STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multi-Center Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in Hematopoietic Cell Transplant (HCT) Recipients with Respiratory Syncytial Virus (RSV) Infection of the Upper Respiratory Tract
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical (drug class)
AUC	area under the curve
$AUC_{0-\infty}$	area under the (concentration time) curves from time zero to infinity; which corresponds to a calculation of mean concentration levels of a therapeutic agent in the body
AUC_{inf}	area under the (concentration-time) curve from time zero to infinity;
% AUC_{exp}	amount of Area Under the Curve that occurred after the last quantifiable sampling time point
BLQ	below the limit of quantification
BMI	body mass index
C_{last}	concentration at the last observed time point
C_{tau}	concentration for a dosing interval
C_{max}	maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CI	confidence interval
CL/F	apparent total clearance of drug from plasma after oral administration
CSR	clinical study report
DAVG	difference between time-weighted average post-baseline and baseline
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report forms
EOT	end of treatment
FAS	Full Analysis Set
FLU-PRO	patient-reported outcome (PRO) measure to standardize the assessment of influenza (FLU) symptoms in clinical studies
HCT	hematopoietic cell transplant
HLT	high level term
HLGT	high level group term
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	identification
IMP	investigational medicinal product
IWRS	Interactive Web Response System
λ_z	terminal disposition rate constant/terminal rate constant
LLOQ	lower limit of quantification
LLT	lower level term
LRTC	lower respiratory tract complication
LRTI	lower respiratory tract infection
MedDRA	medical dictionary for regulatory activities

ml	milliliter
MMRM	mixed-effect model with repeated measures
PD	pharmacodynamics
PK	pharmacokinetics
PP	Per Protocol
PT	preferred term
Q1	first quartile
Q3	third quartile
RT-qPCR	quantitative real time polymerase chain reaction
RSV	respiratory syncytial virus
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
t_{last}	time of last measurable concentration
t_{max}	time to reach maximum (peak) plasma concentration following drug administration
$t_{½}$	an estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural logarithm of 2 by the terminal elimination rate constant (λz)
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULOQ	Upper limit of quantification
URTI	upper respiratory tract infection
VR	ventricular rate
WHO	World Health Organization

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-218-0108. This SAP is based on the study protocol amendment 7 dated 28 March 2016 and the electronic case report forms (eCRF) for this study. The SAP will be finalized before the database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The co-primary objectives of this study are as follows:

To evaluate the effect of presatovir on RSV viral load and development of lower respiratory tract complication (LRTC) in RSV-positive autologous or allogeneic HCT recipients with acute upper respiratory tract infection (URTI) symptoms

The secondary objectives of this study are as follows:

- To evaluate the effect of presatovir on progression to respiratory failure or all-cause mortality
- To evaluate the pharmacokinetics (PK), safety, and tolerability of presatovir

1.2. Study Design

This is a randomized, double-blind, placebo-controlled study evaluating the effect of presatovir on efficacy, PK, safety, and tolerability in HCT recipients with RSV URTI.

All subjects will be permitted to receive the standard of care therapy for RSV infection per their local medical practices, in addition to the investigational medicinal product (IMP).

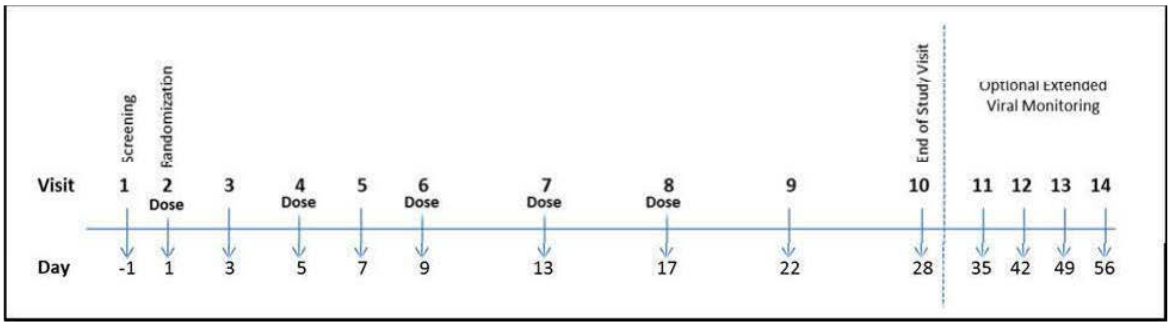
Approximately 200 subjects will be enrolled.

Subjects will be centrally randomized in a 1:1 ratio to receive IMP (presatovir or placebo) and will be stratified by 2 factors:

- Presence or absence of lymphopenia, defined as a lymphocyte count < 200 cells/µL versus ≥ 200 cells/µL of blood
- Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)

A single dose of 200 mg (four 50 mg tablets) of presatovir or placebo will be administered on Study Days 1, 5, 9, 13, and 17. The study will consist of the following visits: screening (Day -1), baseline / randomization/IMP administration (Day 1), PPD Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 7), Visit 6 (Day 9), Visit 7 (Day 13), Visit 8 (Day 17), Visit 9 (Day 22), and end of study (Day 28). PPD

Figure 1-1. Study Visits



1.3. Sample Size and Power

Sample size and power are estimated for the co-primary endpoints with the overall alpha level 0.05 (with alpha = 0.04 allocated to the development of a LRTC and alpha = 0.01 allocated to the time-weighted average change in viral load). The sample size calculations are based on the results observed in a study that evaluated the efficacy of oral and aerosolized ribavirin treatment for preventing progression from upper to lower respiratory tract infection in HCT recipients with RSV infections (unpublished data from Dr. PPD) and published data on currently used antiviral agents for RSV infections. {Shah 2013}

Assuming the time-weighted average change in RSV $\log_{10}$ viral load from Day 1 to Day 9 in the placebo group will be -1 $\log_{10}$ copies/mL, with a standard deviation (SD) of 2, 100 subjects per treatment group will provide over 80% power to detect at least 1 $\log_{10}$ decrease in presatovir group using a 2-sided significance level of 0.01.

Assuming that 30% of subjects in placebo arm will develop a LRTC, 100 subjects per treatment group will provide over 90% power to detect at least 20% reduction in the proportion of LRTC in presatovir group with a 2-sided significance level of 0.04.

Using the fallback approach and the above assumptions for the co-primary endpoints, 100 subjects per arm will provide > 95% power to declare statistical significance in either change in viral load or proportion of subjects with LRTC.

Based on an administrative review of the data occurring in mid-September 2017, Gilead decided to halt the study on 20September2017 at an enrollment of 189 subjects despite the study not achieving complete enrollment of 200 subjects. The decision was made because enrollment of the remaining 11 subjects would have had minimal impact on study outcomes.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analysis

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of safety data in order to protect subject welfare and preserve study integrity. The DMC is to recommend to the sponsor whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications.

Three safety reviews are expected to be required after approximately 25%, 50%, and 75% of the planned 200 subjects are enrolled and complete Day 28 visit or discontinue the study. The regularity of such reviews may also be determined by enrollment rates and evidence of potential safety concerns. Additional reviews may be conducted at the request of the DMC or the sponsor. At each review, all available safety data will be summarized and evaluated.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2. Efficacy Interim Analysis

Three efficacy interim analyses are currently planned for administrative purposes by the internal Gilead staff. These analyses will be performed when approximately 25%, 50% and 75% of the planned 200 subjects are enrolled and complete Day 28 of the study, respectively. A Haybittle-Peto boundary will be used for the alpha spending with an overall alpha of 0.00001 for each interim analysis and overall alpha of 0.05 for the final analysis.

This study will not be stopped early for efficacy based on the interim efficacy analysis results. The purpose of these analyses is to obtain an early assessment of the effect of presatovir. The interim efficacy results will aid internal decision-making on the further development of the presatovir program. If the results are sufficiently positive or informative, the data may be used to plan other Phase 2 and 3 studies, to seek guidance from FDA on the program development in the different subject populations, including the partial clinical hold for the pediatric program.

A Gilead Executive Team including the Vice President (VP) of Clinical Research and the VP of Biometrics will review the unblinded interim efficacy analysis results. Based on this information, the GSI Executive Team will make a decision on whether the results are informative to use in the planning of other Phase 2 and 3 studies, whether to include the results in the response to the FDA on the partial clinical hold for the pediatric program. A GSI unblinded team that is independent of the GS-US-218-0108 Study Team may be formed to support the decisions of the GSI executive team, if needed. This unblinded team will include representatives from Gilead Clinical Research, Biometrics, Regulatory Affairs, and Medical Writing groups who are not directly associated with Study GS-US-218-0108.

The GS-US-218-0108 Study Team will remain blinded to treatment assignments throughout the trial until all subjects have completed the planned study visits and the database has been locked and unblinded.

As of the finalization of this SAP, 2 efficacy interim analyses have been performed in May 2016 and September 2017 after 25% and 75% of the subjects enrolled. An alpha level of 0.00001 was used at each interim analysis using the Haybittle-Peto boundary, and the final analysis will be performed at a 0.05 level of significance.

2.3. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved, and the database has been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

The efficacy analysis of the co-primary and secondary endpoints will be conducted at the overall significance level of 0.05. The fallback procedure {Wiens 2005} will be applied to test the co-primary and secondary endpoints sequentially as described in Section 3.5.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before the study blind is broken for analysis. 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 subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

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

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized in the study.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who took at least 1 full dose of study drug, and had an RSV viral load greater than or equal to the lower limit of quantification (LLOQ) of the RT-qPCR assay in the Day 1 nasal sample, as determined by RT-qPCR at the central lab. This is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set

The Per-Protocol (PP) Analysis Set includes subjects in the FAS who meet the following criteria:

- Did not violate any major inclusion criteria (IC) or exclusion criteria (EC)
  - IC: Received an autologous or allogenic HCT
  - IC: Documented RSV-positive ≤ 6 days prior to Day 1
  - IC: Had respiratory symptoms ≤ 7 days prior to Day
  - IC: Had evaluable baseline chest image (ie, had evidence of new abnormalities consistent with LRTI on chest X-ray; had chest X-ray taken ≤ 48 hours prior to screening)
- Did not have IMP overdose that resulted in an AE
- Did not take invalid (expired, damaged, quarantined, improperly stored, etc) drug
- Was not dispensed incorrect study drug (wrong bottle, drug from another study, etc)

- Missed < 1 dose within the first 9 study days
- Missed < 3 nasal swabs over the course of the study
- Did not receive any prohibited concomitant medications

The specific classification of subjects to be included in the PP analysis set will be finalized prior to database lock. Subjects will be grouped according to the treatment they actually received. This analysis set is to be used for sensitivity analysis of the co-primary and secondary endpoints.

3.1.4. Safety Analysis Set

The Safety Analysis Set includes subjects who received at least 1 dose of study medication. This is the primary analysis set for safety analyses.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all subjects who have been administered at least 1 dose of investigational drug and have at least 1 nonmissing postdose concentration value for presatovir in plasma. This is the primary analysis set for PK summary tables and figures.

PK Substudy Set includes subjects in the PK Analysis Set who elect to participate in extensive PK sampling at the time of informed consent.

3.2. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the PP and Safety Analysis Sets, subjects will be grouped according to the randomized treatment except when their actual treatment differs from randomized treatment for the entire treatment duration. In this case, subjects will be grouped based on actual treatment received. For the analyses based on the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following parameters:

- Presence or absence of lymphopenia, defined as a lymphocyte count < 200 cells/μL versus ≥ 200 cells/μL of blood
- Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)

For subjects with discrepancies between the stratification factor values at randomization (ie, according to IWRS) and the actual values as documented in the eCRF, the actual strata information will be used in the analyses.

In the situation that there is insufficient data in a stratum, that stratum will be pooled with the adjacent stratum, and no subgroup analysis will be conducted. For example, if there are < 4 subjects with lymphopenia, then these 4 subjects will be combined with the subjects without lymphopenia, and no subgroup analysis will be performed for the stratification factor of "presence or absence of lymphopenia".

Efficacy endpoints will be evaluated using stratification factors as covariates in the analysis models (eg, analysis of covariance [ANCOVA]). If there are not enough subjects within a strata (< 4 subjects in 1 of the strata), the stratification factor will not be included in the analysis models.

For continuous efficacy endpoints, the baseline value of the efficacy variable will be included as a covariate in the analysis model.

3.4. Examination of Subject Subsets

Co-primary and secondary efficacy endpoints will be examined in the following subgroups if there is sufficient sample size in the subgroup:

- Stratification factors:
  - Presence or absence of lymphopenia, defined as a lymphocyte count < 200 cells/μL versus ≥ 200 cells/μL of blood
  - Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)
- Sex (male or female)
- Age group (< 65 or ≥ 65 years)
- Race (white or all other races)

Subgroup analyses for other baseline variables such as type of transplant (autologous vs. allogeneic HCT) may be conducted.

Specified safety analyses will be examined in the following subgroups:

- Sex (male or female)
- Age group (< 65 or ≥ 65 years)
- Race (white or all other races)

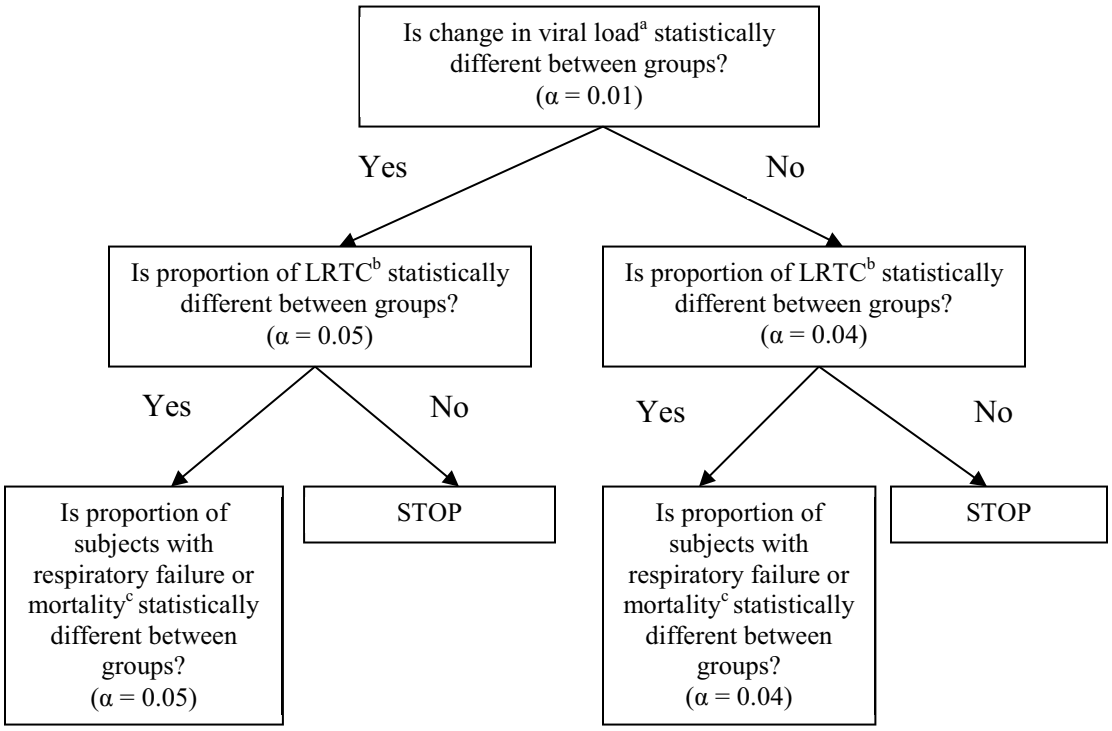
3.5. Multiple Comparisons

This study has 2 co-primary endpoints: the time-weighted average change in RSV $\log_{10}$ viral load from Day 1 to Day 9, and the proportion of subjects who develop a LRTC through Day 28. To control the Type 1 error rate of 0.05 across the co-primary and secondary endpoints, a fallback approach will be applied {Wiens 2005} {Dmitrienko 2008} (see Figure 3-1).

The time-weighted average change in RSV $\log_{10}$ viral load from Day 1 to Day 9 will be tested first at significance level of 0.01. If this null hypothesis (H_{01}) of no difference between the treatment groups is rejected then the proportion of subjects who develop an LRTC (H_{02}) will be tested with significance level of 0.05. Otherwise, the null hypothesis of no difference between treatment groups in the proportion of subjects who develop an LRTC will be tested at significance level of 0.04.

If both of the co-primary null hypotheses (H_{01} and H_{02}) are rejected then the secondary endpoint will be tested at a significance level of 0.05. If only the null hypothesis of no difference between treatment groups in the proportion of subjects who develop an LRTC (H_{02}) is rejected, the secondary endpoint will be tested at a significance level of 0.04. If the hypothesis H_{02} is not rejected then the secondary endpoint will not be tested.

Figure 3-1. Testing of Co-primary and Secondary Endpoints



a Co-primary endpoint: Time-weighted average change in $\log_{10}$ viral load
b Co-primary endpoint: Proportion of subjects who developed LRTC
c Secondary endpoint: Proportion of subjects who either developed respiratory failure (of any cause) requiring mechanical ventilation (invasive or non-invasive) or died prior to or on Day 28

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window

Missing data can have an impact upon the interpretation of the trial data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed.

For laboratory data, a missing baseline value will be replaced with a screening value, if available; otherwise, it will be treated as normal (ie, Grade 0; no toxicity grade) for the summary of graded laboratory abnormalities. A retest value may be used if the first test is invalidated (eg, specimen hemolyzed).

Values will not be imputed for missing vital signs and other safety data. However, a missing baseline value will be replaced with the closest measurement prior to baseline, if available.

Missing viral load data due to premature discontinuation of the study will not be imputed as all available data will be included in the time-weighted average calculations. Intermediate missing viral load data will be imputed using the trapezoidal rule for the time-weighted average calculations, although only viral load data through Day 9 will be included in the primary endpoint calculations. As a sensitivity analysis, mixed-effects model with repeated measures (MMRM) for the absolute values and change from baseline in viral load will be applied. Similar analyses will be performed on FLU-PRO score and O_2 saturation.

All available data for subjects who do not complete the study will be included in the data listings.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process. All data, including outliers, will be included in analyses, unless otherwise specified.

3.7. Data Handling Conventions and Transformations

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within subject. The treatment group to which subjects were randomized (or initially assigned) will be used in the listings.

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with study drug at all, the date when baseline assessment was conducted will be used instead of the first dosing date of study drug. For screen failures, the date when the informed consent was signed will be used for age calculation. If only birth year is collected on the CRF, "01 January" will be used for the unknown birth day and month for the purpose of age calculation, unless age is captured on the CRF.

3.7.1. Data Handling for Efficacy Endpoints

Viral load values below the limit of quantification (BLQ) reported as <LLOQ will be counted as LLOQ-1 in the summaries and order statistics. Viral load values below the limit of detection will be treated as "0". Viral load data will be transformed using the base 10 logarithm before the analyses. In case of zero value, 1 will be added to each viral load measurement before being transformed.

The FLU-PRO score will be calculated as the sum of the scores for all symptoms collected divided by number of symptoms with non-missing score (ie, the number of symptoms collected).

3.7.2. Data Handling for Laboratory Endpoints

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

- A value that is 1 unit less than the LLOQ will be used for calculation of descriptive statistics if the data is reported in the form of "< x" (where x is considered the LLOQ). For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively. However, for direct bilirubin, a value of "< 0.1" will be treated as 0.09 for calculation of summary statistics.

- A value that is 1 unit above the ULOQ will be used for calculation of descriptive statistics if the data is reported in the form of "> x" (where x is considered the limit of quantitation). For example, if the values are reported as > 50 and > 5.0, then values of 51 and 5.1 will be used for calculation of summary statistics, respectively.

- The limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "≤ x" or "≥ x" (where x is considered as the limit of quantitation).

3.7.3. Data Handling for PK Endpoints

Natural logarithm transformation will be used for plasma concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points, where LOQ is corrected for the dilution factor (ie, reported LOQ/dilution factor) for determination of summary and order statistics.

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) will be displayed as "BLQ."

Pharmacokinetic parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Analysis Visit

3.8.1. Definition of Study Day

Study day is the day relative to the date of the first dose of study drug. Study Day 1 will be defined as the day of first dose of study drug administration.

Study day will be derived as follows:

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

3.8.2. Definition of Baseline

In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dose of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered the baseline value.

Baseline for the primary efficacy analysis is defined as the day of the first dose of study medication (Day 1).

Baseline values for other safety and efficacy endpoints are dependent on the schedule of each assessment.

3.8.3. Analysis Visit

Subject visits or measurements might not occur on protocol-specified days or time points. For parameters that will be summarized by visit, the nominal visit as recorded on the eCRF will be used.

For subjects who prematurely discontinue from the study, the results assessed at early termination (ET) will be assigned to the next scheduled visit where the respective data were scheduled to be collected for summary.

Unscheduled visits will not be included in the by-visit summary tables, but will be included in the listings. An unscheduled visit prior to the first dose of study drug may be included in the calculation of baseline value, if applicable.

3.8.4. Selection of Data in the Event of Multiple Records in a Analysis Visit

Depending on the statistical analysis method, single values may be required for each analysis visit. 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 visit.

If multiple nonmissing numeric observations exist in an analysis visit, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If there are multiple records with the same time or no time recorded on the same day, the average (arithmetic or geometric mean, as appropriate) will be used for the baseline value. For the efficacy endpoints, if no measurements occur prior to the time of first dosing of study drug, the first nonmissing value on the first dosing date of study drug will be considered as the baseline value.

- For post-baseline visits:

  — 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.

  — If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

If multiple valid nonmissing categorical observations exist in a window, records will be selected as follows:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected unless otherwise specified.

- For post-baseline visits, 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. If there are multiple records with the same time or no time recorded on the same day, the most conservative value (ie, the worst severity) within the window will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, investigator within a country, and overall. The summary will present the number and percentage of subjects randomized. For each column, the denominator for the percentage calculation will be the total number of subjects randomized for that column.

A similar enrollment table will be provided by randomization stratum and overall. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects within each stratum. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with the IWRS randomization strata that differ from stratification factor data entered in the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and overall. This summary will present the number of subjects screened, the number of subjects randomized, and the number and percentage of subjects in each of the categories listed below:

- Randomized
- Full Analysis Set
- Safety Analysis Set
- Per-Protocol Analysis Set
- Completed treatment with study drug per protocol
- Did not complete study drug treatment with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study
- Completed Extended Viral Load Monitoring Period
- Did not complete Extended Viral Load Monitoring Period with reasons for premature discontinuation of Extended Viral Load Monitoring Period

The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column. The following by-subject listings will be provided by subject ID number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dose date minus first dose date plus 1, regardless of temporary interruptions in study drug administration, and will be expressed in days (recorded to 1 decimal place, eg, 4.5 days). If the last study drug dosing date is missing, the latest study drug end date, clinical visit date, laboratory sample collection date, or vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics (number of subjects [n], mean, SD, median, Q1, Q3, minimum, and maximum), and using the number and percentage of subjects exposed through the following time periods: Day 1 (Baseline), Day 5, Day 9, Day 13, and Day 17. Summaries will be provided by treatment group for the Safety Analysis Set.

Summaries will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided

4.2.2. Adherence to Study Drug

The total number of doses administered will be summarized using descriptive statistics. Adherence is calculated based on the total amount of study drug (mg) administered and the expected amount per protocol:

$$\text{Prescribed Adherence}\,(\%) = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Specified by Protocol}} \right) \times 100$$

Descriptive statistics for adherence (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$ and $\geq 80\%$) will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 entry criterion and the number of subjects who violated specific entry criteria by treatment group based on all enrolled subjects. A by-subject listing will be provided for those subjects who violated at least 1 inclusion or exclusion criterion. The listing will present the entry criterion (or criteria if more than 1 violation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of inclusion/exclusion criteria) will be summarized by treatment group for all Randomization Analysis Set. A by-subject listing will be provided for those subjects with any protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. Age at baseline is calculated in years at the first dosing date of study drug. The summary of demographic data will be provided for the Safety Analysis Set.

In addition, a similar summary table will be provided by stratification factors (ie, presence or absence of lymphopenia and treatment of RSV infection with ribavirin [yes or no] prior to randomization).

A by-subject demographic listing, which includes the date when informed consent was signed, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include stratification factors, body weight (in kg), height (in cm), body mass index (BMI; in kg/m2), RSV types (RSV A or RSV B), vital signs, O_2 saturation, smoking history, RSV viral load, detectable RSV in nasal samples, co-pathogen types, duration of respiratory symptoms prior to the first dosing date, hospitalization status, serum antibody titer to RSV, and FLU-PRO score. These baseline characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. For baseline body weight, height, and BMI, descriptive statistics also will be presented by sex in the same table. In addition, baseline characteristics will be summarized by the consent status of participation in the Extended Viral Load Monitoring (yes or no) and by LRTC occurrence (subjects who did and did not develop LRTC) in a separate table, respectively. The summary of baseline characteristics will be provided for the Safety Analysis Set.

A by-subject listing of the baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

HCT-specific medical history will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. A summary of HCT-specific medical history will be provided for the Safety Analysis Set. No inferential statistics will be generated.

A by-subject listing of medical history (HCT and respiratory conditions) will be provided by subject ID number in ascending order.

General medical history will not be coded, but will be listed only.

6. EFFICACY ANALYSES

6.1. Definition of the Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints of this study are: the time-weighted average change in nasal RSV viral load ($\log_{10}$ copies/mL) from Baseline (Day 1) to Day 9 and the proportion of subjects who develop a LRTC through Day 28.

6.1.1. Time-weighted average change in nasal RSV viral load

The time-weighted average change in nasal RSV viral load ($\log_{10}$ copies/mL) from Baseline (Day 1) to Day 9 as measured by RT-qPCR is defined as:

$$\frac{\sum_{i=a}^{b-1} \{0.5 \times (Y_i + Y_{i+1}) \times (t_{i+1} - t_i)\}}{(t_b - t_a)}$$

where Y_i is the change from Baseline in RSV $\log_{10}$ viral load at Visit i, t is the time at the specified timepoint (the actual study day) , a is the baseline assessment at Day 1, and b is the last assessment at or prior to Day 9 visit.

The time-weighted average change, often referred to as the DAVG, provides the average viral burden change from baseline.

6.1.2. Proportion of subjects who develop a LRTC through Day 28

The proportion of subjects who develop a LRTC through Day 28, defined as 1 of the below, will be adjudicated by an Endpoint Adjudication Committee (EAC).

- Primary RSV LRTI
- Secondary bacterial LRTI
- Lower respiratory tract infection due to unusual pathogens
- Lower respiratory tract complication of unknown etiology

The EAC will review related clinical data to determine whether a LRTC has developed. The EAC's role and responsibilities and the data to be provided to the EAC are described in a mutually agreed upon EAC charter. The EAC charter defines the EAC membership, adjudication process, meeting logistics, and meeting frequency.

6.2. Statistical Hypotheses for the Co-Primary Efficacy Endpoints

The co-primary analyses will test for superiority the 2 null hypotheses in the following sequence:

- H_{01}: There is no difference between presatovir and placebo in the time-weighted average change in RSV $\log_{10}$ viral load from Day 1 to Day 9

- H_{02}: There is no difference between the presatovir and placebo treatment groups in the proportion of subjects who develop an LRTC through Day 28.

The co-primary endpoint analyses will be performed on FAS.

6.2.1. Time-Weighted Average Change in Nasal RSV Viral Load

The treatment difference in the time-weighted average change from Baseline (Day 1) to Day 9 in nasal RSV viral load ($\log_{10}$ copies/mL) will be analyzed using a parametric ANCOVA with the baseline viral load ($\log_{10}$ copies/mL) and stratification factors as covariates in the model. The test will be 2-sided with the significance level of 0.01. Nonparametric methods such as rank-based ANCOVA models or Wilcoxon rank sum tests may be implemented for exploratory purposes.

Adjusted means for each treatment group, 99% confidence interval (CI), and descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) will be presented in the descriptive summaries. Missing viral load data will be handled using the method described in Section 3.6.

6.2.2. Proportion of Subjects Who Develop a LRTC through Day 28

The proportion of subjects who develop a LRTC through Day 28 will be analyzed using a 2-sided Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. The significance level used for the analysis (eg, 0.04 or 0.05) will be determined based upon the decision to reject the null hypothesis of the other co-primary endpoint as described in Section 3.5. The 2-sided 95% CI for the odds ratios between the 2 treatment groups will be constructed based on stratum-adjusted Mantel-Haenszel proportions.

The numbers and percentages of subjects who develop a LTRC through Day 28 will be provided with 95% CIs for the percentages based on the Clopper-Pearson method {Clopper 1934}.

The final analysis will be performed when all randomized subjects either complete Day 28 assessments or discontinue study prematurely.

The analyses of the co-primary endpoints will be repeated using the PP analysis set.

The primary efficacy analyses will also be repeated for the subgroups specified in Section 3.4, including the stratification factors (presence or absence of lymphopenia, treatment of RSV infection with ribavirin [yes or no] prior to randomization, sex, race, age group [< 65 or ≥ 65], type of transplant [autologous HCT or allogeneic HCT]. Adjusted mean and 95% CI will be presented by treatment group for exploratory purposes.

In addition, the effect of various baseline characteristics on the primary outcomes, including the type of transplant, will be explored using regression models with the baseline characteristics included as effects in the model for a sensitivity analysis.

6.3. Secondary Efficacy Endpoints

6.3.1. Definition of Secondary Efficacy Endpoint

Secondary efficacy endpoint is the proportion of subjects who develop respiratory failure requiring mechanical ventilation or died from any cause through Day 28.

Subject will be considered to have an event if either condition is met if subject develops:

- A respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) or
- All-cause mortality through Day 28.

6.3.2. Analysis Methods for Secondary Efficacy Endpoint

A sequential fallback testing procedure described in Section 3.5 will be used to control the overall Type 1 error rate of 0.05 across the primary and secondary endpoints.

The FAS analysis set will be used for all summaries and analyses of the secondary endpoint. Treatment groups will be compared using a 2-sided test.

The proportion of subjects who develop respiratory failure requiring mechanical ventilation or all-cause mortality through Day 28 will be analyzed using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. The 2-sided 95% CI for the odds ratios between the 2 treatment groups will be constructed based on stratum-adjusted Mantel-Haenszel proportions.

If the number of events is small then the exact method will be applied.

The numbers and percentages of subjects who meet the secondary endpoint criteria, who develop respiratory failure requiring mechanical ventilation and who have all-cause mortality through Day 28 will be provided. The 95% CIs for the percentages will be calculated using the Clopper-Pearson method {Clopper 1934}.

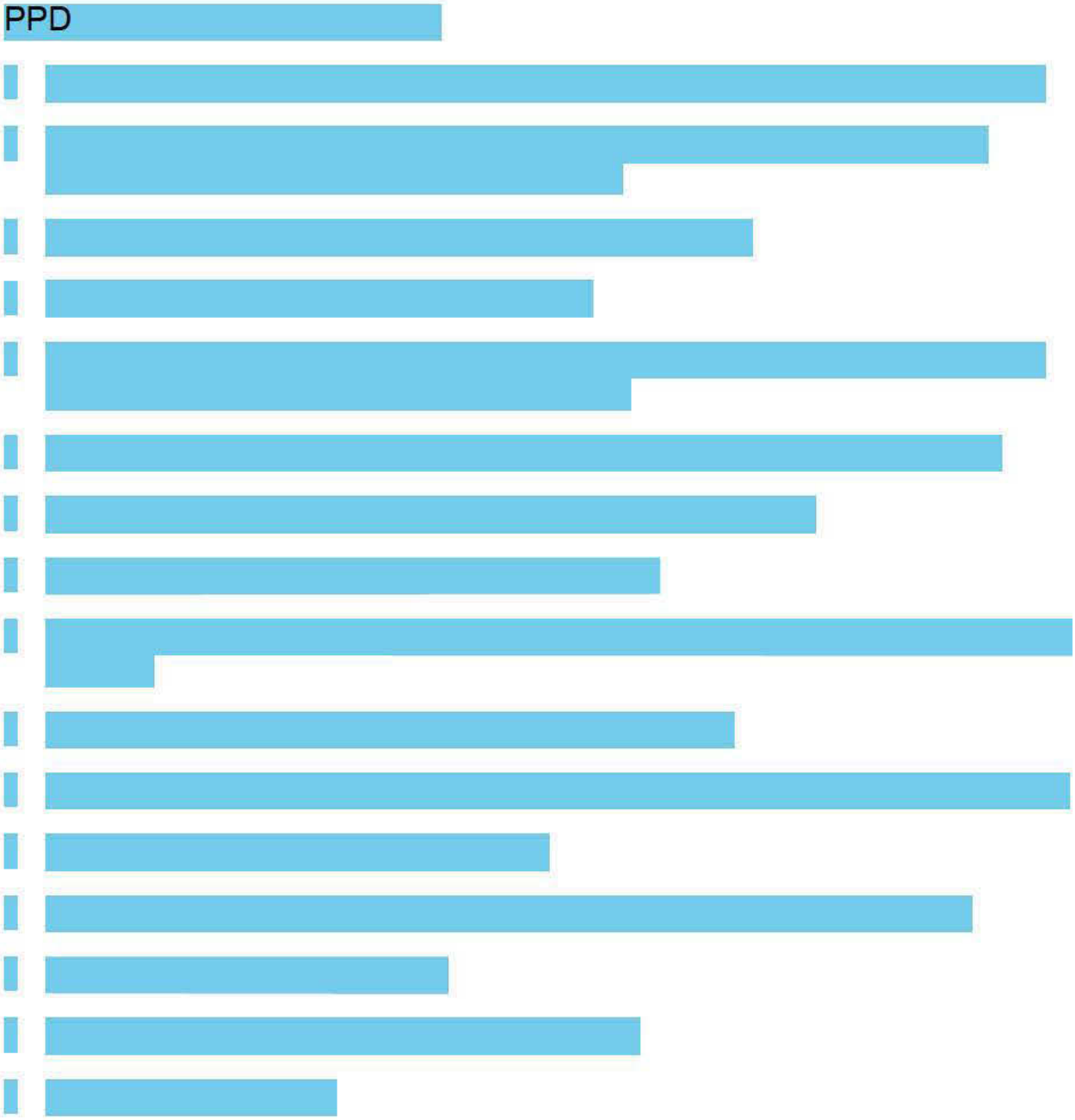
6.3.3. Sensitivity Analysis for Secondary Efficacy Endpoint

Sensitivity analyses of the secondary efficacy endpoint, the proportion of subjects who develop respiratory failure requiring mechanical ventilation or all-cause mortality through Day 28, will be performed in the PP analysis set.

6.4. Exploratory Efficacy Endpoints

6.4.1. Definition of Exploratory Efficacy Endpoints

PPD



6.4.2. Analysis Methods for Exploratory Efficacy Endpoints

PPD


PPD

6.5. Changes From Protocol-Specified Efficacy Analyses

PPD

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1(mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events will be identified and captured as SAEs if AEs met the definitions of a SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events are defined as one or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than visit Day 28, or up to 28 days if a subject withdraws early (prior to Day 28) from the study
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

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

- The AE onset and end dates are the same as or after the month and year (or year) of the first dosing date of study drug
- The AE onset date is the same as or before the month and year (or year) of the Day 28 visit

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.

7.1.6. Summaries of Adverse Events and Deaths

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

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

The number and percentage of subjects 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:

- TEAE by maximum severity
- TEAEs of Grade 3 or higher (by maximum severity)
- TEAEs of Grade 2 or higher
- All TE treatment-related AEs
- All TE treatment-related AEs (by maximum severity)
- TE Treatment-related AEs of Grade 3 or higher (by maximum severity)
- TE Treatment-related AEs of Grade 2 or higher
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of study drug
- All TEAEs leading to premature discontinuation of study
- All AEs leading to death (ie, outcome of death)

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs. All deaths observed in the study will be also included in this summary.

Multiple events will be counted only once per subject 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 subject during the study.

In addition to the above summary tables, all TEAEs and TE treatment-related AEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- All AEs of Grade 2 or higher
- SAEs
- Deaths
- All AEs leading to death (ie, outcome of death)
- AEs leading to premature discontinuation of study drug
- AEs leading to premature discontinuation of study

7.1.7. Additional Analysis of Adverse Events

Summaries (number and percentage of subjects) of AEs (by SOC and PT) will be provided by treatment group using the safety analysis set for the age, gender, and race subgroups.

Summaries (number and percentage) of subjects who experienced any cardiac related events will be provided for each treatment group using the Safety Analysis Set by AE of interest categories and the associated PTs (see Appendix 2).

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 through Day 28. The analysis will be based on values reported in conventional units. When values are below the limit of quantitation, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each post baseline assessment
- Change from baseline at each post baseline assessment

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 post baseline visit will be defined as the visit value minus the baseline value. Laboratory test results collected at unscheduled visits will be included for the baseline. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; SD to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for these laboratory tests will be plotted using a line plot by treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.4.

7.2.1.1. Troponin

Troponin will be collected at the visits pre-specified in the protocol: Day 1, Day 17 and Day 28 (End of study). A shift table of troponin results at postbaseline visit including those obtained for the purposes of standard of care compared with baseline values will be presented by treatment group using the following categories: normal, abnormal, or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

If multiple troponin results exist for one visit due to multiple troponin assay tests performed, the results obtained from Troponin I test will be used for the analysis.

All troponin results, including those not required by the protocol (see protocol Section 6.11.9.2), will be presented in the subject listings.

7.2.2. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, 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 post baseline time point, up to and including Day 28 visit. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any post baseline time point, up to and including Day 28. If the relevant baseline laboratory value is missing, then any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities will be provided by treatment group (subjects categorized according to most severe abnormality grade):

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing post-baseline values in the given study period.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities and marked laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for post-baseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 x ULN (b) > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN
- AST or ALT > 3 x ULN, total bilirubin > 2 x ULN and ALP < 2 x ULN

The summary will include data from all post-baseline visits up to and including Day 28. For individual laboratory tests, subjects will be counted once based on the most severe post-baseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same post-baseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing post-baseline values of all relevant tests at the same post-baseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Body Weight and Vital Signs

Body weight and vital signs (pulse rate, systolic and diastolic blood pressure, body temperature, and respiratory rate) at baseline and each post-baseline assessment, and change from baseline in body weight and vital signs at each post-baseline visit will be summarized for the safety analysis set using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group.

A baseline value will be defined as the last available value collected 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 postbaseline value minus the baseline value.

In the case of multiple values at an assessment, data will be selected for analysis as described in Section 3.8.4. No inferential statistics will be generated.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. Body weight will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The medications will be categorized as prior or concomitant.

7.4.1. Prior Medications

Prior medications are defined as medications taken and stopped prior to or on the first dosing date or continued to take after the first dosing date of study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class and preferred name (using the number and percentage of subjects for each treatment group and overall). A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC drug classes and then by preferred names in order of descending overall frequency within an ATC drug class. For drugs with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

For the purposes of analysis, any medications taken and stopped prior to or on the first dosing date of study drug or continued to take after the first dosing date of study drug will be considered prior medications. Therefore, medications with a start date that is prior to the first dosing date of study drug will be included in the prior medication summary regardless when stop date is (as long as it is on or after the start date is). In addition, a medication with both start and stop dates that are the same as the first dosing date will be included in the summary. If a partial start date is entered, the month and year (if day is missing) or year (if day and month are missing) of the start date are after first dosing date will not be considered prior; otherwise, it is prior. Medications with completely missing start and stop dates will be included in the prior medication summary.

Prior ribavirin use will be summarized separately from other prior medications.

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

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications up to and including Day 28 visit will be summarized by ATC drug class and preferred name (using the number and percentage of subjects for each treatment

group). A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical classes and then by preferred names in descending overall frequency within an ATC drug class. For drugs with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

For the purposes of analysis, any medications started prior to or on the first dosing date of study drug and continued to take after the first dosing date, or started after the first dosing date but no later than last dosing date of study drug will be considered concomitant medications. Therefore, medications with a stop date that is on or prior to the date of first dosing date of study drug or a start date that is 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.

Concomitant ribavirin use will be summarized separately from other concomitant medications.

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

7.5. Electrocardiogram Assessment

A 12-lead ECG will be performed at Visit 2 (Day 1), Visit 8 (Day 17), and Visit 10 (Day 28) and read by a certified cardiologist at a specialized central laboratory. Summaries of ECG assessments will be provided for the Safety Analysis Set

Number and percent of subjects with new ECG abnormalities at postbaseline visits including those assessments obtained for the purpose of standard of care will by summarize by treatments. Only subjects with baseline ECG assessments will be included in this analysis.

A shift table of the ECG assessment at each scheduled visit compared with baseline will be presented by treatment group using the following categories: normal, abnormal, or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG assessments and ECG abnormalities will be provided by subject ID number and visit in chronological order.

No formal statistical testing is planned.

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

No changes from protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

Individual subject presatovir concentration-time data will be displayed using scheduled sampling times. Descriptive statistics (eg, n, mean, standard deviation, %CV, median, and range) will be calculated for plasma concentrations of presatovir at each sampling time.

For PK subgroup, plasma concentrations of presatovir over time will be plotted in semi-logarithmic and linear formats as mean $\pm$ SD. Plasma concentration time data for each subject will be analyzed using standard non-compartmental methods. PK parameters (C_{max}, T_{max}, C_{last}, T_{last}, AUC_{last}, AUC_{inf}, $t_{½}$, CL/F, and V_z/F, as appropriate) of presatovir will be listed and summarized using descriptive statistics.

PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

Pharmacokinetics/pharmacodynamics (PK/PD) relationship may be explored as appropriate.

9. REFERENCES

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10. SOFTWARE

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11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision
10 October 2017	Throughout the document	Made minor editorial changes	The editorial, administrative, and formatting changes were made to Gliead standard template updates, where appropriate, to improve clarity and consistency.
10 October 2017	Section 3.1.3	Updated IPD criteria	This section was updated to align with the IPD amendment and to provide the details.
10 October 2017	Section 3.8.4	Added texts to define the baseline and postbaseline values when multiple records exist	This section was revised to provide more details and clarification.
10 October 2017	Section 4.1	Added two more categories in subject disposition summary	The addition was to provide extra information for subjects enrolled in the Extended Viral Load monitoring period.
10 October 2017	Section 4.2.2	Added by-subject listing of study drug administration and drug accountability	The listings were included to provide individual level data.
10 October 2017	Section 5.3	Updated HCT-specific medical history summary	This section was revised to provide more clarification that the disease-specific summary will be provided by treatment and general medical history will not be coded.
10 October 2017	Section 6.4.2	Removed the related analyses for RSV log10 viral load in the blood	No RSV viral load data in the blood are available due to a lack of validated assays
10 October 2017	Section 7.1.6.1	Added more TEAE tables and listings	The additional AE summaries were included to provide complete safety assessments.
10 October 2017	Section 7.2.1.1	Updated analysis for troponin data	This section was revised to provide the details and clarification for troponin assessment
10 October 2017	Section 7.1.7	Added cardiac adverse event of interest	The cardiac AE of interest were evaluated to comply with FDA mandated cardiac monitoring requirements
10 October 2017	Section 7.2.3	Added liver related laboratory evaluation	The evaluation was added in order to comply with regulatory requirements.
10 October 2017	Section 7.5	Updated analysis for ECG data	This section was revised to provide the details and clarification for ECG

			assessment
10 October 2017	Section 13	Updated Table of Contents for statistical tables, figures, and listings	The Table of Contents was updated to include additional analyses results.
10 October 2017	Appendix 3 and Appendix 4	Added SAS example codes	The example codes were provided for analyses.

12. PROPOSED TABLES, FIGURES AND LISTINGS

12.1. Tables

Table Number	Title	Analysis Set
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15.8.1.2	Enrollment by Randomization Stratum	All Randomized Analysis Set
15.8.1.3	Subject Disposition	All Screened Subjects
15.8.2.1	Eligibility Criteria Deviations	All Randomized Analysis Set
15.8.2.2	Important Protocol Deviations	All Randomized Analysis Set
15.8.3.1.1	Demographics	Safety Analysis Set
15.8.3.1.2	Demographics by Consent for Participating in the Extend Viral Load Monitoring	Safety Analysis Set
15.8.3.1.3	Demographics by Presence or Absence of Lymphopenia	Safety Analysis Set
15.8.3.1.4	Demographics by Actual Ribavirin Use at Baseline	Safety Analysis Set
15.8.3.2.1	Baseline Characteristics	Safety Analysis Set
15.8.3.2.2	Baseline Characteristics by Consent for Participating in the Extend Viral Load Monitoring	Safety Analysis Set
15.8.3.2.3	Baseline Characteristics by LRTC Occurrence	Full Analysis Set
15.8.3.3	Hematopoietic Cell Transplant Medical History	Safety Analysis Set
15.8.4	Adherence to Study Drug	Safety Analysis Set
15.8.5	Analysis Sets	All Randomized Analysis Set
15.9.1.1.1	Time-Weighted Average Change in Nasal RSV Viral Load (log10 copies/ml) from Baseline to Day 9	Full Analysis Set
15.9.1.1.2	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/mL) from Baseline to Day 9	Per Protocol Analysis Set
15.9.1.1.3	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/mL) from Baseline to Day 9	Full Analysis Set (Sensitivity Analysis)
15.9.1.1.4	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/mL) from Baseline to Day 9 by Presence or Absence of Lymphopenia	Full Analysis Set
15.9.1.1.5	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/mL) from Baseline to Day 9 by Actual Ribavirin Use at Baseline	Full Analysis Set
15.9.1.1.6	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/mL) from Baseline to Day 9 by Type of Transplant	Full Analysis Set
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Table Number	Title	Analysis Set
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15.9.1.1.12	Time-Weighted Average Change in Nasal RSV Viral Load (log10 copies/ml) from Baseline to Day 9 by Baseline Viral Load Values	Full Analysis Set
15.9.1.2.1	Proportion of Subjects with Progression to Lower Respiratory Tract Infections through Day 28	Full Analysis Set
15.9.1.2.2	Proportion of Subjects with Progression to Lower Respiratory Tract Infections through Day 28	Per Protocol Analysis Set
15.9.1.2.3	Proportion of Subjects with Progression to Lower Respiratory Tract Infections through Day 28	Full Analysis Set (Sensitivity Analysis)
15.9.1.2.4	Proportion of Subjects with Progression to Lower Respiratory Tract Infections through Day 28 by Presence or Absence of Lymphopenia	Full Analysis Set
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15.9.1.2.6	Proportion of Subjects with Progression to Lower Respiratory Tract Infections through Day 28 by Type of Transplant	Full Analysis Set
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15.9.1.2.9	Proportion of Subjects with Progression to Lower Respiratory Tract Infections through Day 28 by Race	Full Analysis Set
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15.9.2.1.2	Proportion of Subjects Developing Respiratory Failure Requiring Mechanical Ventilation or All-Cause Mortality Through Day 28	Per Protocol Analysis Set
15.9.2.1.3	Proportion of Subjects Developing Respiratory Failure Requiring Mechanical Ventilation or All-Cause Mortality Through Day 28 by Presence or Absence of Lymphopenia	Full Analysis Set

Table Number	Title	Analysis Set
15.9.2.1.4	Proportion of Subjects Developing Respiratory Failure Requiring Mechanical Ventilation or All-Cause Mortality Through Day 28 by Actual Ribavirin Use at Baseline	Full Analysis Set
15.9.3.1.1	RSV Viral Load (log_{10} copies/ml) and Change from Baseline in the Nasal Samples	Full Analysis Set
15.9.3.1.2	RSV Viral Load (log_{10} copies/mL) and Change from Baseline in the Nasal Samples for the Extended Viral Load Monitoring	Full Analysis Set
15.9.3.1.3	RSV Viral Load (log_{10} copies/mL) and Change from Baseline in the Nasal Samples by Consent for Participating in the Extended Viral Load Monitoring	Full Analysis Set
15.9.3.1.4	RSV Viral Load (log_{10} copies/mL) and Change from Baseline in the Nasal Samples by Duration of RSV Symptoms at Baseline	Full Analysis Set
15.9.3.1.5	RSV Viral Load (log_{10} copies/mL) and Change from Baseline in the Nasal Samples by LRTC Occurrence	Full Analysis Set
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15.9.3.4	Proportion of Subjects Requiring Supplemental O2 (≥ 2 L/min for > 24 hours) through Day 28	Full Analysis Set
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15.9.3.9	Time-weighted Average and Time-weighted Average Change from Baseline in FLU-PRO Score	Full Analysis Set
15.9.3.10.1	Number of Hospital Free Days through Day 28	Full Analysis Set
15.9.3.10.2	Number of Hospital Free Days through Day 28	Full Analysis Set (Sensitivity Analysis)
15.9.3.11	Proportion of Subjects Requiring ICU Admission or Equivalent of ICU Care through Day 28	Full Analysis Set
15.9.3.12	Number of Days on Supplemental O_2 through Day 28	Full Analysis Set

Table Number	Title	Analysis Set
15.9.3.13.1	Number of Supplemental O2 Free Days through Day 28	Full Analysis Set
15.9.3.13.2	Number of supplemental O2 free days through Day 28	Full Analysis Set (Sensitivity Analysis)
15.9.3.14	Proportion of Subjects Developing Respiratory Failure Requiring Mechanical Ventilation through Day 28	Full Analysis Set
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15.10.1.2	Summary Statistics of Plasma Parameters	PK Substudy Set
15.11.1.1	Extent of Exposure to Study Drug	Safety Analysis Set
15.11.2.1.1.1	Treatment Emergent Adverse Events: Overall Summary	Safety Analysis Set
15.11.2.1.1.2	Treatment Emergent Adverse Events by Age Group (<65 Years or ≥65 Years): Overall Summary	Safety Analysis Set
15.11.2.1.1.3	Treatment Emergent Adverse Events by Sex (Male or Female): Overall Summary	Safety Analysis Set
15.11.2.1.1.4	Treatment Emergent Adverse Events by Race (White or Others): Overall Summary	Safety Analysis Set
15.11.2.1.2.1	Treatment Emergent Adverse Events by System Organ Class, High Level Term and Preferred Term	Safety Analysis Set
15.11.2.1.2.2	Treatment Emergent Adverse Events by System Organ Class, High Level Term and Preferred Term by Age Group (<65 Years or ≥65 Years)	Safety Analysis Set
15.11.2.1.2.3	Treatment Emergent Adverse Events by System Organ Class, High Level Term and Preferred Term by Sex (Male or Female)	Safety Analysis Set
15.11.2.1.2.4	Treatment Emergent Adverse Events by System Organ Class, High Level Term and Preferred Term by Race (White or Others)	Safety Analysis Set
15.11.2.1.3	Treatment Emergent Adverse Events by Preferred Term	Safety Analysis Set
15.11.2.2.1	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity	Safety Analysis Set
15.11.2.2.2.1	Treatment-Emergent Adverse Events with Severity of Grade 3 or Above by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.2.2.2	Treatment-Emergent Adverse Events with Severity of Grade 2 or Above by System Organ Class and	Safety Analysis Set

Table Number	Title	Analysis Set
	Preferred Term	
15.11.2.2.2.3	Treatment-Emergent Adverse Events with Severity of Grade 3 or Above by Preferred Term	Safety Analysis Set
15.11.2.2.2.4	Treatment-Emergent Adverse Events with Severity of Grade 2 or Above by Preferred Term	Safety Analysis Set
15.11.2.3.1.1	Treatment-Emergent Treatment-Related Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.3.1.2	Treatment-Emergent Treatment-Related Adverse Events by Preferred Term	Safety Analysis Set
15.11.2.3.2	Treatment-Emergent Treatment-Related Adverse Events by Preferred Term, and Severity	Safety Analysis Set
15.11.2.3.3.1	Treatment-Emergent Treatment-Related Adverse Events with Severity of Grade 3 or Above by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.3.3.2	Treatment-Emergent Treatment-Related Adverse Events with Severity of Grade 2 or Above by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.3.3.3	Treatment-Emergent Treatment-Related Adverse Events with Severity of Grade 3 or Above by Preferred Term	Safety Analysis Set
15.11.2.3.3.4	Treatment-Emergent Treatment-Related Adverse Events with Severity of Grade 2 or Above by Preferred Term	Safety Analysis Set
15.11.2.4	Treatment-Emergent Adverse Events of Interest (Cardiac Adverse Event) by System Organ Class and Preferred Term	Safety Analysis Set
15.11.3	Treatment-Emergent Serious Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.1	Treatment Emergent Serious Adverse Event by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.2	Treatment Emergent Serious Adverse Event by Preferred Term	Safety Analysis Set
15.11.4.3.1	Treatment Emergent Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.3.2	Treatment Emergent Treatment-Related Serious Adverse Events by Preferred Term	Safety Analysis Set
15.11.4.4	Treatment-Emergent Serious Adverse Events of Interest (Cardiac Adverse Event) by System Organ Class and Preferred Term	Safety Analysis Set
15.11.5.1	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety Analysis Set
15.11.5.2	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study by System Organ Class and	Safety Analysis Set

Table Number	Title	Analysis Set
	Preferred Term	
15.11.6.1.1	Hematology Test: Hemoglobin (g/dL) and Change from Baseline	Safety Analysis Set
15.11.6.1.2	Hematology Test: Lymphocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.3	Hematology Test: Lymphocytes (%) and Change from Baseline	Safety Analysis Set
15.11.6.1.4	Hematology Test: Monocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.5	Hematology Test: Monocytes (%) and Change from Baseline	Safety Analysis Set
15.11.6.1.6	Hematology Test: Neutrophils (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.7	Hematology Test: Neutrophils (%) and Change from Baseline	Safety Analysis Set
15.11.6.1.8	Hematology Test: Platelets (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.9	Hematology Test: Leukocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.2.1	Chemistry Test: ALT (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.2	Chemistry Test: AST (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.3	Chemistry Test: ALP (SGPT) (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.4	Chemistry Test: Total Bilirubin (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.5	Chemistry Test: Blood Urea Nitrogen (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.6	Chemistry Test: Creatinine (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.7	Chemistry Test: Creatinine Clearance (mL/min) and Change from Baseline	Safety Analysis Set
15.11.6.2.8	Chemistry Test: Albumin (g/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.9	Timed Serum Creatinine (mg/dL) and Change from Baseline by Hourly Timepoint	Safety Analysis Set
15.11.6.4.1.1	Treatment Emergent Laboratory Abnormalities	Safety Analysis Set
15.11.6.4.1.2	Treatment Emergent Laboratory Abnormalities by Age Group (<65 Years or ≥65 Years)	Safety Analysis Set
15.11.6.4.1.3	Treatment Emergent Laboratory Abnormalities by Sex (Male or Female)	Safety Analysis Set

Table Number	Title	Analysis Set
15.11.6.4.1.4	Treatment Emergent Laboratory Abnormalities by Race (White or Others)	Safety Analysis Set
15.11.6.4.2	Treatment Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
15.11.6.4.3	Treatment Emergent Marked Laboratory Abnormalities	Safety Analysis Set
15.11.6.5	Liver-Related Laboratory Abnormalities	Safety Analysis Set
15.11.6.6.1	Shift in Troponin Results	Safety Analysis Set
15.11.6.6.2	Subjects with Abnormal Troponin Results at Postbaseline through Day 28	Safety Analysis Set
15.11.7.1.1	Vital Signs: Diastolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.2	Vital Signs: Systolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.3	Vital Signs: Pulse (beats per minute) and Change from Baseline	Safety Analysis Set
15.11.7.1.4	Vital Signs: Respiration (breaths per minute) and Change from Baseline	Safety Analysis Set
15.11.7.1.5	Vital Signs: Temperature (Celsius) and Change from Baseline	Safety Analysis Set
15.11.7.2.1	Body Weight (kg) and Change from Baseline	Safety Analysis Set
15.11.7.3.1	Prior Medication by Drug Class and Preferred Drug Name	Safety Analysis Set
15.11.7.3.2	Concomitant Medication by Drug Class and Preferred Drug Name	Safety Analysis Set
15.11.7.3.3	Prior Ribavirin Use	Safety Analysis Set
15.11.7.3.4	Concomitant Ribavirin Use	Safety Analysis Set
15.11.9.1	Shift in Electrocardiogram Assessment Results	Safety Analysis Set
15.11.9.2	Subject with New Abnormalities ECG at Post-baseline	Safety Analysis Set

12.2. Figures

Figure	Title	Analysis Set
15.8.1	Histogram of Number of Subjects Enrolled by Site	All Randomized Analysis Set
15.8.2	Histogram of Number of Subjects Enrolled by Country	All Randomized Analysis Set
15.9.1.1	Median (Q1, Q3) Viral Load (log_{10} copies/mL) at Each Visit	Full Analysis Set
15.9.1.2	Median (Q1, Q3) Change from Baseline in Viral Load (log_{10} copies/mL) at Each Visit	Full Analysis Set
15.9.1.3	Median (Q1, Q3) Viral Load (log_{10} copies/mL) at Each Visit by Duration of RSV Symptom	Full Analysis Set
15.9.1.4	Median (Q1, Q3) Change from Baseline in Viral Load (log_{10} copies/mL) at Each Visit by Duration of RSV Symptom	Full Analysis Set
15.9.1.5	Median (Q1, Q3) Viral Load (log_{10} copies/mL) at Each Visit by LRTC Occurrence	Full Analysis Set
15.9.1.6	Median (Q1, Q3) Change from Baseline in Viral Load (log_{10} copies/mL) at Each Visit by LRTC Occurrence	Full Analysis Set
15.9.3.1.1	Median (Q1, Q3) FLU-PRO Score at Each Visit	Full Analysis Set
15.9.3.1.2	Median (Q1, Q3) Change from Baseline in FLU-PRO Score at Each Visit	Full Analysis Set
15.9.3.2.1	Median (Q1, Q3) O2 Saturation at Each Visit	Full Analysis Set
15.9.3.2.2	Median (Q1, Q3) Change from Baseline in O2 Saturation at Each Visit	Full Analysis Set
15.10.1.1.1	Mean (SD) Plasma Concentrations vs. Time	PK Substudy Set
15.10.1.1.2	Individual Data of Plasma Concentration vs. Time	PK Analysis Set
15.11.6.1.1	Median (Q1, Q3) Hematology: Hemoglobin (g/L) by Visit	Safety Analysis Set
15.11.6.1.2	Median (Q1, Q3) Hematology: Lymphocytes (x10^3/µL) by Visit	Safety Analysis Set
15.11.6.1.3	Median (Q1, Q3) Hematology: Lymphocytes (%) by Visit	Safety Analysis Set
15.11.6.1.4	Median (Q1, Q3) Hematology: Monocytes (x10^3/µL) by Visit	Safety Analysis Set
15.11.6.1.5	Median (Q1, Q3) Hematology: Monocytes (%) by Visit	Safety Analysis Set
15.11.6.1.6	Median (Q1, Q3) Hematology: Neutrophils (x10^3/µL) by Visit	Safety Analysis Set
15.11.6.1.7	Median (Q1, Q3) Hematology: Neutrophils (%) by Visit	Safety Analysis Set
15.11.6.1.8	Median (Q1, Q3) Hematology: Leukocytes (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.1.9	Median (Q1, Q3) Hematology: Platelet Count (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.2.1	Median (Q1, Q3) Chemistry: ALT (SGPT) (U/L) by Visit	Safety Analysis Set

Figure	Title	Analysis Set
15.11.6.2.2	Median (Q1, Q3) Chemistry: AST (SGOT) (U/L) by Visit	Safety Analysis Set
15.11.6.2.3	Median (Q1, Q3) Chemistry: Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
15.11.6.2.4	Median (Q1, Q3) Chemistry: Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
15.11.6.2.5	Median (Q1, Q3) Chemistry: Blood Urea Nitrogen (mg/dL) by Visit	Safety Analysis Set
15.11.6.2.6	Median (Q1, Q3) Chemistry: Creatinine (mg/dL) by Visit	Safety Analysis Set
15.11.6.2.7	Median (Q1, Q3) Chemistry: Creatinine Clearance (mL/min) by Visit	Safety Analysis Set
15.11.6.2.8	Median (Q1, Q3) Chemistry: Albumin (g/dL) by Visit	Safety Analysis Set
15.11.7.1.1	Median (Q1, Q3) Vital Signs: Diastolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
15.11.7.1.2	Median (Q1, Q3) Vital Signs: Systolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
15.11.7.1.3	Median (Q1, Q3) Vital Signs: Pulse (beats per minute) by Visit	Safety Analysis Set
15.11.7.1.4	Median (Q1, Q3) Vital Signs: Respiration (breaths per minute) by Visit	Safety Analysis Set
15.11.7.1.5	Median (Q1, Q3) Vital Signs: Temperature (Celsius) by Visit	Safety Analysis Set

12.3. Listings

Listing	Title	Analysis Set
16.1.6	Subjects Who Received Study Drug from Specific Batches	Safety Analysis Set
16.1.7	Randomization Schema and Codes	All Randomized Analysis Set
16.2.1.1	Subject Profiles	All Randomized Analysis Set
16.2.1.2	Enrollment	All Randomized Analysis Set
16.2.1.3	Subject Disposition	All Randomized Analysis Set
16.2.1.4	Reasons for Screen Failure	Subjects Screened but Not Enrolled
16.2.2.1	Eligibility Criteria Deviations	All Randomized Analysis Set
16.2.2.2	Important Protocol Deviations	All Randomized Analysis Set
16.2.2.3	Randomization Stratification Discrepancies Between IWRS and Clinical Database	All Randomized Analysis Set
16.2.2.4	Subjects who Received Incorrect Study Drug	All Randomized Analysis Set
16.2.3.1	Subjects Excluded from Any Analysis Set	All Randomized Analysis Set
16.2.3.2	Subjects Who Were in the Full Analysis Set but Excluded from the Per Protocol Analysis Set	Full Analysis Set
16.2.4.1	Demographics	All Randomized Analysis Set
16.2.4.2	Baseline Characteristics	All Randomized Analysis Set
16.2.4.3.1	Hematopoietic Cell Transplant Medical History	All Randomized Analysis Set
16.2.4.3.2	Medical History	All Randomized Analysis Set
16.2.4.4.1	Prior and Concomitant Medications	All Randomized Analysis Set
16.2.4.4.2	Prior and Concomitant Ribavirin	All Randomized Analysis Set
16.2.5.1	Study Drug Administration	All Randomized Analysis Set
16.2.5.2	Subjects Who Prematurely Discontinued Study Drug	All Randomized Analysis Set
16.2.5.3	Study Drug Accountability	All Randomized Analysis Set
16.2.5.4.1	Pharmacokinetic Sampling Details and Concentrations	PK Analysis Set
16.2.5.4.2	Pharmacokinetic Parameter	PK Substudy Set
16.2.6.1	Viral Load Measurements	Full Analysis Set
16.2.6.2	Progression to Lower Respiratory Tract Infection	Full Analysis Set
16.2.6.3	Chest Image Results	Full Analysis Set
16.2.6.4	Hospitalizations and ICU	Full Analysis Set
16.2.6.5	Oxygen Saturation	Full Analysis Set
16.2.6.6	Supplemental Oxygen Use	Full Analysis Set
16.2.6.7	Mechanical Ventilation	Full Analysis Set

Listing	Title	Analysis Set
16.2.6.8	FLU-PRO Measurements	Full Analysis Set
16.2.6.9	Healthcare Related Efficacy Endpoints	Full Analysis Set
16.2.6.10	RSV Antibody Titer	All Randomized Analysis Set
16.2.7.1	All Adverse Events	Safety Analysis Set
16.2.7.2.1	Deaths	All Screened Subjects
16.2.7.2.2	Adverse Events Leading to Death	Safety Analysis Set
16.2.7.3	Serious Adverse Events	Safety Analysis Set
16.2.7.4.1	Adverse Events with Severity of Grade 3 or Higher	Safety Analysis Set
16.2.7.4.2	Adverse Events with Severity of Grade 2 or Higher	Safety Analysis Set
16.2.7.5.1	Adverse Events Leading to Premature Discontinuation of Study Drug	Safety Analysis Set
16.2.7.5.2	Adverse Events Leading to Premature Discontinuation of Study	Safety Analysis Set
16.2.8.1.1.1	Hematology Results: Part 1	Safety Analysis Set
16.2.8.1.1.2	Hematology Results: Part 2	Safety Analysis Set
16.2.8.1.1.3	Hematology Results: Part 3	Safety Analysis Set
16.2.8.1.2.1	Chemistry Results: Part 1	Safety Analysis Set
16.2.8.1.2.2	Chemistry Results: Part 2	Safety Analysis Set
16.2.8.1.2.3	Timed Serum Creatinine Results	Safety Analysis Set (PK Subgroup Set)
16.2.8.1.4	Treatment Emergent Marked Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.5	Treatment Emergent Grade 3 or Higher Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.6	Liver-Related Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.7	Laboratory Tests Reference Ranges	Safety Analysis Set
16.2.8.1.8	Laboratory Test – Troponin	Safety Analysis Set
16.2.8.2.1	Vital Sign Measurements	Safety Analysis Set
16.2.8.2.2	Body Weight, Height and BMI	Safety Analysis Set
16.2.8.3	Overall ECG Assessment	Safety Analysis Set
16.2.8.4	Pregnancy Report	Safety Analysis Set
16.2.8.5	General Comments	All Randomized Analysis Set

13. APPENDICES

Appendix 1. Study Procedures Table

	Visit 1: Screening (Day -1)	Visit 2: Baseline Assessments, Randomization, and Treatment Assessments (Day 1)	Visit 3[q]: Day 3 (±24 hours)	Visit 4: Day 5 (±24 hours)	Visit 5: Day 7 (±24 hours)	Visit 6: Day 9 (±24 hours)	Visit 7: Day 13 (±24 hours)	Visit 8: Day 17 (±24 hours)	Visit 9: Day 22 ±24 hours)	Visit 10: End of study/ Day 28 (+3 days)	Optional Extended Viral Monitoring[m]			
											Visit 11: Day 35 (±48 hours)	Visit 12: Day 42 ±48 hours	Visit 13: Day 49 (±48 hours)	Visit 14: Day 56 (±48 hours)
Must complete visit in the hospital or clinic	X	X	X[j]	X		X	X	X	X	X				
Written Informed Consent	X													
Medical History and Demographics	X													
Chest X-Ray	X[a]													
Screening Labs	X[b]													
Urine or Serum Pregnancy Test[c]	X	X		X		X	X	X						
FLU-PRO		X		X		X								
Vital Signs (inc. O_2 Saturation[d])	X	X	X[o]	X	X[o]	X	X	X	X	X				
Height	X													
Weight	X	X		X		X	X	X	X	X				
12-lead ECG		X						X		X				
Local Troponin Testing[p]		X						X		X				

	Visit 1: Screening (Day -1)	Visit 2: Baseline Assessments, Randomization, and Treatment Assessments (Day 1)	Visit 3[q]: Day 3 (±24 hours)	Visit 4: Day 5 (±24 hours)	Visit 5: Day 7 (±24 hours)	Visit 6: Day 9 (±24 hours)	Visit 7: Day 13 (±24 hours)	Visit 8: Day 17 (±24 hours)	Visit 9: Day 22 ±24 hours)	Visit 10: End of study/ Day 28 (+3 days)	Optional Extended Viral Monitoring[m]			
											Visit 11: Day 35 (±48 hours)	Visit 12: Day 42 ±48 hours	Visit 13: Day 49 (±48 hours)	Visit 14: Day 56 (±48 hours)
Safety Labs [e]		X		X		X	X	X	X	X				
RSV antibody titer		X								X				
RSV Viremia		X		X		X	X	X	X	X				
Nasal Samples[f]	X[r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Local RSV testing	X[s]								X[l]					
Randomization		X												
IMP Administration		X		X		X	X	X						
PK sample		X[g]	X[i]	X[h]		X[h]			X[h]					
Serum creatinine		X[k]				X[k]								
Adverse Events	X	X	X[n]	X	X[n]	X	X	X	X	X	X[n]	X[n]	X[n]	X[n]
Assess ICU admissions, hospitalizations, standard of care test results, mechanical ventilation, and supplemental O_2		X	X[o]	X	X[o]	X	X	X	X	X				
Concomitant Medications	X	X	X[o]	X	X[o]	X	X	X	X	X				

a Chest X-ray obtained < 48 hours prior to Screening may be used
b Existing values collected ≤ 6 days prior to Screening may be used
c Required for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy
d On room air

e Central laboratory testing: hematology and serum chemistry to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB
f 2 samples total, 1 from each nostril – collected prior to dosing on dosing days
g For subjects in the PK subgroup only: Collected 1 (±15 min), 2 (±15 min), 4 (±30 min) and 6 hours (±30 min) post-dose
h For all subjects: collected pre-dose on Day 5, pre-dose and 2 hours (±15 min) post-dose on Day 9, and anytime on Day 22
i For subjects in the PK subgroup only: PK is collected anytime during Visit 3 and Visit 3 must occur in clinic.
j For subjects in the PK subgroup only. Subjects not participating in the PK subgroup can have this visit completed at home by a home nursing vendor or by the study coordinator or designee.
k For subjects in the PK subgroup only: Blood draw for serum creatinine 2 hours (±15 min) post dose on Day 1 and Day 9 (Visit 2 and Visit 6)
l Only for subjects who agree to the optional extended viral monitoring at the time of consent.
m Only for subjects who agree to the optional extended viral monitoring at the time of consent and test positive (or inconclusive) for RSV at Visit 9 (Day 22)
n Assessment of procedure-related AEs only, if home visit
o Not required if home visit
p Local troponin testing will be done pre-dose in accordance with the standard assay available and used at the site. Point-of-care "rapid" troponin tests are not acceptable for protocol-mandated troponin testing.
q Visit 3: Day 3 is an optional study visit for subjects not participating in the PK subgroup.
r For Japan sites only, 2 nasal swab samples will be obtained at Screening, 1 for local RSV testing and 1 for testing at the central laboratory. At Baseline, only 1 sample will be obtained for central lab testing.
s Subjects who were not tested for RSV as standard of care may consent to the study and be tested for RSV during the Screening visit.

Appendix 2. Cardiac Adverse Events of Interest

The following search criteria are used to identify cardiac adverse events:

- All PTs from Cardiac disorders SOC
- Narrow scope PTs from the below SMQs, and associated sub-SMQs:
  - Cardiac arrhythmias (SMQ)
  - Cardiac failure (SMQ)
  - Cardiomyopathy (SMQ)
  - Ischaemic heart disease (SMQ)
  - Torsade de pointes/QT prolongation (SMQ)
- Select PTs from HLTs:
  - Cardiac histopathology procedures,
  - Skeletal and cardiac muscle analyses,
  - Arterial therapeutic procedures (excluding aortic),
  - ECG investigations, Cardiac function diagnostic procedures,
  - Heart rate and pulse investigations

Duplicate PTs were removed where necessary.

Appendix 3. Sample SAS Code for MMRM Model

The following model statement may be used for the analyses of viral load, FLU-PRO, O2 saturation, respiratory rate and EQ5D VAS scale as described in Sections 6.2.2 and 6.3.2:

```
proc mixed data=change;
  class trt visit subjid strata;
  model change = baseline strata trt visit trt*visit / s ddfm=kr;
  repeated visit / type=un subject=subjid(trt);
  lsmeans trt*visit / cl;
run;
```

Note that since the response variable is change from baseline, the Visit 2 (baseline) value will always be 0 and should not be included in the above model.

An unstructured covariance will be assumed (type=un); if there are convergence or model fitting issues, then the alternative covariance structure of Toeplitz will be assumed (type=toep).

Appendix 4. Sample SAS Code for Negative Binomial Model

The following model statement may be used for the analyses of number of hospitalization-free day, and supplemental oxygen-free day described in Sections 6.2.2 and 6.3.2:

```
proc genmod data=dataset;
   class trt strata;
   model count = trt strata / offset=logt dist=NB;
run;
```

where logt is the offset parameter defined as the natural logarithm of study duration for each subject to account for potential differential study durations.

In the event that the negative binomial model fails to converge, a zero-inflated negative binomial model may be fit (dist=ZINB).