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 Hospitalized Adults with Respiratory Syncytial Virus (RSV) Infection
Name of Test Drug:	Presatovir (GS-5806)
Study Number:	GS-US-218-1227
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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BLQ	below the limit of quantification
BMI	body mass index
CFS	clinical frailty scale
CI	confidence interval
CL/F	apparent total clearance of drug from plasma after oral administration
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
CP	conditional power
CRF	case report form
CSR	clinical study report
%CV	coefficient of variation
DAVG	difference between time-weighted average post-baseline and baseline
DMC	data monitoring committee
ECG	electrocardiogram
EOT	early of termination
FAS	full analysis set
FDA	Food and Drug Administration
HLT	high level term
HLGT	high level group term
ICH	International Conference on Harmonisation
ICU	intensive care unit
IMP	investigational medicine product
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
LLT	lower level term
MedDRA	medical dictionary for regulatory activities
ml	milliliter
MMRM	Mixed-effect model with repeated measures
PK	pharmacokinetics
PP	per protocol
PT	preferred term
Q1	first quartile

Q3	third quartile
RSV	respiratory syncytial virus
RT-qPCR	quantitative real time polymerase chain reaction
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	Treatment-emergent adverse events
TFLs	tables, figures, and listings
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-218-1227. This SAP is based on the study protocol Amendment 4 dated 17 November 2015 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

Primary Objective

- To evaluate the effects of presatovir on respiratory syncytial virus (RSV) viral load in RSV-positive adults hospitalized with acute respiratory infectious symptoms.

Secondary Objectives

- To evaluate the effect of presatovir on change in the FLU-PRO score from Baseline
- To assess the effect of presatovir on the length of hospital stay
- To evaluate the effect of presatovir on the rate of unplanned healthcare encounters (clinic visits, emergency room visits, urgent care visits, and rehospitalizations) related to a respiratory illness after discharge
- To examine the pharmacokinetics (PK), safety, and tolerability of presatovir

1.2. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multi-center study to evaluate the antiviral effect, PK, safety, and tolerability of presatovir in RSV positive adults who have been hospitalized. The study will be conducted at approximately 70 centers in Australia, Canada, Europe, Hong Kong, Israel, New Zealand, South Korea, and the United States.

Eligible subjects will be randomized in a 1:1 ratio to receive either presatovir or matching placebo, stratified into one of the following 4 categories: no chronic airways or lung disease, chronic obstructive pulmonary disease (COPD), asthma, and other chronic airways or lung disease. Subjects will receive 1 dose of presatovir or matching placebo and will be followed for 28 days post-dose.

1.3. Sample Size and Power

Sample size calculations are based on results observed in subjects who received placebo in Study GS-US-218-0103 (Phase 2a challenge study). Assuming time-weighted average change in $\log_{10}$ viral load from Baseline (Day 1) to Day 5 in the placebo group will be -2.9 $\log_{10}$ copies/ml with a corresponding standard deviation (SD) of 2.3, there is approximately 80% power to detect a 1 $\log_{10}$ reduction in time-weighted average change in viral load with 85 subjects per group, using a 2-sided 0.05-level test. Given an evaluable rate of 85%, a total of 200 subjects will need to be randomized into the study.

2. TYPE OF PLANNED ANALYSIS

This SAP describes the analyses to be conducted for Study GS-US-218-1227 after all subjects have completed the study. This SAP also describes the interim analyses that will be conducted to support decision making on continuation of the study.

2.1. Data Monitoring Committee Analyses

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of efficacy and safety data as specified in the DMC charter and provide a recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, or the study should continue as planned, or the study should continue with modifications. The DMC will review safety data as described in Section 2.2.1 and efficacy data for the futility interim analysis as described in Section 2.2.2. While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

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

2.2. Interim Analyses

2.2.1. Safety Analyses

Three safety reviews are expected to be required after approximately 25%, 50%, and 75% of the planned 200 subjects are enrolled and complete Day 5 of the study, respectively. 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.

2.2.2. Interim Futility Analyses

Two futility interim analyses are planned after approximately 25% and 50% of the planned 200 subjects are enrolled and complete Day 5 of the study. The DMC will review unblinded interim efficacy results and make a recommendation for early termination per pre-specified futility criteria to Gilead Executive Management as outlined in the DMC Charter. These analyses offer the opportunity to assess if there is any evidence of beneficial clinical effect. The primary endpoint, time-weighted average change in $\log_{10}$ viral load from Day 1 through Day 5, will be evaluated for this purpose in these analyses. Stopping the study for little evidence of GS-5806 benefit will be considered if the conditional power (CP) is < 20%. If a decision is made to stop the trial based on an interim analysis, the database will be cleaned and locked for the subsequent final analysis. Appendix 2 provides the formula of the calculation of the conditional power and example SAS codes.

2.2.3. Interim Efficacy Analyses

In addition to the futility analyses that will be evaluated by the DMC, two efficacy interim analyses are currently planned for administrative purposes by the internal Gilead staff. The timing of these efficacy interim analyses will be adjusted based on the enrollment rate. There is no plans to stop the study early for efficacy based on the interim efficacy analysis results. The purpose of interim efficacy analyses is to obtain an early assessment of the effect of GS-5806 on the primary and secondary endpoints. The interim efficacy results will aid internal decision-making on the further development of the GS-5806 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 with the FDA on requirements for registration in the immunocompromised population in conjunction with other relevant studies, and to include in the response to the FDA on the partial clinical hold for the pediatric program.

A Haybittle-Peto boundary are used for the alpha spending, with an alpha of 0.00001 for each interim analysis and an alpha of 0.05 for the final analysis, to control the overall Type I error rate at 0.05. If additional efficacy analyses are needed, the same alpha of 0.00001 is used, and the alpha level for the final analysis is adjusted accordingly.

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, and whether to schedule a meeting with the FDA to discuss registration in the immunocompromised population. A GSI unblinded team that is independent of the GS-US-218-1227 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-218-1227. If the GSI Executive Team decides to use the results to help inform the planning of Phase 2 and Phase 3 studies, then the unblinded support team will perform more extensive ad-hoc analyses, will support protocol development, and will support the development of briefing packages to be submitted to the FDA to discuss the proposed Phase 3 studies, as needed.

The GS-US-218-1227 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.

A separate document, the Interim Analysis Communication Plan, outlines the specific procedures and guidelines to be followed by Gilead at the time of any unblinded interim analysis and the resulting controlled dissemination of interim analysis data.

2.3. Final Analyses

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

The primary efficacy analysis will be conducted on time-weighted average change of RSV $\log_{10}$ viral load from Day 1 through Day 5 at an adjusted significance level of 0.05 so that the overall Type 1 error rate can be controlled at the 0.05 level. The boundaries of significance levels to reject the null hypothesis at the 2 interim efficacy and the final analyses of the primary endpoint are shown in the following table.

Table 2-1. Significance Levels to Reject the Null Hypothesis at Interim and Final Analyses

Analysis	Significance Levels to Reject the Null Hypothesis (H_0)
Interim Efficacy 1	< 0.00001
Interim Efficacy 2	< 0.00001
Final	< 0.05

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

By-subject listings will be presented for all subjects in the relevant analysis sets, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the 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, 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 includes all subjects who were randomized into the study, and received at least a partial dose of study medication.

3.1.3. Evaluable Analysis Set

The Evaluable Analysis Set includes include those who have an RSV $\log_{10}$ viral load greater than the lower limit of quantification (LLOQ) of the RT-qPCR assay in the Day 1 nasal swab sample, have a minimum of 3 nasal swabs (including baseline swab; swabs do not have to be consecutive) within a 5 days period after enrollment, not including the screen swab, and have completed IMP administration.

This is the primary analysis set for all efficacy endpoints.

3.1.4. Per Protocol Analysis Set

The Per Protocol (PP) analysis set includes subjects in the Evaluable Analysis Set who meet the following criteria:

- Did not violate the following major inclusion criteria (IC)
  - New onset or acute worsening of at least 1 upper or lower respiratory infectious symptom ≤ 5 days prior to screening:
  - Documented to be RSV-positive as per protocol
- Did not violate the following major exclusion criteria (EC)
  - Use of any investigational medicinal product in the 28 days prior to screening, **OR** use of any investigational monoclonal antibody within 4 months or 5 half-lives of screening, whichever is longer, **OR** use of any investigational RSV vaccine ever
  - Subjects taking a moderate or strong cytochrome P450 (CYP) enzyme inducer within 2 weeks prior to the first dose of IMP
  - Chronic use (> 28 days of use) of systemic immunosuppressive agents (ie, alkylating agents, calcineurin inhibitors, immunophilin-binding but not a calcineurin inhibitor, antimetabolites, polyclonal antibodies, monoclonal antibodies) during the 28 days prior to screening, or anticipated use during the 28 days following screening
  - Use of oral prednisone or other corticosteroid equivalent to:
    - > 20mg/day for > 14 days prior to screening is not permitted.
    - > 20mg/day for ≤ 14 days, including corticosteroids received during current hospitalization (ie, bolus doses), is permitted.
    - ≤ 20mg/day, regardless of duration, is permitted.
- Administered > 75% of study drug

This analysis set is the secondary analysis set for efficacy endpoints.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes all subjects who received 1 dose of study medication.

This is the primary analysis set for safety analyses.

3.1.6. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all subjects in the Safety Analysis Set who have evaluable PK data at the time points of interest. This is the primary analysis set for all PK analyses.

3.1.7. Biomarker Analysis Set

The Biomarker Analysis Set includes all subjects in the Safety Analysis Set who have evaluable on-study biomarker measurements. This is the primary analysis set for all biomarker analyses.

3.2. Subject Grouping

For analyses based on the Evaluable Analysis Set and PP Analysis set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set, 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, stratified into 1 of the following categories: 1) no chronic airways or lung disease, 2) COPD, 3) asthma, or 4) other chronic airways or lung disease, and randomized to receive study treatment via IWRS.

If there are discrepancies in stratification factor values between the IWRS and the clinical source document, the values recorded in the clinical source document will be used for analyses.

Efficacy endpoints will be evaluated using stratification factors as covariates for analyses, as specified in Section 6. In the event the number of subjects within a stratum of the stratification factor is small (eg, ≤ 4 subjects), the stratum will be pooled with the smallest stratum for analyses; the smallest stratum is defined as that stratum having the fewest number of subjects.

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

3.4. Examination of Subject Subgroups

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

- Stratification factor (No chronic airways or lung disease, COPD, Asthma, or Other chronic airways or lung disease)

The primary endpoint will also be examined by RSV type (RSV A or RSV B) and duration of RSV symptoms (≤ median duration or > median duration).

The safety endpoints will be examined using the following subgroups:

- Age (< 65 years and ≥ 65 years)
- Sex (male and female)

3.5. Multiple Comparisons

In order to account for multiple hypothesis testing of endpoints, a sequential testing procedure will be used to control the Type 1 error rate of 0.05 across the primary and secondary endpoints, testing for differences between treatment groups. The primary endpoint analysis will serve as the gatekeeper for the secondary analyses, ie, the primary efficacy hypothesis must be rejected at the 2-sided 0.05 significance level before the efficacy hypotheses for the secondary efficacy endpoints can be evaluated.

If the primary null hypothesis is rejected, then the following key secondary endpoints will be tested sequentially at the 2-sided 0.05 alpha significance level in the order listed below based upon the closed testing procedure {Dmitrienko 2003}.

- Time-weighted average change in FLU-PRO score from Day 1 to Day 5
- Duration of hospital stay following investigational medicine product (IMP) administration
- Rate of unplanned medical encounters (clinic visits, emergency room visits, urgent care visits, and rehospitalizations) related to a respiratory illness after initial hospitalization discharge through Day 28

If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4. The handling of missing data in analyses of the efficacy endpoints is discussed in Section 6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analyses.

3.7. Data Handling Conventions and Transformations

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 any study drug, the randomization date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the eCRF, "01 January" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

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

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

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

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

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, log-transformed data) or nonparametric analysis methods may be used, as appropriate.

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 post-baseline time points.

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."

3.8. Analysis Visit

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and 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

Therefore, study day 1 is the day of first dose of study drug administration.

3.8.2. Analysis Visit

The nominal visit as recorded on the eCRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exception will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum post-baseline toxicity grade.
- For subjects who prematurely discontinue from the study, early termination (ET) data will be assigned to the next scheduled visit where the respective data were scheduled to be collected.

3.8.3. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis visit. If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. 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 these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered 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 values:

  — 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 non-missing categorical observations exist for one visit, 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 at the same time or no time recorded on the same day, the value with the lowest severity will be selected unless otherwise specified.

- For postbaseline values:

  — 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 value with the worst severity will be used.

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 enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical source documents, the value collected in the clinical source documents will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical source documents 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. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not randomize with reasons subjects not randomized, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- Full Analysis Set
- Evaluable Analysis Set
- Safety Analysis Set
- Per-Protocol Analysis Set
- PK Analysis Set
- Biomarker Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. 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 identification (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 dosing date minus first dosing date plus 1, and will be expressed in days using up to 1 decimal place (eg, 4.5 days).

The total duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).

Summaries will be provided by treatment group for the Safety Analysis Set. No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of tablets administered will be summarized using descriptive statistics.

The presumed total number of tablets administered to a subject will be determined by the data collected on the study drug administration eCRF using the following formula:

$$\begin{aligned}&\text{Total Number of Tablets Administered}\\&= \text{No. of Tablets Administered at Day 1/Baseline}\end{aligned}$$

The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study.

The level of prescribed adherence will be expressed as a percentage using the following formula:

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

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, ≤ 75% and > 75%) will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

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, but enrolled in the study 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 eligibility criterion and the number of subjects who did not meet specific entry criteria by treatment group based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that 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 selected inclusion/exclusion criteria) will be summarized by treatment group for All Randomized Analysis Set. A by-subject listing will be provided for those subjects with any protocol deviation.

5. BASELINE DATA

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. The summary of demographic data will be provided for the Safety Analysis Set and Evaluable Analysis Set.

In addition, a similar summary table will be provided by the stratification factor.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Weight (kg)
- Height (cm)
- Body mass index (BMI; in kg/m^2)
- RSV types (RSV A or RSV B)
- Vital signs (pulse rate, systolic and diastolic blood pressure, body temperature, and respiratory rate)
- Smoking history
- Viral load value
- Detectable RSV in nasal swab samples
- Co-pathogen types
- Duration of respiratory symptoms prior to the first dosing date of study drug
- Stratification factor
- Clinical frailty scale (CFS) score
- FLU-PRO score
- Duration of hospitalization prior to the first dosing date of study drug

- Neutrophil/Lymphocyte ratio
- Lymphocyte/Monocyte ratio
- Platelet/Lymphocyte ratio
- log(CRP)/Eosinophil ratio

These baseline characteristics will be summarized by treatment groups and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set and Evaluable Analysis Set. No formal statistical testing is planned.

In addition, these baseline characteristics will be summarized by treatment groups for the stratification factor.

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 general conditions (ie, conditions not specific to the disease being studied).

General medical history will be summarized by treatment group and overall by the number and percentage of subjects with each prepopulated condition. A summary of general medical history will be provided for the Safety Analysis Set.

No formal statistical testing is planned.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoints

The primary efficacy endpoint for this study is the time-weighted average change in $\log_{10}$ viral load from Day 1 to Day 5, 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 = the change from Baseline in RSV $\log_{10}$ viral load at Visit i

t = the time at the specified timepoint (the actual study day)

a = the baseline assessment at Day 1

b = the last assessment at or prior to Day 5

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

6.1.2. Analysis for the Primary Efficacy Endpoints

The primary analysis will test the null hypothesis that there is no difference between the presatovir and placebo treatment groups in the time-weighted average change in nasal RSV viral load (log10 copies/mL) from Baseline (Day 1) to Day 5 versus the alternative hypothesis that there is a difference.

The primary analysis will be performed on subjects included in the Evaluable Analysis Set. To test the null hypothesis that there is no difference between the presatovir and placebo treatment groups in the time-weighted average change on viral load, a parametric analysis of covariance (ANCOVA) model with corresponding baseline viral load, CFS score, and stratification factor as covariates will be used, at a 2-sided 0.05 level. Adjusted means and 95% confidence intervals (CIs) will be provided.

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Viral load values below the limit of detection (LOD) will be assigned as 0 if it is reported in the form of 'not detected'. A value of 1 unit less than the LOQ will be used for analysis if viral load is reported in the form of "< x" (where x is considered the LOQ). Viral load data will be transformed using the base 10 logarithm for the analyses and summaries. To account for 0 values, 1 will be added to each viral load measurement before being transformed.

The primary analysis will be generated for the subgroups specified in Section 3.4 including the stratification factor (no chronic airways or lung disease, COPD, asthma, and other chronic airways or lung disease).

6.1.3. Sensitivity Analysis for Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint will be performed in the PP analysis set.

6.1.4. Imputation of Missing Data

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.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Time-weighted average change in the FLU-PRO score from Baseline to Day 5
- Duration of hospital stay following IMP administration
- Rate of unplanned medical encounters (clinic visits, emergency room visits, urgent care visits, and rehospitalizations) related to a respiratory illness after initial hospital discharge through Day 28

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

In order to account for multiple hypothesis testing of endpoints, a sequential 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 Evaluable Analysis Set will be used for all summaries and analyses of secondary efficacy endpoints. All secondary endpoints will be analyzed using 2-sided tests to compare treatment differences.

Time-weighted average change in the FLU-PRO score from Baseline to Day 5 will be analyzed using an ANCOVA model with the baseline FLU-PRO value, CFS score and the stratification factor as covariates. Adjusted means and 95% CIs will be presented for this analysis.

The total number of hospitalization-free days will be the sum of the individual hospitalization-free days on the study period, where subjects accrue 1 hospitalization–free day for each day that they are not in the hospital and are alive after study entry. Subjects who die prior to Day 28 (inclusive) or are in hospital on all days of the 28-day study period are assigned

0 hospitalization-free days. The number of hospitalization-free day will be analyzed using a negative binomial model with the stratification factor as a covariate, and an offset parameter to account for the on-study duration. Appendix 5 provides some sample SAS model statements for the negative binomial model.

The rate of unplanned medical encounters related to respiratory illness after initial hospitalization discharge through Day 28 is defined as the number of events per subject and calculated as:

$$rate = \frac{total\ number\ of\ unplanned\ medical\ encounters\ over\ all\ subjets}{total\ number\ of\ subjects}$$

The number of unplanned medical encounters after initial hospitalization will be summed up for each subject. The rate of unplanned medical encounters related to respiratory illness after initial hospitalization discharge through Day 28 will be analyzed using a negative binomial regression method with the stratification factor as a covariate. Appendix 6 provides some sample SAS model statements for analysis.

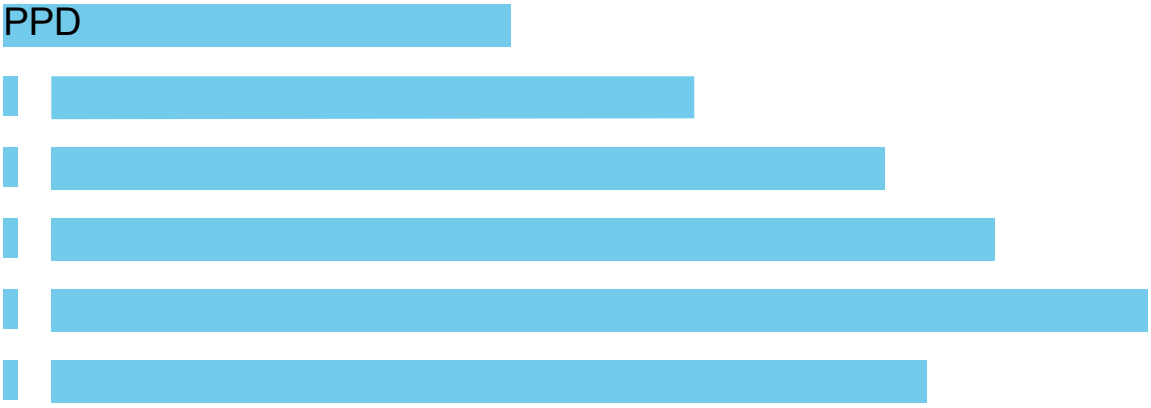
6.2.3. Sensitivity Analysis for Secondary Efficacy Endpoints

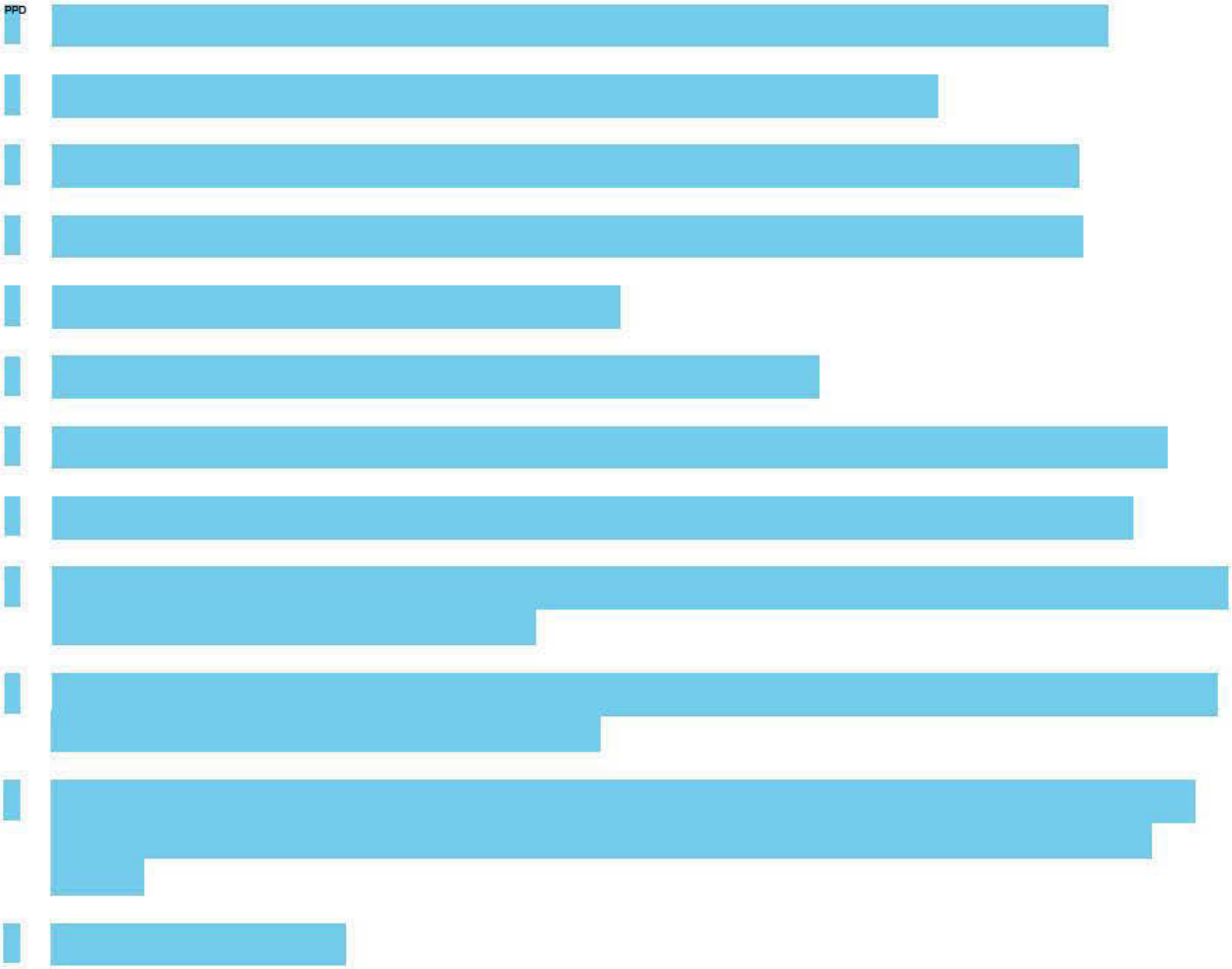
The following sensitivity analyses will be performed:

- The secondary efficacy endpoints will be performed in the PP analysis set.
- The rate of unplanned medical encounters related to respiratory illness after initial hospitalization discharge through Day 28 will also be analyzed using a negative binomial regression method with the stratification factor, and duration of initial hospitalization as covariates.
- The total number of hospitalization-free days up to 28 days will be analyzed using a negative binomial model with the stratification factor as a covariate, and an offset parameter to account for the on-study duration.

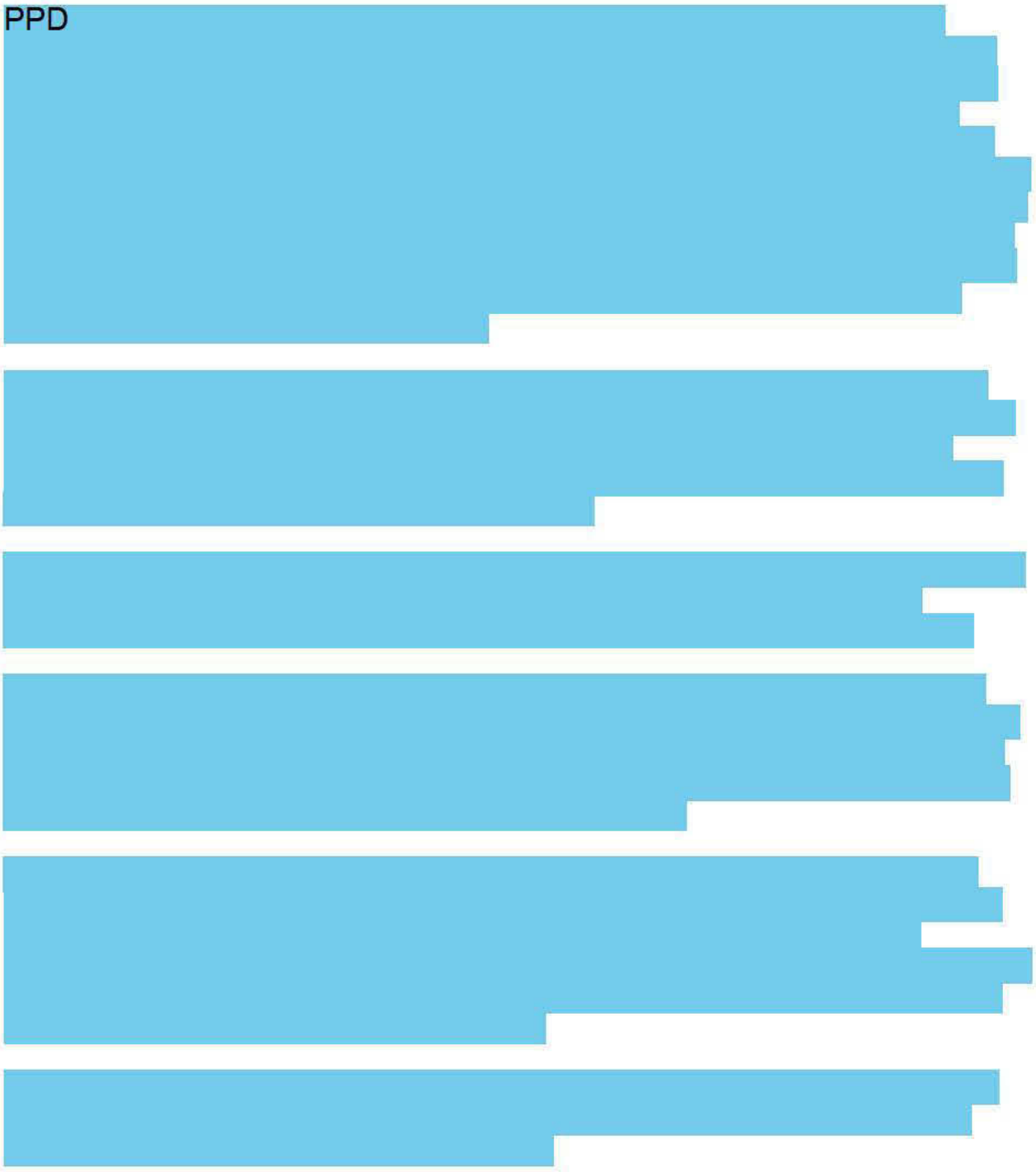
6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints





6.3.2. Analysis Methods for Exploratory Efficacy Endpoints


PPD

6.4. Changes From Protocol-Specified Efficacy Analyses

PPD

The following changes were made from the protocol-specified efficacy analyses:

- The efficacy endpoint, duration of hospitalization, and number of days of supplemental O_2 use, were changed to the number of hospitalization-free days and the number of supplemental O_2-free days through Day 28 respectively, to account for death on study.

- The stratification factor is added as a covariate into analysis models for efficacy endpoints.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events will be coded using the current version of 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 provided in the AE dataset.

7.1.2. Adverse Event Severity

Severity of adverse events will be determined by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening). The severity 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 case report form (CRF) 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 SAEs that were specified in the study protocol. SAEs 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 (TEAE) are defined as 1 or both of the following:

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent (TE) AEs will be summarized based on the Safety Analysis Set

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 who experienced any cardiac events will be provided for each treatment group using the Safety Analysis Set by AE of interest categories and the associated PTs (see Appendix 3).

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to Day 28. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as

such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolized 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, and serum chemistry 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 formal testing will be generated.

7.2.1. Summaries of Numeric Laboratory Results

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

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

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

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

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (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 postbaseline time point, up to and including Day 28. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

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 postbaseline 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

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit.

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities
- Marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing postbaseline values up to and including Day 28.

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 postbaseline 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. Vital Signs

Descriptive statistics will be provided by treatment group for vital signs as follows:

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

Median (Q1, Q3) of the observed values for vital signs will be plotted by treatment group and visit.

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 post-baseline visit will be defined as the post-baseline value minus the baseline value.

In the case of multiple values at a visit assessment, data will be selected for analysis as described in Section 3.8.3. 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 and height will be included in the vital signs listing, if space permits. If not, they will be provided in the baseline characteristics listing given they were only collected at Baseline.

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.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 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 classes and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 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 class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date 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 prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug plus 4 days will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

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

7.5. Electrocardiogram Results

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 central assessment of ECG results at postbaseline visit including the assessments obtained for the purpose of standard of care compared with baseline values will be presented by treatment group using the following categories: normal, no new abnormality, new abnormality, 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 post-baseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG central assessment and ECG abnormalities, including those not required by the protocol (ie. standard of care), will be provided by subject ID number and time point in chronological order.

7.6. Other Safety Measures

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 post-baseline 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.

A by-subject listing for all troponin results, including those not required by the protocol (ie, standard of care), will be provided by subject ID number and visit in chronological order.

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

7.7. Changes From Protocol-Specified Safety Analyses

In accordance with the DMC Charter, an additional safety DMC meeting was scheduled to occur after approximately 75% of the subjects were enrolled. The winter 2016/2017 RSV season resulted in higher rates of enrollment for this study compared to previous RSV seasons. Due to

quicker than expected enrollment and the time required to prepare for a DMC meeting, it would not have been possible to hold the planned DMC meeting prior to all subjects completing treatment with presatovir. Since Gilead would not have been able to take action based on the findings of the DMC, the DMC Chairperson agreed to forgo the meeting.

It was decided to end enrollment on 24May2017 when 190 subjects have been enrolled, even if full enrollment was not reached as the study was sufficiently powered for the primary endpoint so that the data of this study could be reviewed in conjunction with data from other two RSV studies (GS-US-218-1797 and GS-US-218-1502) in order to make informed decisions about ongoing development of the presatovir program.

8. PHARMACOKINETIC ANALYSES

Individual subject concentration data for presatovir (GS-5806) will be listed and summarized using descriptive statistics. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be calculated for individual subject concentration data by time point.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at pre-dose and one-half of the lower LOQ for post-dose time points.

The following table will be provided for presatovir:

- Individual subject concentration data and summary statistics

The following figures will be provided for presatovir:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median post-dose concentration values that are ≤ lower LOQ will not be displayed in the figures and remaining points connected.

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

9. BIOMARKER ANALYSES

To characterize the post-baseline changes in the levels of biomarkers, % baseline for biomarkers over time will be summarized at baseline and post-dose visits for the biomarker analysis set.

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

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit
- %baseline defined as (post-baseline/baseline)*100
- Percent change from baseline defined as ((postbaseline-baseline)/baseline)*100

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. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values, change from baseline, % baseline endpoint and percent change from baseline for each biomarker will be plotted using a line plot by treatment group and visit.

10. REFERENCES

Dmitrienko A, Offen WW, Westfall PH. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. Statist Med 2003;22 (15):2387-400.

Lachin JM. A review of methods for futility stopping based on conditional power. Stat Med 2005;24 (18):2747-64.

11. SOFTWARE

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

12. SAP REVISION

Revision Date	Section	Summary of Revision	Reason for Revision
17 August 2017	Throughout the document	Made minor editorial changes	The editorial, administrative, and formatting changes and updates were made to align with Amendment 4 released on 17 November 2015 and Gliead standard template updates, where appropriate, to improve clarity and consistency.
17 August 2017	Section 1	Updated protocol amendment number from 3.0 to 4.0	The protocol was amended after the SAP approval.
17 August 2017	Section 2.2.2	Removed the conditional power calculation formula	The details were provided in Appendix 2.
17 August 2017	Section 2.2.3	Added the texts to state the existing of the communication plan	The procedures and guidelines to be followed by Gilead at the time of any unblinded interim analysis were also provided in the communication plan for transparency.
17 August 2017	Section 3.1.2	Redefined the Per Protocol Analysis Set	The definition of Per Protocol Analysis Set was modified to align with the updated Important Protocol Deviation plan.
17 August 2017	Section 3.1.7	Added Biomarker Analysis Set	The analysis set for Biomarker data was defined.
17 August 2017	Section 3.4	Modified the list of subgroup analysis for efficacy endpoints	The list of subgroup analysis was modified to exclude sex, age, race and smoking status, and instead to include RSV type and duration of RSV symptoms as these subgroup analyses were deemed more clinically meaningful.
17 August 2017	Section 4.2	Added calculation for drug exposure and adherence	This section was revised to provide more details and clarification.
17 August 2017	Section 9	Added Biomarker Analysis	The analysis methods for Biomarker data were included.
17 August 2017	Section 5.2	Added the blood count differential ratios	The blood count differential ratios were added to better understand the study population.

Revision Date	Section	Summary of Revision	Reason for Revision
17 August 2017	Section 5.3	Added analysis for coded medical history	Medical history was decided later to be coded to provide a better understanding of the study population, and then summary statistics were provided.
17 August 2017	Section 6.1	Added handling of LOD and LOQ for viral load data	The details were provided for handling viral load values below LOD and LOQ in the analysis. This section was also revised to provide more details and clarification.
17 August 2017	Section 6.2.3	Added additional sensitivity analyses for the secondary endpoints	The additional sensitivity analyses were explored to understand the endpoints better.
17 August 2017	Section 6.1.3 and Section 6.2.3	Removed sensitivity analysis for efficacy endpoints using the FAS	The FAS includes those RSV negative subjects, hence the efficacy analysis based on the FAS was deemed not clinically meaningful.
17 August 2017	Section 6.3	Added the new exploratory endpoint of PPD	PPD
17 August 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
17 August 2017	Section 7.2.3	Added liver related laboratory evaluation	The evaluation was added in order to comply with regulatory requirements.
17 August 2017	Section 7.5	Added ECG assessment	The assessment of ECG data reviewed by the central reader was added in Amendment 4 in order to comply with FDA mandated cardiac monitoring requirements. The statistical analysis was provided accordingly.
17 August 2017	Section 7.6	Added Troponin assessment	The assessment of troponin was added in Amendment 4 in order to comply with FDA mandated cardiac monitoring requirements. The statistical analysis was provided accordingly.
17 August 2017	Section 8	Excluded PK parameter analyses	The analyses for PK parameters were removed as it was decided by the PK team as there is no need to generate PK parameters. The section was also revised to provide more details and for clarification.

Revision Date	Section	Summary of Revision	Reason for Revision
17 August 2017	Section 13	Updated Table of Contents for statistical tables, figures, and listings	The Table of Contents was updated to include additional analyses results.
17 August 2017	Appendix 1	Updated study procedure table	The schedule of assessment was updated based on Amendment 4 due to the addition of extra study procedures to comply with FDA mandated cardiac monitoring requirements.
17 August 2017	Appendix 2	Updated the conditional power calculation formula and SAS example codes	The formula was revised to allow different sample sizes observed from treatment groups at interim analysis.
17 August 2017	Appendix 4, Appendix 5 and Appendix 6	Added SAS example codes	The example codes were provided for analyses.

13. PROPOSED TABLES, FIGURES AND LISTINGS

13.1. Tables

Table	Title	Analysis Set
15.8.1.1	Enrollment by Country and Investigator	All Randomized Analysis Set
15.8.1.2	Enrollment by Stratification Stratum	All Randomized Analysis Set
15.8.1.3	Subject Disposition	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 Stratification Factor	Safety Analysis Set
15.8.3.1.3	Demographics	Evaluable Analysis Set
15.8.3.2.1	Baseline Characteristics	Safety Analysis Set
15.8.3.2.2	Baseline Characteristics by Stratification Factor	Safety Analysis Set
15.8.3.2.3	Baseline Characteristics	Evaluable Analysis Set
15.8.3.3	Medical History	Safety Analysis Set
15.8.4	Adherence to Study Medications	Safety Analysis Set
15.8.5	Analysis Sets	All Randomized Analysis Set
15.9.1.1	Time-weighted Average Change in Nasal Viral Load (log_{10} copies/mL) from Baseline to Day 5	Evaluable Analysis Set
15.9.1.2	Time-weighted Average Change in Nasal Viral Load (log_{10} copies/ mL) from Baseline to Day 5	PP Analysis Set
15.9.1.3	Time-weighted Average Change in Nasal Viral Load (log_{10} copies/ mL) from Baseline to Day 5 by Stratification Factor	Evaluable Analysis Set
15.9.1.4	Time-weighted Average Change in Nasal Viral Load (log_{10} copies/ mL) from Baseline to Day 5 by RSV Type	Evaluable Analysis Set
15.9.1.5	Time-weighted Average Change in Nasal Viral Load (log_{10} copies/ mL) from Baseline to Day 5 by Duration of RSV Symptom	Evaluable Analysis Set
15.9.2.1.1	Time-weighted Average Change in FLU-PRO Score from Baseline to Day 5	Evaluable Analysis Set
15.9.2.1.2	Time-weighted Average Change in FLU-PRO Score from Baseline to Day 5	PP Analysis Set

Table	Title	Analysis Set
15.9.2.1.3	Time-weighted Average Change in FLU-PRO Score from Baseline to Day 5 by Stratification Factor	Evaluable Analysis Set
15.9.2.2.1	Number of Hospitalization-Free Day Following IMP Administration through Day 28	Evaluable Analysis Set
15.9.2.2.2	Number of Hospitalization-Free Day Following IMP Administration through Day 28	PP Analysis Set
15.9.2.2.3	Number of Hospitalization-Free Day Following IMP Administration through Day 28 by Stratification Factor	Evaluable Analysis Set
15.9.2.2.4	Number of Hospitalization-Free Day Following IMP Administration	Evaluable Analysis Set (Sensitivity Analysis)
15.9.2.3.1	Rate of Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28	Evaluable Analysis Set
15.9.2.3.2	Rate of Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28	PP Analysis Set
15.9.2.3.3	Rate of Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28 by Stratification Factor	Evaluable Analysis Set
15.9.2.3.4	Rate of Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28	Evaluable Analysis Set (Sensitivity Analysis)
15.9.3.1	RSV Viral Load (log_{10} copies/ml) and Change from Baseline in the Nasal Samples	Evaluable Analysis Set
15.9.3.2	Time-weighted Average and Average Change from Baseline in Nasal RSV Viral Load (log_{10} copies/ mL) at Each Visit	Evaluable Analysis Set
15.9.3.3	Respiratory Rate and Change from Baseline at Each Visit	Evaluable Analysis Set
15.9.3.4	O_2 Saturation and Change from Baseline at Each Visit	Evaluable Analysis Set
15.9.3.5.1	Number of Supplemental O_2-free Day During Study	Evaluable Analysis Set
15.9.3.5.2	Number of Supplemental O_2-free Day up to 28 Days (Sensitivity Analysis)	Evaluable Analysis Set
15.9.3.6	Time-weighted Average and Average Change from Baseline in FLU-PRO Total Score	Evaluable Analysis Set
15.9.3.7	FLU-PRO Score and Change from Baseline at Each Visit	Evaluable Analysis Set
15.9.3.8	Number of Subjects Transferred to the ICU During Hospitalization	Evaluable Analysis Set
15.9.3.9	Number of Subjects Developing Respiratory Failure Requiring Mechanical Ventilation During Hospitalization	Evaluable Analysis Set
15.9.3.10	Number of Subjects Discharged to a Nursing Home or Intermediate Care/Rehabilitation Facility for Subjects not Originating at Said Facilities	Evaluable Analysis Set
15.9.3.11.1	Number of Subjects with Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28	Evaluable Analysis Set

Table	Title	Analysis Set
15.9.2.11.2	Number of Subjects with Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28	PP Analysis Set
15.9.2.11.3	Number of Subjects with Unplanned Medical Encounters Related to Respiratory Illness after Initial Hospital Discharge through Day 28 by Stratification Factor	Evaluable Analysis Set
15.9.2.11.4	Rate of Unplanned Visits at Each Facility (Clinic Visits, Emergency Room Visits, Urgent Care Visits, and Rehospitalizations) After Initial Hospitalization Discharge through Day 28	Evaluable Analysis Set
15.9.2.11.5	Number of Subjects with Unplanned Visits at Each Facility (Clinic Visits, Emergency Room Visits, Urgent Care Visits, and Rehospitalizations) After Initial Hospitalization Discharge through Day 28	Evaluable Analysis Set
15.9.3.12	Deaths through Day 28	Evaluable Analysis Set
15.9.3.13	EQ5D-5L Visual Analog Scale (VAS) and Change from Baseline at Each Visit	Evaluable Analysis Set
15.10.1	Individual Data and Summary Statistics of Plasma Concentration (ng/mL) at Protocol Specified Sampling Time	PK Analysis 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
15.11.2.1.2.1	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
15.11.2.1.3	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 Preferred Term	Safety Analysis Set
15.11.2.2.2.3	Treatment-Emergent Adverse Events with Severity of Grade 3 or Above by Preferred Term	Safety Analysis Set

Table	Title	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, 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 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 Events Related to Study Drug by System Organ Class and 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 Preferred Term	Safety Analysis Set
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/uL) 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/uL) and Change from Baseline	Safety Analysis Set

Table	Title	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/uL) 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/uL) 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 (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.4	Chemistry Test: 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
15.11.6.3.1	Biomarker Test: hsCRP (mg/dL) and Change from Baseline	Biomarker Analysis Set
15.11.6.3.2	Biomarker Test: Procalcitonin (ng/mL) and Change from Baseline	Biomarker Analysis Set
15.11.6.3.3	Biomarker Test: Interferon Gamma IP-10 (pg/mL) and Change from Baseline	Biomarker 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
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	Shift in Troponin Results	Safety Analysis Set
15.11.7.1.1	Vital Signs: Systolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.2	Vital Signs: Diastolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.3	Vital Signs: Pulse (beats per min) and Change from Baseline	Safety Analysis Set
15.11.7.1.4	Vital Signs: Temperature (Celsius) 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

Table	Title	Analysis Set
15.11.9.1	Shift in Electrocardiogram Results	Safety Analysis Set
15.11.9.2	Subject with New ECG Abnormalities at Postbaseline	Safety Analysis Set

13.2. Figures

Figure	Title	Analysis Set
15.8.1	Histogram of Enrollment by Country	All Randomized Analysis Set
15.8.2	Histogram of Enrollment by Site	All Randomized Analysis Set
15.9.1.1	Median (Q1, Q3) Viral Load (log10 copies/ mL) at Each Visit	Evaluable Analysis Set
15.9.1.2	Median (Q1, Q3) Change from Baseline in Viral Load (log10 copies/ mL) at Each Visit	Evaluable Analysis Set
15.9.1.3	Median (Q1, Q3) Viral Load (log10 copies/ mL) at Each Visit by Duration of RSV Symptoms at Enrollment	Evaluable Analysis Set
15.9.1.4	Median (Q1, Q3) Change from Baseline in Viral Load (log10 copies/ mL) at Each Visit by Duration of RSV Symptoms at Enrollment	Evaluable Analysis Set
15.9.2.1	Median (Q1, Q3) FLU-PRO Total Score by Visit	Evaluable Analysis Set
15.9.2.2	Median (Q1, Q3) Change from Baseline in FLU-PRO Total Score	Evaluable Analysis Set
15.9.3.1	Median (Q1, Q3) Respiratory Rate by Visit	Evaluable Analysis Set
15.9.3.2	Median (Q1, Q3) Change from Baseline in Respiratory Rate by Visit	Evaluable Analysis Set
15.9.4.1	Median (Q1, Q3) O2 Saturation by Visit	Evaluable Analysis Set
15.9.4.2	Median (Q1, Q3) Change from Baseline in O2 Saturation by Visit	Evaluable Analysis Set
15.10.1.1.1	Mean (SD) Plasma Concentrations vs. Time	PK Analysis 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 Test: Hemoglobin (g/dL) by Visit	Safety Analysis Set
15.11.6.1.2	Median (Q1, Q3) Hematology Test: Lymphocytes (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.1.3	Median (Q1, Q3) Hematology Test: Lymphocytes (%) by Visit	Safety Analysis Set
15.11.6.1.4	Median (Q1, Q3) Hematology Test: Monocytes (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.1.5	Median (Q1, Q3) Hematology Test: Monocytes (%) by Visit	Safety Analysis Set
15.11.6.1.6	Median (Q1, Q3) Hematology Test: Neutrophils (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.1.7	Median (Q1, Q3) Hematology Test: Neutrophils (%) by Visit	Safety Analysis Set
15.11.6.1.8	Median (Q1, Q3) Hematology Test: Leukocytes (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.1.9	Median (Q1, Q3) Hematology Test: Platelet Count (x10^3/uL) by Visit	Safety Analysis Set

Figure	Title	Analysis Set
15.11.6.2.1	Median (Q1, Q3) Chemistry Test: ALT (U/L) by Visit	Safety Analysis Set
15.11.6.2.2	Median (Q1, Q3) Chemistry Test: AST (U/L) by Visit	Safety Analysis Set
15.11.6.2.3	Median (Q1, Q3) Chemistry Test: Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
15.11.6.2.4	Median (Q1, Q3) Chemistry Test: Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
15.11.6.2.5	Median (Q1, Q3) Chemistry Test: Blood Urea Nitrogen (mg/dL) by Visit	Safety Analysis Set
15.11.6.2.6	Median (Q1, Q3) Chemistry Test: Creatinine (mg/dL) by Visit	Safety Analysis Set
15.11.6.2.7	Median (Q1, Q3) Chemistry Test: Creatinine Clearance (mL/min) by Visit	Safety Analysis Set
15.11.6.3.1.1	Median (Q1, Q3) Biomarker Test: hsCRP (mg/dL) by Visit	Biomarker Analysis Set
15.11.6.3.1.1	Median (Q1, Q3) Biomarker Test: Change from Baseline in hsCRP (mg/dL) by Visit	Biomarker Analysis Set
15.11.6.3.1.3	Median (Q1, Q3) Biomarker Test: %Baseline in hsCRP by Visit	Biomarker Analysis Set
15.11.6.3.1.4	Median (Q1, Q3) Biomarker Test: Percent Change from Baseline in hsCRP by Visit	Biomarker Analysis Set
15.11.6.3.2.1	Median (Q1, Q3) Biomarker Test: Procalcitonin (ng/mL) by Visit	Biomarker Analysis Set
15.11.6.3.2.2	Median (Q1, Q3) Biomarker Test: Change from Baseline in Procalcitonin (ng/mL) by Visit	Biomarker Analysis Set
15.11.6.3.2.3	Median (Q1, Q3) Biomarker Test: %Baseline in Procalcitonin by Visit	Biomarker Analysis Set
15.11.6.3.2.4	Median (Q1, Q3) Biomarker Test: Percent Change from Baseline in Procalcitonin by Visit	Biomarker Analysis Set
15.11.6.3.3.1	Median (Q1, Q3) Biomarker Test: Interferon Gamma IP-10 (pg/mL) by Visit	Biomarker Analysis Set
15.11.6.3.3.2	Median (Q1, Q3) Biomarker Test: Change from Baseline in Interferon Gamma IP-10 (pg/mL) by Visit	Biomarker Analysis Set
15.11.6.3.3.3	Median (Q1, Q3) Biomarker Test: 10 %Baseline in Interferon Gamma IP-10 by Visit	Biomarker Analysis Set
15.11.6.3.3.4	Median (Q1, Q3) Biomarker Test: Percent Change from Baseline in Interferon Gamma IP-10 by Visit	Biomarker Analysis Set
15.11.7.1.1	Median (Q1, Q3) Vital Signs: Systolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
15.11.7.1.2	Median (Q1, Q3) Vital Signs: Diastolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
15.11.7.1.3	Median (Q1, Q3) Vital Signs: Pulse Rate (beats per min) by Visit	Safety Analysis Set

Figure	Title	Analysis Set
15.11.7.1.4	Median (Q1, Q3) Vital Signs: Temperature (Celsius) by Visit	Safety Analysis Set

13.3. 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 Database Values	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 Evaluable Analysis Set but Excluded from the Per Protocol Analysis Set	Evaluable 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	Medical History	All Randomized Analysis Set
16.2.4.4	Prior and Concomitant Medications	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
16.2.6.1	Viral Load Measurements	Safety Analysis Set
16.2.6.2	FLU-PRO Measurements	Evaluable Analysis Set
16.2.6.3	Hospitalizations, ICU and Mechanical Ventilation	Evaluable Analysis Set
16.2.6.4	Healthcare Utilization	Evaluable Analysis Set
16.2.6.5.1	Supplemental Oxygen Assessment	Evaluable Analysis Set
16.2.6.5.2	Daily Supplemental Oxygen Use	Evaluable Analysis Set
16.2.6.6	Supplemental Oxygen Assessment prior to RSV Infection	Evaluable Analysis Set
16.2.6.7.1	EQ5D-5L Visual Analog Scale (VAS)	Evaluable Analysis Set
16.2.6.7.2	EQ5D-5L Descriptive System Score	Evaluable Analysis Set
16.2.6.8	Healthcare Related Efficacy Endpoints	Evaluable Analysis Set

Listing	Title	Analysis Set
16.2.7.1	Adverse Events	Safety Analysis Set
16.2.7.2.1	Deaths	Safety Analysis Set
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
16.2.8.1.2.1	Chemistry Results: Part 1	Safety Analysis Set
16.2.8.1.2.2	Chemistry Results: Part 2	Safety Analysis Set
16.2.8.1.3	Biomarker Results	Biomarker Analysis Set
16.2.8.1.4	Treatment Emergent Marked Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.5	Treatment Emergent Grade 3 or Above Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.6	Liver-Related Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.7	Laboratory Test Reference Ranges	
16.2.8.1.8	Laboratory Test Troponin Results	Safety Analysis Set
16.2.8.2	Vital Sign	Safety Analysis Set
16.2.8.3.1	Overall ECG Assessment	Safety Analysis Set
16.2.8.3.2	12-Lead ECG Results	Safety Analysis Set
16.2.8.4	Pregnancy Report	Safety Analysis Set
16.2.8.5	General Comments	All Randomized Analysis Set

14. APPENDICES

Appendix 1. Schedule of Assessment

	Day −1 Screening[a]	Day 1 Baseline	Day 2	Day 3	Day 5	Day 7	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (+ 7 days)
Written Informed Consent	x[b,c]								
RSV and Influenza testing	x[d]								
Nasal Sampling for RSV viral load testing		x	x	x	x	x	x		
Nasal Sampling for Additional Testing		x[e]							
Demographics	x								
Vital Signs / O_2 saturation	x	x[f]	x	x	x	x	x		
Medical History		x							
12-lead ECG		x[g]					x		
Hematology	x[h]	x		x	x		x		
Serum Chemistry	x[h]	x		x	x		x		
Troponin[m]		x					x		
PK blood draw		x[i]		x	x				
RSV antibody titer blood draw		x[j]					x		
Biomarker blood draw		x[j]			x				
Pregnancy Test	x[k]						x[l]		
Clinical Frailty Score		x							
FLU-PRO		x	x	x	x	x	x		
EQ5D-5L		x	x	x	x	x	x		
Healthcare Utilization Assessment						x	x	x	x
Drug Dosing		x							
Adverse Events	x	x	x	x	x	x	x	x	x

	Day −1 Screening[a]	Day 1 Baseline	Day 2	Day 3	Day 5	Day 7	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (+ 7 days)
Supplemental Oxygen Use Diary	x	x	x	x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x	x	x
Collection of Clinical Data for Cardiac-Related Tests		x	x	x	x	x	x	x	x

a Baseline (Day 1) visit to occur within 28 hours of Screening (ie signing the first consent form). Day 1 (Baseline) through Day 7 will occur 24 hours ± 4 hours apart, with no procedures occurring on Days 4 and 6.
b Patients anticipated to be eligible for this study will be consented for RSV testing of nasal samples.
c Patients who are RSV positive will be approached to consent for the screening and treatment phase of the study.
d Sampling technique and assay determined by local laboratory methods.
e Co-viral testing, prior to dosing, analyzed at central laboratory
f To include height and weight at Day 1. At Day 1 vital signs will be obtained 5-10 minutes prior to dosing and at 15 and 30 minutes after dosing.
g At Day 1/Baseline two ECGs will be obtained. The first will be obtained prior to dosing; the second will be obtained 2 hours ± 30 minutes after dosing.
h If no recent laboratory values are available from current hospitalization.
i To be drawn 2 hours ± 30 minutes after dosing.
j To be drawn prior to dosing.
k Urine pregnancy test will be performed at Screening in women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy.
l Serum pregnancy test will be performed on Day 14 in women unable to confirm menopause, hysterectomy, and/or bilateral oophorectomy.
m Troponin will be collected twice at Baseline; one sample will be collected pre-dose, the second sample will be collected 2 hours ± 30 minutes after dosing. All troponin samples will be tested at the local laboratory.

Appendix 2. Conditional Power Calculation for Futility Interim Analysis

Conditional power is defined as the probability of obtaining a statistically significant favorable result at the final analysis (at 2-sided alpha level α_D), given the data observed at the interim and assuming that future data is generated with a fixed true effect and sampling variation. The fix true effect could be the observed point estimate at the interim or an effect hypothesized to be true.

Under the current trend, the CP is calculated based on the formula below {Lachin 2005}:

$$CP = \Phi\left\{\frac{\frac{b}{t} - Z_{(1-\frac{\alpha}{2})}}{\sqrt{1-t}}\right\}$$

Where

t = information fraction at time of interim analysis, defined as the proportion of expected patients or events observed so far, calculated as

$$t = \frac{[\hat{\sigma}^2(\frac{1}{n_1} + \frac{1}{n_2})]^{-1}}{[\hat{\sigma}^2(\frac{1}{N_1} + \frac{1}{N_2})]^{-1}}$$

b = B-value, given by $b = Z_t/\sqrt{t}$, and Z_t is the observed statistic at information time t,

$$Z_t = \frac{\hat{\mu}_1 - \hat{\mu}_2}{\sqrt{\hat{\sigma}^2(\frac{1}{n_1} + \frac{1}{n_2})}}$$

$\hat{\mu}_1$ = interim sample means in arm A

$\hat{\mu}_2$ = interim sample means in arm B

$\hat{\sigma}$ = pooled sample standard deviation

n_1 = sample sizes at the interim analysis for arm A

n_2 = sample sizes at the interim analysis for arm B

N_1 = total sample size at final analysis for arm A

N_2 = total sample size at final analysis for arm B

$z_{(1-\alpha/2)}$ = $(1-\alpha/2)^{th}$ quantile of the standard normal distribution

$\Phi(.)$ = cumulative standard normal distribution function

SAS Example Codes for Conditional Power Calculation

```
/************************************************************************/
/* Conditional Power (CP) Calculation
/* Note: this program is developed to calculates the probability of
/*       statistical significance at final analysis
/*       given data observed at interim and assumed future data trend
/*
/* Input Parameters:
/*     NN1 = total number of subjects planned at final analysis in arm A
/*     NN2 = total number of subjects planned at final analysis in arm B
/*     sd = common standard deviation
/*     n1 = number of subjects observed at interim analysis in arm A
/*     n2 = number of subjects observed at interim analysis in arm B
/*     ss1 = standard deviation observed at interim analysis in arm A
/*     ss2 = standard deviation observed at interim analysis in arm B
/*     x1 = sample mean observed at interim analysis in arm A
/*     x2 = sample mean observed at interim analysis in arm B
/*     alpha = 2-sided alpha level at final analysis
/************************************************************************/

%macro CP_calc(NN1, NN2, sd, n1, n2, x1, x2, ss1, ss2, alpha, beta, Fvalue);

      %let nume = %sysevalf((&n1-1)*&ss1*&ss1 + (&n2-1)*&ss2*&ss2);
      %let denm = %sysevalf(&n1 + &n2 - 2);
      %let s = %sysevalf(%sysfunc(sqrt(&nume/&denm)));

      %let an = %sysevalf((1/&n1) + (1/&n2));

       %let z_t = %sysevalf(%sysfunc(sqrt(&Fvalue)));

      %let operator= <=;

      %if %sysevalf(&x1 &operator &x2) %then %do;
        %let z_t = %sysevalf(-&z_t);
       %end;

      %put &z_t;

      %let bn = %sysevalf((1/&NN1) + (1/&NN2));
      %let cn = %sysevalf(&s*&s*&an);
      %let dn = %sysevalf(&s*&s*&bn); /*assume equal variance*/
      %let t = %sysevalf((1/&cn)/(1/&dn));
      %put &t;

      %let b = %sysevalf(&z_t*%sysfunc(sqrt(&t)));
      %put &b;

      %let z_alpha = %sysevalf(%sysfunc(probit(1-&alpha/2))); * (alpha)th quantile of
standard normal distribution;
      %let zp = %sysevalf((&b/&t - &z_alpha)/%sysfunc(sqrt(1-&t)));

      %let CP = %sysevalf(%sysfunc(probnorm(&zp)));

      %put &CP;

      %let zp_alter = %sysevalf((&b + %sysfunc(probit(1-&beta))-
&t*(%sysfunc(probit(1-&alpha/2)) + %sysfunc(probit(1-&beta))))/%sysfunc(sqrt(1-&t)));
    %let CP_alter = %sysevalf(%sysfunc(probnorm(&zp_alter)));
```

```
      %put &zp_alter;
      %put &CP_alter;
%mend;

/* Example macro call */
%CP_calc(NN1=85, NN2=85, sd=2.3, n1=20, n2=20, x1=-1.09, x2=-0.67, ss1=1.069,
ss2=0.664, alpha=0.05, beta=0.2, Fvalue=2.314658); run;
```

Appendix 3. 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 4. Sample SAS Codes 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 Section 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 5. Sample SAS Codes 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 Section 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).

Appendix 6. Sample SAS Codes for Rate Analysis with Negative Binomial Model

The following model statement may be used for the analyses of rate of unplanned medical encounters described in Section 6.2.2:

```
proc genmod data=dataset;
          class trt;
          model c = trt / dist=poisson offset=logn;
          estimate 'treatment rate ratio' trt 1 -1;
          lsmeans trt / diff exp cl;
run;
```

where logn is the offset parameter defined as the natural logarithm of total number of subjects for each treatment group, and c is the number of events within each treatment group.