STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2b, Randomized, Controlled Trial Evaluating GS-5806 in Lung Transplant (LT) Recipients with Respiratory Syncytial Virus (RSV) Infection
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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT FIGURES 4
LIST OF ABBREVIATIONS 5
1. INTRODUCTION 7
1.1. Study Objectives 7
1.2. Study Design 7
1.3. Sample Size and Power 8
2. TYPE OF PLANNED ANALYSES 9
2.1. Data Monitoring Committee Analysis 9
2.2. Main Study Analysis 9
2.3. Final Analysis 9
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 10
3.1. Analysis Sets 10
3.1.1. All Randomized Analysis Set 10
3.1.2. Full Analysis Set 10
3.1.3. Per Protocol Analysis Set 11
3.1.4. Safety Analysis Set 11
3.1.5. Pharmacokinetic Analysis Set 11
3.2. Subject Grouping 11
3.3. Strata and Covariates 12
3.4. Examination of Subject Subgroups 12
3.5. Multiple Comparisons 12
3.6. Missing Data and Outliers 13
3.6.1. Missing Data 13
3.6.2. Outliers 13
3.7. Data Handling Conventions and Transformations 13
3.8. Analysis Visit 14
3.8.1. Definition of Study Day 14
3.8.2. Analysis Visit 14
3.8.3. Selection of Data in the Event of Multiple Records 15
4. SUBJECT DISPOSITION 16
4.1. Subject Enrollment and Disposition 16
4.2. Extent of Study Drug Exposure and Adherence 17
4.2.1. Duration of Exposure to Study Drug 17
4.2.2. Adherence to Study Drug 17
4.3. Protocol Deviations 18
5. BASELINE CHARACTERISTICS 19
5.1. Demographics 19
5.2. Other Baseline Characteristics 19
5.3. Medical History 20
6. EFFICACY ANALYSES 21
6.1. Primary Efficacy Endpoints 21
6.1.1. Definition of the Co-Primary Efficacy Endpoints 21
6.1.2. Analysis for the Co-Primary Efficacy Endpoints 21
6.1.3. Sensitivity Analysis for Primary Efficacy Endpoints 22

6.1.4. Imputation of Missing Data 22
6.2. Secondary Efficacy Endpoints 22
6.2.1. Definition of Secondary Efficacy Endpoints 22
6.2.2. Analysis Methods for Secondary Efficacy Endpoints 22
6.2.3. Sensitivity Analysis for Secondary Efficacy Endpoints 23
6.2.4. Imputation of Missing Data 23
6.3. Exploratory Efficacy Endpoints 23
6.3.1. Definition of Exploratory Efficacy Endpoints 23
6.3.2. Analysis Methods for Exploratory Efficacy Endpoints 24
6.4. Other Exploratory Efficacy Endpoint 26
6.5. Changes from Protocol-Specified Efficacy Analyses 26
7. SAFETY ANALYSES 27
7.1. Adverse Events and Deaths 27
7.1.1. Adverse Event Dictionary 27
7.1.2. Adverse Event Severity 27
7.1.3. Relationship of Adverse Events to Study Drug 27
7.1.4. Serious Adverse Events 27
7.1.5. Treatment-Emergent Adverse Events 27
7.1.6. Summaries of Adverse Events and Deaths 28
7.1.7. Additional Analysis of Adverse Events 29
7.2. Laboratory Evaluations 29
7.2.1. Summaries of Numeric Laboratory Results 30
7.2.2. Graded Laboratory Values 30
7.2.3. Liver-related Laboratory Evaluations 31
7.3. Vital Signs 32
7.4. Prior and Concomitant Medications 33
7.4.1. Prior Medications 33
7.4.2. Concomitant Medications 33
7.5. Electrocardiogram Assessment 34
7.6. Other Safety Measures 34
7.7. Changes From Protocol-Specified Safety Analyses 35
8. PHARMACOKINETIC (PK) ANALYSES 36
9. OPTIONAL REGISTRY ANALYSES 37
10. REFERENCES 38
11. SOFTWARE 39
12. SAP REVISION 40
13. PROPOSED TABLES, FIGURES AND LISTINGS 41
13.1. Tables 41
13.2. Figures 47
13.3. Listings 49
13.4. Optional Registry Listings 51
14. APPENDICES 52

Appendix 1. Study Procedures Table 52
Appendix 2. Alpha Allocation Approach 57
Appendix 3. Cardiac Adverse Events of Interest 58
Appendix 4. Sample SAS Code for Negative Binomial Model 59
Appendix 5. Sample SAS Code for MMRM Model 60

LIST OF IN-TEXT FIGURES

Figure 1-1. Study Visits 8

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (drug class)
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CSR	clinical study report
DAVG	difference between time-weighted average post-baseline and baseline
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report forms
EOT	end of treatment
FAS	Full Analysis Set
FLU-PRO	patient-reported outcome (PRO) measure to standardize the assessment of influenza (FLU) symptoms in clinical studies
HLT	high level term
HLGT	high level group term
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	identification
IMP	investigational medicinal product
IWRS	Interactive Web Response System
LLT	lower level term
LT	lung transplant
LOQ	limit of quantification
MedDRA	medical dictionary for regulatory activities
ml	milliliter
MMRM	mixed-effect model with repeated measures
PD	pharmacodynamics
PK	pharmacokinetics
PP	Per Protocol
PT	preferred term
Q1	first quartile
Q3	third quartile
RSV	respiratory syncytial virus
RT-qPCR	quantitative real time polymerase chain reaction
SAP	statistical analysis plan

SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
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-218-1797. This SAP is based on the study protocol amendment 2 dated 12 September 2016 and the electronic case report forms (eCRF). The SAP will be finalized before the database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the effect of presatovir (GS-5806) on nasal RSV viral load in RSV-positive lung transplant (LT) recipients with acute respiratory symptoms

The secondary objectives of this study are as follows:

- To evaluate the effect of presatovir on clinical sequelae of RSV infection and on measures of lung function
- To evaluate the pharmacokinetics (PK), safety, and tolerability of presatovir

1.2. Study Design

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

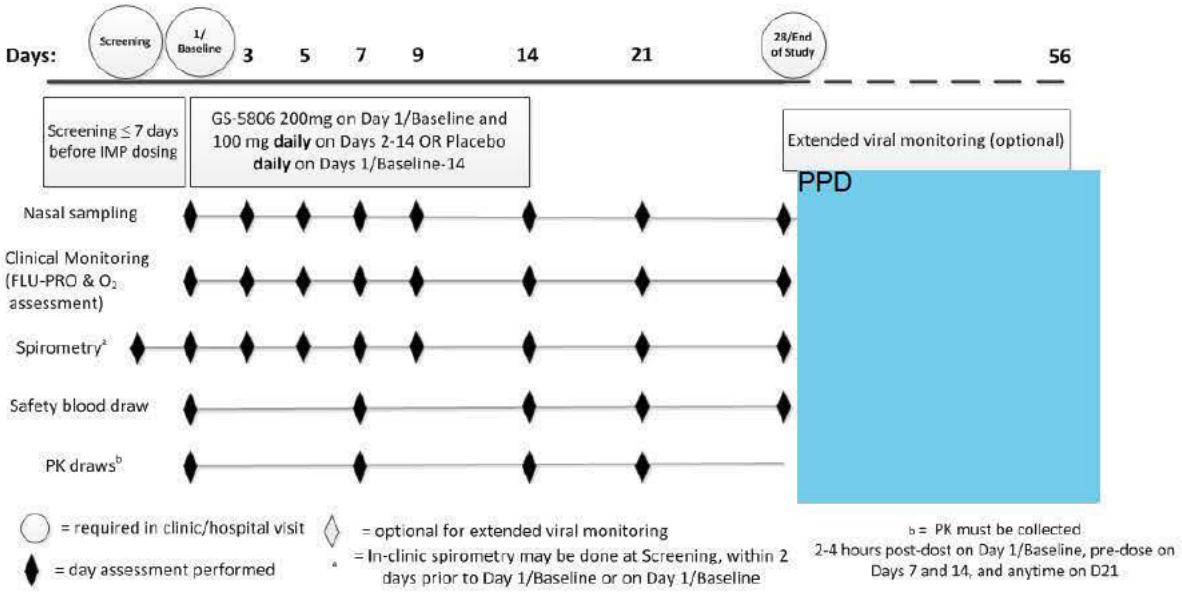
Approximately 60 RSV positive subjects with acute respiratory symptoms will be enrolled from approximately 40 centers. All subjects will be permitted to receive the standard-of-care therapy for RSV infection per their local medical practices, in addition to the investigational medicinal product (IMP).

Subjects will be randomized in a 2:1 ratio to receive presatovir administered as a 200-mg dose on Day 1/Baseline, followed by a 100-mg dose daily on Days 2 through 14 or placebo-to-match (PTM) once daily for a total of 14 days. Subjects will be stratified by 2 factors:

- Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)
- Use of palivizumab or IVIG (yes or no)

Subjects will be followed for a total of 28 days in the main study, during which a total of 8 study visits will be performed to assess safety, tolerability, PK, and viral loads. PPD

Figure 1-1. Study Visits



1.3. Sample Size and Power

Sample size calculations are based on results observed from 3 studies:

1) A study that evaluated the efficacy of oral and aerosolized ribavirin treatment for preventing progression from upper to lower respiratory tract infection in hematopoietic cell transplant recipients with RSV infections (unpublished data from Dr. Roy Chemaly)

2) A study conducted by Zamora et al that evaluated the treatment of RSV infection in LT recipients

3) GS-US-218-1227, an on-going Phase 2 study that is evaluating the antiviral effects of presatovir in hospitalized adults with RSV infection.

The sample size calculation assumes the time-weighted average change in RSV $\log_{10}$ viral load from Day 1/Baseline through Day 7 in the placebo group will be -1.5 $\log_{10}$ copies/mL with a corresponding standard deviation (SD) of 1.2. Based on these assumptions and the 2:1 allocation ratio to receive presatovir or placebo, with 34 subjects in the presatovir group and 17 subjects in the placebo group, there is at least 85% power to detect a 1.2 log difference in time-weighted average change in $\log_{10}$ viral load between presatovir and placebo using a 2-sided 0.04-level test in the co-primary endpoint including all subjects in the Full Analysis Set (FAS). There is 85% power to detect a 1.5 log difference with 17 subjects in the presatovir group and 9 subjects in the placebo group in the co-primary endpoint analysis of the subjects in the FAS with ≤ median duration of RSV symptoms prior to the date of the first dose of study medication in the overall population using a 2-sided 0.017-level test, assuming a SD of 1.2. Given an evaluable rate of 85%, a total of 60 subjects will need to be randomized into the study.

2. TYPE OF PLANNED ANALYSES

2.1. Data Monitoring Committee Analysis

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

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

One safety review was originally scheduled to occur after approximately 50% of the planned 60 subjects had been enrolled and had completed Day 28 visit or discontinued the study. This DMC review was cancelled due to the reasons specified in Section 7.7.

2.2. Main Study Analysis

After all subjects have completed the main study portion, outstanding data queries have been resolved or adjudicated as unresolvable, and the data from the main portion of the study has been cleaned and finalized, the study blind will be broken and the analysis of the data collected at the main study portion will be performed.

2.3. Final Analysis

After subjects who chose to participate in the optional registry have completed the study, and all data have been cleaned and finalized, the final analysis of the data will be performed.

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, and visit date. 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 and the reasons for their exclusion, will be summarized by treatment group.

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who took at least 1 full dose of study drug, and have an RSV viral load greater than or equal to the lower limit of quantification (LLOQ) of the RT-qPCR assay in the Day 1/Baseline nasal sample, as determined by RT-qPCR at the central lab. The subgroup analysis set includes subjects in the FAS who have the duration of RSV symptoms prior to the date of the first dose of study medication ≤ a median value of the distribution of the duration of RSV symptoms in the overall FAS population. The FAS and the subgroup analysis set will be used as the primary analysis sets for efficacy analyses.

3.1.3. Per Protocol Analysis Set

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

- Did not violate the following major exclusion criteria (EC)
  - EC #2: Use of a strong or moderate cytochrome P450 enzyme (CYP) inducer within 2 weeks prior to drug dosing
  - EC #16: An estimated eGFR <30 mL/min/1.73m^2 obtained ≤ 7 days prior to Screening
  - EC #17: ALT or AST > 5 times the ULN obtained ≤ 7 days prior to Screening
  - EC #18: Clinically significant elevations in total bilirubin (TB)
- Did not violate the following major inclusion criteria (IC)
  - IC #3: Had new onset respiratory symptoms or acute worsening of chronic preexisting symptoms ≤ 7 days prior to IMP administration on Day 1/Baseline
- Missed ≤ 2 doses (4 tablets) over the course of treatment
- Missed < 3 nasal swab samples over the course of the study

The PP Analysis Set is the secondary analysis set for efficacy analyses.

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 full dose of study drug. This is the primary analysis set for safety analyses.

3.1.5. Pharmacokinetic Analysis Set

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

3.2. Subject Grouping

For analyses based on the FAS 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 the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. For the PK Analysis Set, 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 2:1 ratio using a stratified randomization schedule. Stratification will be based on the following parameters:

- Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)
- Use of palivizumab or IVIG (yes or no)

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

Efficacy endpoints will be evaluated using stratification factors as covariates for analyses, as specified in Section 6. If there are a small number of subjects (eg, ≤ 4 subjects) within a stratum of the stratification factor, then the stratum will be collapsed with the adjacent stratum for the analysis.

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 efficacy endpoint will be examined using the following subgroup:

- RSV type (RSV A or RSV B)

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 the co-primary efficacy endpoints, an appropriate alpha allocation was numerically derived utilizing the inherent correlation between the test statistics (details provided in Appendix 2), which preserves the overall significance level of testing the primary endpoint at 0.05 (2-sided). Specifically, the alpha level for the overall FAS population will be 0.04 and the alpha level for the subgroup population (subjects in the FAS with duration of RSV symptoms prior to the date of the first dose of study medication ≤ a median value of the distribution of RSV symptom duration in the overall FAS population) will be 0.017.

If the primary null hypothesis is rejected, then the following secondary endpoints will be tested sequentially, based upon the closed testing procedure {Dmitrienko 2003}.

- Time-weighted average change in FLU-PRO score from Day 1/Baseline through Day 7

- Percent change from study baseline in FEV_1% predicted value at Day 28/End of Study

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 analysis.

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

Therefore, study day 1 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.

- Data collected on an extended viral load monitoring visit will be summarized as a separate visit, and labeled as Day 35, 42, 49, and 56.

3.8.3. Selection of Data in the Event of Multiple Records

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 dose date of study drug will be considered as the baseline value.

- 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 average will be taken, unless otherwise specified.

If multiple valid, non-missing, categorical measurements exist for one visit, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If 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 database, the value collected in the clinical database 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 database at the time of data finalization will be provided.

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

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not randomized 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
- Safety Analysis Set
- Per-Protocol Analysis Set
- PK Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed Main Study Portion
- Did not complete the Main Study Portion with reasons for premature discontinuation of Main Study Portion
- Completed Extended Viral Load Monitoring Period
- Did not complete the Extended Viral Load Monitoring Period with reasons for premature discontinuation of Extended Viral Load Monitoring Period

For the status of study drug and main study portion 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 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. The data collected in eCRF will be used for the analyses.

4.2.1. Duration of Exposure to Study Drug

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

The total duration of exposure to study drug will be summarized using descriptive statistics (number of subjects [n], mean, SD, median, Q1, Q3, minimum, and maximum), and using the number and percentage of subjects exposed through the following time periods: Day 1(Baseline), Day 3, Day 5, Day 7, Day 9 and Day 14. 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 drug accountability eCRF using the following formula:

$$\text{Total Number of Tablets Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

If a bottle is dispensed and the bottle is returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing), it will be assumed that a subject did not take all study drugs as prescribed during the period for which the bottle is dispensed.

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, $< 75\%$, $\geq 75\%$ to $< 85\%$ and $\geq 85\%$) 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 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 inclusion or exclusion criterion. The listing will present the eligibility criterion (or criteria if more than 1deviation) 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 the All Randomized Analysis Set. A by-subject listing will be provided for those subjects with any protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set.

In addition, a similar summary table will be provided by the consent status of participation in the Extended Viral Load Monitoring (yes or no).

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Height (cm)
- Weight (kg)
- 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
- Detectable RSV in nasal swab samples
- Co-pathogen types
- Duration of respiratory symptoms prior to the first dosing date
- FLU-PRO score
- FEV_1 actual value (L)
- FEV_1% predicted value

- FVC actual value (L)
- FVC% predicted value
- Stratification factors
- Hospitalization
- Have a new prescription for home oxygen therapy (yes or no)

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. In addition, baseline characteristics will be summarized by the consent status of participation in the Extended Viral Load Monitoring (yes or no) in a separate table. The summary of baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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

5.3. Medical History

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

Lung transplant specific medical history (eg, transplant types, presence of chronic lung allograft dysfunction [CLAD], presence of bronchiolitis obliterans syndrome [BOS], BOS grade, and cytomegalovirus [CMV] status, and time from transplant to the first dosing date) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables with each prepopulated condition. A summary of lung transplant specific medical history will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints of this study are: the time-weighted average change in nasal RSV viral load (log_{10} copies/mL) from Day 1/Baseline through Day 7 in the overall FAS population and in the subgroup population (defined as subjects in the FAS with duration of RSV symptoms prior to first dose of study medication ≤ a median value of the distribution of RSV symptom duration in the overall FAS population).

The time-weighted average change in nasal RSV viral load (log_{10} copies/mL) from Baseline (Day 1) to Day 7 as measured by RT-qPCR is defined as:

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

where Y_i is the change from Baseline in RSV log_{10} viral load at Visit *i*, *t* is the time at the specified timepoint (the actual study day), *a* is the baseline assessment at Day 1, and *b* is the last assessment at or prior to Day 7 visit.

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 Co-Primary Efficacy Endpoints

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

- H_{01}: There is no difference between presatovir and placebo in the time-weighted average change in RSV log_{10} viral load from Day 1 to Day 7 in the FAS

- H_{02}: There is no difference between presatovir and placebo in the time-weighted average change in RSV log_{10} viral load from Day 1 to Day 7 in the FAS with whose duration of RSV symptoms prior to the first dosing date of study medication is ≤ median of the symptom duration distribution in the overall FAS population

To test the null hypothesis above, a parametric analysis of covariance (ANCOVA) model with corresponding baseline viral load and stratification factors (treatment of RSV infection with ribavirin and use of palivizumab or IVIG) as covariates will be used, at a 2-sided 0.05 level. Adjusted means and 95% confidence intervals (CIs) will be provided. The stratified Wilcoxon rank sum test will be implemented as a sensitivity analysis. The tests will be 2-sided with significance levels specified in Section 3.5.

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 the 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.

6.1.3. Sensitivity Analysis for Primary Efficacy Endpoints

The following sensitivity analyses will be performed:

- The primary endpoint time-weighted average change in nasal RSV viral load from Baseline to Day 7 will be analyzed in the PP analysis set.
- The primary endpoint time-weighted average change in nasal RSV viral load from Baseline to Day 7 will be analyzed for subjects in FAS who have at least one postbaseline nasal swab sample through Day 7.

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

The secondary efficacy endpoints of this study are as follows:

- Time-weighted average change in FLU-PRO score from Day 1/Baseline through Day 7
- Percent change from study baseline in FEV_1% predicted value at Day 28/End of Study

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

FEV_1 % predicted value is calculated as a percent of the 'predicted values' for the patients of similar characteristics (height, age, sex, and sometimes race and weight). The method based on {Hankinson 1999} (aka NHANES III, 1999) will be used to calculate the FEV_1 % predicted value.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

The FAS analysis set will be used for all summaries and analyses of the secondary endpoints.

The treatment difference in the time-weighted average change in FLU-PRO score from Day 1/Baseline to Day 7 will be analyzed using an ANCOVA model with the baseline FLU-PRO score and stratification factors as covariates.

The treatment difference in the percent change from study baseline in FEV_1 % predicted value at Day 28 will be analyzed using an ANCOVA model with the study baseline FEV_1 % predicted value and stratification factors as covariates. The study baseline FEV_1 % predicted value is defined as the lowest FEV_1 % predicted value collected on or prior to the first dosing date if multiple non-missing numeric assessments exist. The data collected on eCRF will be used for the analyses.

6.2.3. Sensitivity Analysis for Secondary Efficacy Endpoints

The following sensitivity analyses will be performed:

- Percent change from study baseline in FEV_1 % predicted value at Day 28 will be analyzed in the PP analysis set.
- Time-weighted average change in FLU-PRO will be analyzed in the PP analysis set.
- Time-weighted average change in FLU-PRO will be analyzed for subjects in FAS who have at least one postbaseline FLU-PRO data through Day 7.

6.2.4. Imputation of Missing Data

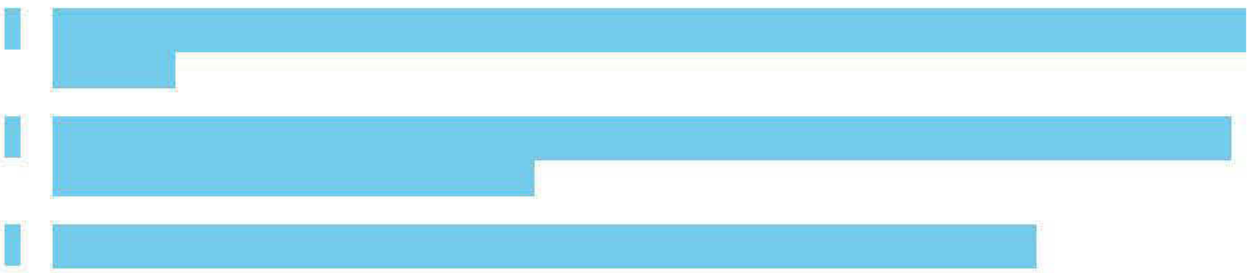
Missing FLU-PRO data due to premature discontinuation of the study will not be imputed as all available data will be included in the time-weighted average calculations. Intermediate missing FLU-PRO data will be imputed using the trapezoidal rule for the time-weighted average calculations.

Missing FEV_1 % predicted value will not be imputed given only 2 assessments are used for analysis (ie, data collected at study baseline and Day 28 visit).

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

PPD



PPD

6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

PPD


PPD

PPD

6.4. Other Exploratory Efficacy Endpoint

PPD

6.5. Changes from Protocol-Specified Efficacy Analyses

PPD

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events will be identified and captured as SAEs if AEs met the definitions of 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 (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date up to the Day 28 visit, 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 the Day 28 visit

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. 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 and PT, and treatment group. For other AEs described below, summaries will be provided by SOC and PT, and treatment group:

- TEAE by maximum severity
- TEAEs of Grade 3 or higher
- 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
- 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 (main study portion)
- 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 (with the death date on or after the study drug start date up to Day 28) 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, TE treatment-related AEs, and TE SAE 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 (main study portion)

7.1.7. Additional Analysis of Adverse Events

Summaries (number and percentage) of subjects who experienced any adverse 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 to assign 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, 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 lab test and 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 postbaseline 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 postbaseline visits up to and including Day 28. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline 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 postbaseline values of all relevant tests at the same postbaseline 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 body weight and vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline 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 postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits will be included for the baseline value selection.

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

In the case of multiple values at a visit assessment, data will be selected for analysis as described in Section 3.8.3. No formal statistics testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. Body weight, height and BMI 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 the Screening/Baseline visit.

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 medical classes and then by preferred term in order of descending overall frequency with in 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.

Prior ribavirin, palivizumub, and IVIG use will be summarized separately from other prior general medications.

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 medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any

medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

Concomitant ribavirin, palivizumub, and IVIG use will be summarized separately from other concomitant general medications.

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 Assessment

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

A by-subject listing for ECG central assessments and ECG abnormalities, including those not required by the protocol (ie, standard of care), will be provided by subject ID number and visit 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 medical care) compared with baseline values will be presented by treatment group using the following categories: normal, abnormal, or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

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

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, the initial safety DMC meeting was scheduled to occur after approximately 50% of the subjects were enrolled. The winter 2016/2017 RSV season resulted in a higher rate 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 the findings of the DMC would not have been actionable upon subjects in the study, the DMC Chairperson agreed to forgo the meeting

8. PHARMACOKINETIC (PK) ANALYSES

Individual subject concentration data for presatovir 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 presented 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 predose and one-half of the lower LOQ for postdose 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 postdose 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. OPTIONAL REGISTRY ANALYSES

PPD

- PPD
- PPD
- PPD
- PPD
- PPD

PPD

10. REFERENCES

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

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159 (1):179-87.

11. SOFTWARE

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

12. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

13. PROPOSED TABLES, FIGURES AND LISTINGS

13.1. Tables

Table Number	Title	Analysis Set
15.8.1.1	Enrollment by Country and Investigator	All Randomized Analysis Set
15.8.1.2	Enrollment by Randomization Stratum	All Randomized Analysis Set
15.8.1.3	Subject Disposition	All Screened Subject Randomized Analysis Set
15.8.2.1	Eligibility Criteria Deviations	All Randomized Analysis Set
15.8.2.2	Important Protocol Deviations	All Randomized Analysis Set
15.8.3.1.1	Demographics	Safety Analysis Set
15.8.3.1.2	Demographics by Consent for Participating in the Extend Viral Load Monitoring	Safety Analysis Set
15.8.3.2.1	Baseline Characteristics	Safety Analysis Set
15.8.3.2.2	Baseline Characteristics by Consent for Participating in the Extend Viral Load Monitoring	Safety Analysis Set
15.8.3.3	Lung Transplant Medical History	Safety Analysis Set
15.8.4	Adherence to Study Medications	Safety Analysis Set
15.8.5	Analysis Sets	All Randomized Analysis Set
15.9.1.1.1	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/ml) from Baseline to Day 7	Full Analysis Set
15.9.1.1.2	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/ml) from Baseline to Day 7	Per Protocol Analysis Set
15.9.1.1.3	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/ml) from Baseline to Day 7	Subjects in FAS with at Least One Postbaseline Nasal Sample (Sensitive Analysis)
15.9.1.1.1	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/ml) from Baseline to Day 7 by RSV Type	Full Analysis Set (Subgroup Analysis)
15.9.1.2.1	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/ml) from Baseline to Day 7 for Subjects Whose RSV Symptoms prior to the First Dose of Study Medication is ≤ Median of RSV Symptoms Distribution in the Overall Population	Full Analysis Set
15.9.1.2.2	Time-Weighted Average Change in Nasal RSV Viral Load (log_{10} copies/ml) from Baseline to Day 7 for Subjects Whose RSV Symptoms prior to the First Dose of Study Medication is ≤ Median of RSV Symptoms Distribution in the Overall Population	Per Protocol Analysis Set

Table Number	Title	Analysis Set
15.9.2.1.1	Time-Weighted Average Change in FLU-PRO Total Score from Baseline to Day 7	Full Analysis Set
15.9.2.1.2	Time-Weighted Average Change in FLU-PRO Total Score from Baseline to Day 7	Per Protocol Analysis Set
15.9.2.1.3	Time-Weighted Average Change in FLU-PRO Total Score from Study Baseline to Day 7	Subjects in FAS with at Least One Postbaseline FLU-PRO Score (Sensitive Analysis)
15.9.2.2.1	Percent Change from Study Baseline in Forced Expiratory Volume in 1 second (FEV_1) % Predicted Value at Day 28	Full Analysis Set
15.9.2.2.2	Percent Change from Study Baseline in Forced Expiratory Volume in 1 second (FEV_1) % Predicted Value at Day 28	Per Protocol Analysis Set
15.9.3.1.1	RSV Viral Load (log_{10} copies/ml) and Change from Baseline in the Nasal Samples by Visit	Full Analysis Set
15.9.3.1.2	RSV Viral Load (log_{10} copies/ml) and Change from Baseline in the Nasal Samples by Consent for Participating in the Extend Viral Load Monitoring	Full Analysis Set
15.9.3.2	Time-weighted Average and Time-weighted Average Change from Baseline in Nasal RSV Viral Load (log_{10} copies/ml) by Visit	Full Analysis Set
15.9.3.3.1	Proportion of Subjects with Detectable RSV in the Nasal Samples by Visit	Full Analysis Set
15.9.3.3.2	Proportion of Subjects with Detectable RSV in the Nasal Samples by Consent for Participating in the Extend Viral Load Monitoring	Full Analysis Set
15.9.3.4	Percent and Actual Change from Baseline in FVC on Absolute Value (Liter) and % Predicted Value at Day 28/End of Study	Full Analysis Set
15.9.3.5	Proportion of Subjects Experienced ≥ 10% drop from Baseline of Either FEV_1 or FVC (Based on Both Absolute [liters] and % Predicted Measures) by Day 28/End of Study	Full Analysis Set
15.9.3.6	FLU-PRO Score and Change from Baseline by Visit	Full Analysis Set
15.9.3.7	Time-weighted Average and Time-weighted Average Change in FLU-PRO Total Score by Visit	Full Analysis Set
15.9.3.8.1	Number of Days Admitted to the Hospital through Day 28/End of Study	Full Analysis Set
15.9.3.8.2	Number of Hospital-free Days through Day 28/End of Study	Full Analysis Set
15.9.3.9.1	Number of Days Admitted to the ICU through Day 28/End of Study	Full Analysis Set
15.9.3.9.2	Number of ICU-free Days through Day 28/End of Study	Full Analysis Set

Table Number	Title	Analysis Set
15.9.3.10	Proportion of Subjects Developing Respiratory Failure Which Require Noninvasive or Invasive Mechanical Ventilation through Day 28/End of Study	Full Analysis Set
15.9.3.11	Number of Ventilator-free Days through Day 28/End of Study	Full Analysis Set
15.9.3.12	Proportion of Subjects Who Require a New Prescription for Home Oxygen Therapy by Day 28/End of Study	Full Analysis Set
15.10.1.1	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 and Preferred Term	Safety Analysis Set
15.11.2.1.2.2	Treatment Emergent Adverse Events by System Organ Class 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 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
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

Table Number	Title	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
15.11.3	Treatment-Emergent Serious Adverse Events Leading to Death by Preferred Term	Safety Analysis Set
15.11.4.1	Treatment Emergent Serious Adverse Event by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.2	Treatment Emergent Serious Adverse Event by Preferred Term	Safety Analysis Set
15.11.4.3.1	Treatment Emergent Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.3.2	Treatment Emergent Treatment-Related Serious Adverse Events by Preferred Term	Safety Analysis Set
15.11.5.1	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
15.11.5.3.1	Treatment-Emergent Adverse Events of Interest (Cardiac Adverse Events) by System Organ Class and Preferred Term	Safety Analysis Set
15.11.5.3.2	Treatment-Emergent Serious Adverse Events of Interest (Cardiac Adverse Event) by System Organ Class and Preferred Term	Safety Analysis Set
15.11.6.1.1	Hematology Test: Hemoglobin (g/L) and Change from Baseline	Safety Analysis Set
15.11.6.1.2	Hematology Test: Lymphocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.3	Hematology Test: Lymphocytes (%) and Change from Baseline	Safety Analysis Set
15.11.6.1.4	Hematology Test: Monocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.5	Hematology Test: Monocytes (%) and Change from Baseline	Safety Analysis Set

Table Number	Title	Analysis Set
15.11.6.1.6	Hematology Test: Neutrophils (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.7	Hematology Test: Neutrophils (%) and Change from Baseline	Safety Analysis Set
15.11.6.1.8	Hematology Test: Platelets (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.9	Hematology Test: Leukocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.2.1	Chemistry Test: AST (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.2	Chemistry Test: ALT (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.3	Chemistry Test: Alkaline Phosphatase (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.2.4	Chemistry Test: Total Bilirubin (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.5	Chemistry Test: Blood Urea Nitrogen (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.6	Chemistry Test: Creatinine (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2.7	Chemistry Test: Creatinine Clearance (mL/min) and Change from Baseline	Safety Analysis Set
15.11.6.4.1.1	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 Above 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: Diastolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.2	Vital Signs: Systolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.3	Vital Signs: Pulse Rate (beats per minute) and Change from Baseline	Safety Analysis Set
15.11.7.1.4	Vital Signs: Respiration Rate (breaths per minute) and Change from Baseline	Safety Analysis Set

Table Number	Title	Analysis Set
15.11.7.1.5	Vital Signs: Temperature (Celsius) and Change from Baseline	Safety Analysis Set
15.11.7.1.6	Vital Signs: O_2 Saturation (%) and Change from Baseline	Safety Analysis Set
15.11.7.3.1	Prior Medication by Drug Class and Preferred Drug Name	Safety Analysis Set
15.11.7.3.2	Concomitant Medication by Drug Class and Preferred Drug Name	Safety Analysis Set
15.11.7.3.3	Prior Ribavirin, Palivizumub, and IVIG by Drug Class and Preferred Drug Name	Safety Analysis Set
15.11.7.3.4	Concomitant Ribavirin, Palivizumub, and IVIG by Drug Class and Preferred Drug Name	Safety Analysis Set
15.11.9.1	Shift in Electrocardiogram Assessment Results	Safety Analysis Set
15.11.9.2	Subjects with New Abnormalities ECG at Post-baseline	Safety Analysis Set

13.2. Figures

Figure	Title	Analysis Set
15.8.1	Histogram of Number of Subjects Enrolled by Site	All Randomized Analysis Set
15.8.2	Histogram of Number of Subjects Enrolled by Country	All Randomized Analysis Set
15.9.1.1	Mean (SD) Viral Load (log_{10} copies/ml) at Each Visit	Full Analysis Set
15.9.1.2	Mean (SD) Change from Baseline in Viral Load (log_{10} copies/ml) at Each Visit	Full Analysis Set
15.9.2.1.1	Mean (SD) FLU-PRO Score at Each Visit	Full Analysis Set
15.9.2.1.2	Mean (SD) Change from Baseline in FLU-PRO Score at Each Visit	Full Analysis Set
15.9.2.2.1	Mean (SD) FEV_1% Predicted Value at Each Visit	Full Analysis Set
15.9.2.2.2	Mean (SD) Change from Baseline in FEV_1% Predicted Value at Each Visit	Full Analysis Set
15.9.3.1	Mean (SD) FVC Value (L) at Each Visit	Full Analysis Set
15.9.3.2	Mean (SD) Change from Baseline in FVC Value at Each Visit	Full Analysis Set
15.10.1.1	Mean (SD) Plasma Concentrations 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/µL) 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/µL) 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/µL) 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
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

Figure	Title	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
15.11.7.1.1	Median (Q1, Q3) Vital Signs: Diastolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
15.11.7.1.2	Median (Q1, Q3) Vital Signs: Systolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
15.11.7.1.3	Median (Q1, Q3) Vital Signs: Pulse Rate (beats/min) by Visit	Safety Analysis Set
15.11.7.1.4	Median (Q1, Q3) Vital Signs: Respiration Rate (breaths/ min) by Visit	Safety Analysis Set
15.11.7.1.5	Median (Q1, Q3) Vital Signs: Temperature (Celsius) by Visit	Safety Analysis Set
15.11.7.1.6	Median (Q1, Q3) Vital Signs: O_2 Saturation (%) by Visit	Safety Analysis Set

13.3. Listings

Listing	Title	Analysis Set
16.1.6	Subjects Who Received Study Drug from Specific Batches	All Randomized 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 CRF	All Randomized Analysis Set
16.2.2.4	Subjects Who Received Incorrect Study Drug	All Randomized Analysis Set
16.2.3.1	Subjects Excluded from Any Analysis Set	All Randomized Analysis Set
16.2.3.2	Subjects Who were in the Full Analysis Set but Excluded from the Per Protocol Analysis Set	Full Analysis Set
16.2.4.1	Demographics	All Randomized Analysis Set
16.2.4.2	Baseline Characteristics	All Randomized Analysis Set
16.2.4.3.1	Lung Transplant Medical History	All Randomized Analysis Set
16.2.4.3.2	Medical History	All Randomized Analysis Set
16.2.4.4.1	Prior and Concomitant Medications	All Randomized Analysis Set
16.2.4.4.2	Prior and Concomitant Ribavirin, Palivizumub and IVIG	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 and Adherence	All Randomized Analysis Set
16.2.5.4	Pharmacokinetic Sampling Details and Concentrations	PK Analysis Set
16.2.6.1	Viral Load Measurements	Full Analysis Set
16.2.6.2	FLU-PRO Measurements	Full Analysis Set
16.2.6.3	Spirometry Measurements Collected on Clinical Database	Full Analysis Set
16.2.6.4	Spirometry History	All Randomized Analysis Set
16.2.6.5	Hospitalization	Full Analysis Set
16.2.6.6	ICU	Full Analysis Set
16.2.6.7	Mechanical Ventilation	Full Analysis Set

Listing	Title	Analysis Set
16.2.6.8	Supplemental Oxygen Assessment (New Prescription for Home Oxygen Therapy)	Full Analysis Set
16.2.6.9	Supplemental Oxygen Use Prior to RSV Infection	Full Analysis Set
16.2.6.10	Healthcare Related Efficacy Endpoints	Full Analysis Set
16.2.6.11	Spirometry Data Collected by Handheld Spirometer	Full Analysis Set
16.2.7.1	All Adverse Events	Safety Analysis Set
16.2.7.2.1	Deaths	All Randomized 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
16.2.8.1.4	Treatment Emergent Marked Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.5	Treatment Emergent Grade 3 or Higher Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.6	Liver-Related Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.7	Laboratory Tests Reference Ranges	
16.2.8.1.8	Laboratory Test Troponin Results	Safety Analysis Set
16.2.8.2	Vital Sign Measurements and Oxygen Saturation	Safety Analysis Set
16.2.8.3	Overall ECG Assessment	Safety Analysis Set
16.2.8.4	Pregnancy Report	Safety Analysis Set

13.4. Optional Registry Listings

PPD

14. APPENDICES

Appendix 1. Study Procedures Table

Main Study

	Screening	Day 1 /Baseline[a]	Day 3 (±24 hours)	Day 5 (±24 hours)	Day 7 (±24 hours)	Day 9 (±24 hours)	Day 14 (±24 hours)	Day 21 (±24 hours)	Day 28/ End of Study (+2 days)	Early Term	Optional Extended Viral Monitoring[i] Day 35 (±2 days)	Day 42 (±2 days)	Day 49 (±2 days)	Day 56 (±2 days)
Written Informed Consent	X										PPD			
Medical History and Demographics	X													
Height and Weight	X													
Spirometry[l]	X	X	X	X	X	X	X	X	X	X				
Vital Signs	X	X			X		X	X	X	X				
FLU-PRO Questionnaire[e]		X	X	X	X	X	X	X	X	X				
Nasal Sampling for local PCR Testing[b]	X							X						
Nasal Sampling for central PCR Testing		X	X	X	X	X	X	X	X	X				
PPD)		X		X	X			X						

	Screening	Day 1 /Baseline[a]	Day 3 (±24 hours)	Day 5 (±24 hours)	Day 7 (±24 hours)	Day 9 (±24 hours)	Day 14 (±24 hours)	Day 21 (±24 hours)	Day 28/ End of Study (+2 days)	Early Term	Optional Extended Viral Monitoring[i] Day 35 (±2 days)	Day 42 (±2 days)	Day 49 (±2 days)	Day 56 (±2 days)
O_2 requirement assessment		X	X	X	X	X	X	X	X	X	PPD			
Local urine or Serum Pregnancy Test[d]	X				X		X							
Screening Labs [c]	X													
Safety Labs[f]		X			X		X	X	X	X				
12-lead ECG[p]		X							X	X				
Local Troponin Testing[o]		X							X	X				
RSV antibody titer		X							X	X				
PPD		X												
Plasma Biomarker Samples		X			X		X	X						
HLA antibody		X							X					
PK sample[j]		X			X		X	X		X				
Randomization		X												
IMP Administration[k]		X	X	X	X	X	X							
Adverse Events[q]	X	X	X	X	X	X	X	X	X	X				
Concomitant Medications	X	X	X	X	X	X	X	X	X	X				
IMP Accountability		X	X	X	X	X	X	X		X				

	Screening	Day 1 /Baseline[a]	Day 3 (±24 hours)	Day 5 (±24 hours)	Day 7 (±24 hours)	Day 9 (±24 hours)	Day 14 (±24 hours)	Day 21 (±24 hours)	Day 28/ End of Study (+2 days)	Early Term	Optional Extended Viral Monitoring[i] Day 35 (±2 days)	Day 42 (±2 days)	Day 49 (±2 days)	Day 56 (±2 days)
Collection of Clinical Data for Cardiac-Related tests		X	X	X	X	X	X	X	X	X	PPD			
Spirometry, BAL, Pathology, Microbiology, & Radiology Data Collection[n]									X					
Oxygen saturation assessment	X	X	X	X	X	X	X	X	X	X				

a If all lab results and procedures are available and satisfy the inclusion/exclusion criteria, Screening and Day 1/Baseline may occur on the same day.

b Subjects must be documented to be RSV positive by local PCR testing methods ≤ 7 days prior to IMP administration on Day 1/Baseline. In cases where a RSV infection is suspected but either RSV testing is not performed as a part of standard medical care, not performed rapidly (eg via a point-of-care test), or a RSV screening test is performed using a non-PCR-based assay, additional local RSV testing using a PCR-based assay can be performed at Screening using an upper or lower respiratory tract specimen collected by standard local procedure. PPD

c Existing values collected ≤ 7 days prior to Screening may be used to determine subject study eligibility

d Required for females subjects of childbearing potential. Must be done locally at Screening, within 1 day prior to IMP administration, and on Days 7 and 14. When available, existing local pregnancy tests obtained prior to Screening may be used, provided the testing was completed within 1 day prior to IMP administration.

e Self-administered by all subjects on Days 1/Baseline, 3 5, 7, 9, 14, 21, and 28.

f Central safety labs include: sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, creatine kinase (CK), and complete blood count (CBC) at Day 1/Baseline, Day 28/End of Study, and Early Termination.

g PPD

h IMP accountability will be performed on Day 1/Baseline and on Days 3, 5, 7, 9, 14, and 21. If a subject withdraws early (prior to Day 21), IMP accountability will be performed.

i PPD

j For all subjects: collected 2-4 hours post-dose on Day 1/Baseline, pre-dose on Days 7 and 14, and anytime on Day 21. If a subject terminates early from the study (prior to Day 21), a PK sample will be collected.

k IMP administration/dosing will occur daily from Day 1/Baseline through Day 14. On Days 1/Baseline, 7, and 14, IMP administration will be directly observed and on Days 3, 5, and 9, IMP administration may be observed during home visits or if subject comes into the hospital/clinic. On non-required hospital/clinic visits (Days 8, 10, 11, 12, and 13) subjects will self-administer the IMP at home.

l Spirometry testing measurements, obtained by certified respiratory therapists or other nurses/technicians trained in pulmonary function testing, will be obtained at Screening or on Day 1/Baseline and Day 28/End of Study. The study Day 1/Baseline forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) must be obtained *prior to IMP administration*. Alternatively, measures of FEV_1 and FVC obtained for the purposes of patient care within 2 days prior to Day 1/Baseline may be used to satisfy the Screening / Day1/Baseline spirometry measurements. However, these tests must have been obtained at the local site of subject enrollment and the same spirometry machine should be utilized for the Day 28 measurement.The Day 28/End of Study spirometry measurements do not have to be obtained the same day as the clinic visit, but must be performed within the study visit window (±2 days). Spirometry measures performed as part of standard clinical care within the visit window will be acceptable. Handheld spirometry measures will also be obtained by the subject at Days1/Baseline, 3, 5, 7, 9, 14, 21, and 28/End of Study. Handheld spirometry measures must be obtained in the presence of study staff at Day 1/Baseline and at Day 28/End of Study. In addition, all spirometry measurements obtained at unplanned study times, as part of standard clinical care during the study period, will be collected.

m PPD

n All the following standard-of-care results available from Screening/Baseline through Day 28/End of Study will be collected by Day 28/End of Study for all subjects: spirometry data, BALF (a 5 mL aliquot of the BAL fluid (BALF) sample from any lobe is requested for this study. This specimen will be stored and shipped to a central laboratory for analysis of presatovir levels and other potential biomarker measures) analyses, including cell profiles and microbiologic studies, microbiologic data reports on respiratory (lung tissue, sputum, BAL, nasal or nasopharyngeal fluid/washes) and blood culture samples, radiologic images of the chest (chest radiographs and CT scans only) and the associated radiology interpretation reports, electronic copies of all lung pathology images, and the associated pathology interpretation reports, and whether the subject died (yes or no), date of death, and autopsy report. Baseline spirometry values after lung transplant and within 3-months prior to the current active RSV infection will also be collected.

o Local troponin testing will be done in accordance with the standard assay available and used at the site. If the subject is seen at the site for any reason (eg, hospitalization, clinic or site visit) between Days 2 to 14, a blood dreaw for troponin measurement is required. If the subject is at the site on more than 1 occasion between this timeframe, only 1 protocol-mandated measurement is required, but it should be obtained at the earliest feasible time and during the same study visit as the ECG measurement described below.

p If the subject is seen at the site for any reason (eg, hospitalization, clinic or site visit) between Days 2 to 14, a 12-lead ECG is required. If the subject is at the site on more than 1 occasion between this timeframe, only 1 protocol-mandated ECG measurement is required, but it should be obtained at the earliest feasible time and during the same study visit as the troponin measurement described above.

q Only procedural related AEs are to be collected during the extended viral monitoring portion of the study


PPD

Appendix 2. Alpha Allocation Approach

There are 2 test statistics in the study design, denoted by Z_k for kth population (1 = overall; 2 = subgroup population [including subjects who are in the FAS whose duration of RSV symptoms prior to the first dose of study medication is ≤ median of the distribution of duration of RSV symptoms in the overall FAS population] with prevalence b_1). Specifically, $b_1 = 0.5$ for 50th percentile threshold.

For alpha spending across the 2 tests for the primary endpoint of time-weighted average change in viral load from baseline to Day 7, the following rules are implemented, where c_k denotes the rejection boundary for the kth population:

- Pre-fix rejection boundaries ($c_1 = 2.054$) for the final analysis in the overall population

$\tilde{Z} = (Z_1, Z_2)$ is a vector of standardized test statistics that follow a multivariate normal distribution with mean $\tilde{\mu} = (\mu_1, \mu_2)$. For a very large clinical trial and assuming no prognostic or predictive effect of duration of RSV symptoms prior to the first dose on the primary endpoint, the variance-covariance matrix for the vector $\tilde{Z}$ can be shown to be:

$$\sum = \begin{pmatrix} 1 & \sqrt{b_1} \\ \sqrt{b_1} & 1 \end{pmatrix}$$

Under the null hypothesis, $\tilde{\mu} = (0, 0)$. Given the above rules and the variance-covariance matrix Σ, the table below presents the rejection boundaries for the final analysis, which can be numerically calculated such that the overall type I error rate is maintained at the 2-sided 0.05 level.

Rejection Boundaries

	Final Analysis	
Analysis Population/Subset	**Z scale**	**p-value**
Overall population	2.054	0.04
Subgroup population (b1= 0.5)	2.379	0.017

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 (excl aortic),
  - ECG investigations, Cardiac function diagnostic procedures,
  - Heart rate and pulse investigations

Duplicate PTs are removed where necessary.

Appendix 4. Sample SAS Code for Negative Binomial Model

The following model statement may be used for the analyses of number of hospitalization day, ICU-free day, and ventilator-free day described in Section 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 due to early discontinuations.

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

Appendix 5. Sample SAS Code for MMRM Model

The following model statement can be used for the analyses of viral load and FLU-PRO as described in Section 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).