessed as 0 ("No") or 1 ("Yes").

Domain	Items	Scoring	Minimum Data Requirement
Nose	Runny or dripping nose Congested or stuffy nose Sneezing Sinus pressure	Arithmetic mean of 4 items within **Nose** domain	Daily score for 3 of 4 items must be present to calculate domain score
Throat	Scratchy or itchy throat Sore or painful throat Difficulty swallowing	Arithmetic mean of 3 items within **Throat** domain	Daily score for 2 of 3 items must be present to calculate domain score
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	Arithmetic mean of 3 items within **Eyes** domain	Daily score for 2 of 3 items must be present to calculate domain score
Chest/Respiratory	Trouble breathing Chest congestion Chest tightness Dry or hacking cough Wet or loose cough Coughing Coughed up mucus or phlegm	Arithmetic mean of 7 items within **Chest/Respiratory** domain	Daily score for 5 of 7 items must be present to calculate domain score
Gastrointestinal	Felt nauseous Stomach ache How many times did you vomit? How many times did you have diarrhea?	Arithmetic mean of 4 items within **Gastrointestinal** domain	Daily score for 3 of 4 items must be present to calculate domain score
Body/Systemic	Headache Head congestion Felt dizzy Lack of appetite Sleeping more than usual Body aches or pains Weak or tired Chills or shivering Felt cold Felt hot Sweating	Arithmetic mean of 11 items within **Body/Systemic** domain	Daily score for 8 of 11 items must be present to calculate domain score

Domain	Items	Scoring	Minimum Data Requirement
Sense*	Loss Smell Loss Taste	Arithmetic mean of 2 items within **Sense** domain	Daily score for 1 of 2 items must be present to calculate domain score
Total	All above 34 items	Arithmetic mean of all 34 items within FLU-PRO	In the presence of missing data, the above conditions for the calculation of all domain scores must be met in order to calculate the FLU-PRO total score.

* Newly added for COVID-19.

22) Symptom alleviation and time to baseline symptom alleviation

1. Baseline symptoms: Baseline symptoms are the symptoms at day 1 and score ≥1.
   - Item 1 to 34 of the FLUPRO are symptoms. Global assessments (last 6 items in the questionnaire) are not symptoms.
   - Each subject's baseline symptoms including number of symptoms likely are different.
   - For alleviation of baseline symptoms, only need to follow the symptoms presented (≥1) at day 1
     - If a participant has 5 baseline symptoms, only the 5 symptoms will be followed to derive alleviation.
     - If a symptom (e.g. coughing) is not one of the baseline symptoms and has a score >1 post baseline, the symptom will not be considered to derive the subject's baseline symptom alleviation.
     - If participant has no symptom ≥1 at baseline, alleviation status for the participant is missing for all visit.
     - If Day 1 symptoms ≥1 symptoms from Day 2 and later are all missing, the alleviation status for the symptom is missing for all visits.
2. Alleviation of a symptom:
   - Symptom scored as 2 or higher at baseline are scored as 0 or 1 at postbaseline
   - Symptom scored as 1 at baseline are scored as 0 at postbaseline
   - for two consecutive days - need to be confirmed with 2 visits
     - one missing day between two visits (that meets the alleviation definition) is allowed, but 2 or more days of missing is not considered reach alleviation
     - for Day 14 (or last assessment on Day x), if the symptom meets definition of alleviation, and day 13 (or Day x -1) also meets the definition of alleviation, then it is considered as confirmed. One missing day is allowed for the confirmation of Day 14 or last assessment, i.e if day 13 (or Day x-1) is missing and Day 12 (or Day x-2) meets the definition of alleviation, then it is considered as confirmed.

Examples:

	Day														Alleviation for a symptom on day	
Example	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
1	2	2	2	1	1	1	0	0	0	0	0	0	0	0	4	baseline 2 or higher needs to be 1 or 0
2	2	2	2	0	1	1	0	0	0	0	0	0	0	0	4	baseline 2 or higher needs to be 1 or 0
3	2	2	2	0	2	1	1	0	0	0	0	0	0	0	6	day 4 is not confirmed
4	3	2	2	1	1	1	0	2	1	1	0	0	0	0	4	still on day 4 if worsen after confirmation
5	1	1	1	0	0	0	1	0	1	1	0	0	0	0	4	Worsening on day7
6	1	1	1	1	0	0	0	0	0	0	0	0	0	0	5	baseline 1 needs to be 0
7	2	2	2	1	.	1	0	0	0	0	0	0	0	0	4	allow one missing
8	2	2	2	1	.	.	1	1	.	0	0	0	0	0	*7*	*day 4 is not confirmed if there are two or more days' response missing, re-start the check for confirmation*
9	2	2	2	2	2	2	2	2	4	2	2	2	2	1	*14*	*censor*
10	2	2	2	2	2	2	2	2	2	2	2	2	1	.	*13*	*censor*
11	2	2	2	2	2	2	2	2	2	2	2	2	1	1	13	*Confirmed on day 13 and 14*
12	2	2	2	2	2	2	2	2	1	.	.	.	.	.	9	*censor*
13	2	2	2	2	2	2	2	2	1	1	.	.	.	.	9	*Confirmed on day 9 and 10*

Yellow –Confirmed alleviation, Tan – Not confirmed, Blue - Worsening

3. Alleviation of baseline symptoms for a participant

   The alleviation status for a participant at each visit is

   - Yes, if all confirmed baseline symptom alleviation status are Yes.
   - if > 25% of symptoms are missing, then alleviation status is No, else ignore missing.
   - No, if any baseline symptom alleviation status is No.

4. Tim to alleviation of baseline symptoms

   First day of participant level alleviation status equals Yes. If a participant has not achieved symptom alleviation at last FLUPRO assessment, the participant will be censored at the date of last FLUPRO assessment. For symptom alleviation of a domain, the last assessment date is only among those baseline symptoms within the domain.

23) Covid-19 medications include: Chloroquine, Hydroxychloroquine, IV remdesivir, Bamlanivimab, Casirivimab/Imdevimab, Molnupiravir, Lopinavir-ritonavir, and Ribavirin.

   Additional medication may be included during final review of Concomitant medications prior to data finalization and documented in a separate programming specification.

24) Glucose

   Fasting is not required per protocol for collecting Glucose sample, mixed fasting Glucose and non-fasting Glucose results are presented in the dataset. Lab abnormality for Glucose will be summarized as follows:

   — if fasting glucose is collected at baseline, max TE lab toxicity grade is selected for post-baseline fasting glucose, max post-baseline toxicity grade (i.e. not TE toxicity grade) is selected for the post-baseline glucose regardless fasting status.

   — if non-fasting glucose is collected at baseline, TE lab toxicity grade is selected for post-baseline non-fasting glucose, max post-baseline toxicity grade is selected for the post-baseline glucose regardless fasting status.

   — Max TE lab toxicity grade for fasting glucose and non-fasting glucose, max post-baseline toxicity grade for fasting glucose and non-fasting glucose will be summarized separately in the lab abnormality table.

   — In the any TE lab toxicity section of the lab abnormality table, max post-baseline toxicity grade will be included.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	07-Jun-2021 15:06:42
PPD	Clinical Research eSigned	07-Jun-2021 19:02:43