CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2b, Randomized, Controlled Trial Evaluating GS-5806 in Lung Transplant (LT) Recipients with Respiratory Syncytial Virus (RSV) Infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	114498	
EudraCT Number:	2015-002287-16	
Clinical Trials.gov Identifier:	NCT02534350	
Indication:	Respiratory Syncytial Virus (RSV)	
Protocol ID:	GS-US-218-1797	
Gilead Study Director or CPM:	Name: Telephone:	PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile:	Timothy R. Watkins, MD, MSc PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1 :	09 June 2015 2 December 2015

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

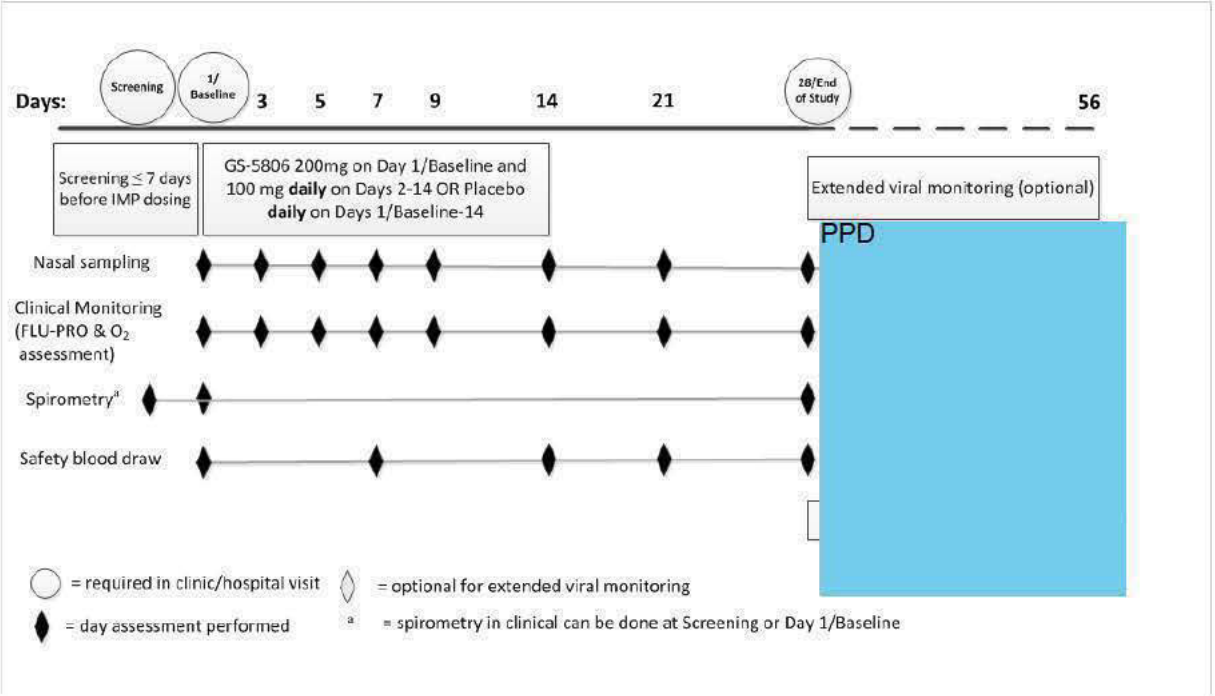
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2b, Randomized Controlled Trial Evaluating GS-5806 in Lung Transplant (LT) Recipients with Respiratory Syncytial Virus (RSV) Infection
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	114498 2015-002287-16 NCT02534350
Study Centers Planned:	Approximately 40 centers in North America, Australia, and Europe
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 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
Study Design:	Randomized, double-blind, placebo-controlled study evaluating the effect of presatovir on efficacy, PK, safety, and tolerability in LT recipients with RSV infection. 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. All 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)

At time of informed consent, subjects will be presented with the options to:

P
P
D

Figure 3-1: Study Design



Number of Subjects Planned:	Approximately 60 RSV-positive subjects

Target Population:	Males and females ≥18 years of age who have had a LT and have a documented RSV infection
Duration of Treatment:	14 days of treatment; 28 days of total subject participation in main study portion
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3.

Key Inclusion Criteria

1) Males and females ≥18 years of age who have received a LT (single or double) or heart/lung transplant > 90 days prior to Screening
2) Confirmed to be RSV-positive by local polymerase chain reaction (PCR) testing (starting from when the upper or lower respiratory tract sample is obtained) ≤ 7 days prior to IMP administration on Day 1/Baseline
3) New onset or acute worsening, if the symptom is chronic, of at least 1 of the following respiratory symptoms ≤ 7 days prior to IMP administration on Day 1/Baseline: nasal congestion, earache, runny nose, cough, sore throat, shortness of breath, or wheezing
4) A negative urine or serum pregnancy test for female subjects of childbearing potential (unless surgically sterile or greater than 2 years post-menopause) at Screening or prior to Randomization on Day 1/Baseline
5) Agreement from male and female subjects of childbearing potential who engage in heterosexual intercourse to use protocol specified method(s) of contraception as described in Appendix 6

Key Exclusion Criteria

Related to concomitant or previous medication use:

1) Use of any investigational agents within 30 days, **OR** use of any investigational monoclonal anti-RSV antibodies within 4 months or 5 half-lives of Screening, whichever is longer, **OR** use of any prior investigational RSV vaccines
2) Use of a strong or moderate cytochrome P450 enzyme (CYP) inducer including but not limited to rifampin, St. John's Wort, carbamazepine, phenytoin, efavirenz, bosentan, etravirine, modafinil, and nafcillin, within 2 weeks prior to the first dose of IMP

Related to transplant history:

3) Recipient of any other organ transplant prior to Screening, with the exception of a LT (single or double) or heart/lung transplant

Related to medical condition at Screening:

4) Known viral coinfection (including but not limited to influenza, metapneumovirus, human rhinovirus, parainfluenza, cytomegalovirus, or coronavirus) in the upper or lower respiratory tract ≤ 14 days prior to Screening unless discussed with the medical monitor and deemed acceptable

5) Active systemic infection or infectious pneumonia of any etiology (ie, bacterial, viral [other than RSV] or fungal), including aspiration pneumonia, that is considered clinically significant by the investigator unless discussed with the medical monitor and deemed acceptable

Related to laboratory values:

6) Clinically significant kidney dysfunction as defined by:

   An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) study 4 parameter equation obtained from screening laboratory measurements or via local laboratory measurements obtained ≤ 7 days prior to Screening. The eGFR may be manually calculated or the reported eGFR value may be used, but any automatically calculated eGFR must be calculated using the MDRD equation.

7) Clinically significant liver function test abnormalities as defined by an ALT or AST > 5 times the upper limit of normal (ULN) obtained in screening laboratory measurements or via local laboratory measurements obtained ≤ 7 days prior to Screening

8) Clinically significant elevations in total bilirubin (TB), as determined by the investigator

Study Procedures/ Frequency:

Study Procedures

Questionnaire: The FLU-PRO questionnaire will be self-administered by all subjects on Days 1/Baseline, 3, 5, 7, 9, 14, 21, and 28/End of Study.

Vital signs (VS): Vital signs (temperature, heart rate, respiratory rate, and blood pressure) will be collected from all subjects at Screening and on Days 1/Baseline, 7, 14, 21, and 28/End of Study.

Oxygen Requirement Assessment: The requirement for oxygen will be assessed according to whether the subject requires a new home oxygen prescription (any supplemental oxygen, yes or no). All subjects will have an oxygen requirement assessment determined on Days 1/Baseline, 3, 5, 7, 9, 14, 21, and 28/End of Study.

Oxygen Saturation Assessment

Oxygen saturation will be collected on Day 1/Baseline and Days 3, 5, 7, 9, 14, 21, and 28/End of Study. Refer to section 6.7.5.1 for additional information.

Laboratory tests:

- **RSV Screening Tests:** In cases where a RSV infection is suspected but either RSV testing is not performed as a part of standard medical care, 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.
- A serum or urine pregnancy test must be performed at Screening or on Day 1/Baseline prior to Randomization, and prior to IMP administration on Days 7 and 14.
- Screening labs will also include a measure of the subject's creatinine, AST, ALT, and TB. When available, existing laboratory values ≤ 7 days prior to Screening may be used for eligibility assessment.
- Blood specimens for safety labs include measures of the subject's sodium, potassium, chloride, CO2, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, creatine kinase (CK), and complete blood count (CBC). These are measured on Days 1/Baseline, 7, 14, 21, and Day 28/End of Study and will be collected from all subjects. Additionally, blood specimens for troponin testing will be collected from all subjects at Day 1/Baseline, Day 28/ End of Study, and if the subject is seen at the site for any reason (eg, hospitalization, clinic, or site visit) between Days 2 to 14. Refer to section 6.7.6 for additional information.
- Blood specimens for HLA (human leukocyte antigen) antibodies will be collected from all subjects on Day 1/Baseline and Day 28/End of Study.
- Blood specimens for RSV antibody titers will be collected from all subjects on Day 1/Baseline and Day 28/End of Study.

- Blood specimens for PK measurements will be collected from all subjects at the following time points: 2-4 hours post-dose at Day 1/Baseline, pre-dose on Days 7 and 14, and any time on Day 21. A PK sample will be collected if a subject early terminates from the study prior to Day 21.
- Blood specimens for plasma biomarker measurements (Type 1 CXCL9, 10, 11, IL-18, IL-12, p70, TNF-α, Type 17 - CCL2 [MCP-1], CCL3 [MIP1α], CCL5 [RANTES], CCL11 [Eotaxin], TGF-β, IL-17, CCL20, IL-1β, IL-1ra, IL-6, IL-12 p40 and IL-23) will be collected from all subjects on Days 1/Baseline, 7, 14, and 21.
- PPD [redacted].

Spirometry: 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. Subjects will also be issued a handheld spirometer for self-administered spirometry testing. These handheld spirometry measures will be collected specifically in the presence of study staff at Days 1/Baseline, 3, 5, 7, 9, 14, 21, and 28/End of Study.

The study baseline forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) can be obtained as part of the Screening or Day 1 visit, but must be obtained *prior to IMP administration*.

The Day 28/End of Study spirometry measurements by the certified respiratory therapist 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. However, measures from the handheld spirometer must also be obtained in the presence of study staff on the same day as the site-specific Day 28/End of Study spirometry measurements.

In addition to the study-specific measures described above, all spirometry and other measurements of pulmonary function obtained at unplanned study times, as part of standard clinical care during the study period, will be collected. The highest baseline value spirometry tests ascertained after lung transplant (before enrollment into this trial), as well as spirometry values measured within a 3 month period prior to the current active RSV infection will also be collected.

Nasal sampling: Nasal sampling will be performed on Days 1/Baseline, 3, 5, 7, 9, 14, 21 and 28/End of Study. All samples must be collected prior to IMP administration. Two nasal samples will be obtained, 1 from each nostril, each time nasal sampling is performed. If a bronchoscopy is planned the same day as nasal sampling, nasal samples should be obtained, if possible, prior to the bronchoscopy and before any topical anesthetic (eg, lidocaine) is applied in the nostrils. Samples will be stored and shipped to a central laboratory for testing according to specifications in the lab manual. Nasal sampling may also be done at Screening, per local practice routine, for RSV Screening Testing as outlined above.

RSV testing: All subjects must be documented to be RSV-positive as determined by local PCR testing methods ≤ 7 days prior to IMP administration on Day 1/Baseline. For all study-related nasal samples, 1 of the nasal samples collected at study visits will be analyzed at a central laboratory using RT-qPCR to determine RSV viral load and the presence of other viruses. The remaining sample may be used for sequencing to evaluate the development of resistant RSV strains and testing of other respiratory viruses.

Electrocardiogram (ECG): A pre-dose ECG at Day 1/Baseline and Day 28/End of Study, along with one additional ECG if the subject is seen at clinic between Days 2 to 14 will be obtained from all subjects. Refer to section 6.7.7 for additional information.

Clinical Data Collection for Cardiac-Related Tests: Aside from the protocol-specified ECG and troponin collection, additional cardiac-related tests are not required for this study. However, throughout the study period (Baseline/Day 1 through Day 28/End of Study) if any cardiac-related testing is performed as part of standard clinical care, or as part of AE/SAE evaluation and/or follow-up, these results will be collected, including but not limited to the following:

- ECG tracings and reports of any ECG performed
- All troponin testing
- Other cardiac enzyme testing (eg, all CK, CK-MB, etc)
- Cardiac stress testing
- Echocardiographic imaging (resting and stress testing)
- Cardiac perfusions scans
- Cardiac MRIs
- Any additional procedure used to evaluate cardiac conditions

Subject death: Whether the subject died (yes or no), the date of death, and the results of any autopsy reports will be collected. This data will be collected during the main study portion (Day 1/Baseline through Day 28/End of Study) and during the optional Registry.

Bronchoalveolar lavage (BAL) samples: Bronchoscopies are not required as part of this study. However, when a BAL is performed as a part of standard clinical care during the main study portion (Day 1/Baseline through Day 28/End of Study) and during the optional Registry), 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 according to specifications in the lab manual. Clinical results, including cell count analyses and microbiology reports, from any BALF testing performed as part of standard clinical care will also be collected during the main study portion (Day 1/Baseline through Day 28/End of Study) and during the optional Registry. In addition, if a BAL is performed as a part of standard clinical care at Screening, and a RSV Screening test is required to satisfy inclusion criteria under the condition(s) outlined above, excess BALF may be submitted for local RSV PCR-based testing.

Lung biopsy results: Lung biopsies are not required as part of this study. However, when a tissue biopsy is obtained as a part of standard clinical care during the main study portion (Day 1/Baseline through Day 28/End of Study) and during the optional Registry, clinical results from studies of tissue pathology and microbiology including copies of electronic pathology images, microbiology stains/reports, and the associated pathology interpretation reports, will be collected.

Microbiology results: Microbiology testing is not required as part of this study. However, when it is obtained as a part of standard clinical care during the main study portion (Day 1/Baseline through Day 28/End of Study) and during the optional Registry, the results of all microbiologic data reports on respiratory (lung tissue, sputum, BAL, nasal or nasopharyngeal fluid/washes) and blood culture samples will be collected.

Radiology Imaging: Radiology imaging is not required as part of this study. However, when it is obtained as a part of standard clinical care during the main study portion (Day 1/Baseline through Day 28/End of Study) and during the optional Registry, radiologic images done of the chest (chest radiographs and CT scans only) and the associated radiology interpretation reports will be collected.

PPD

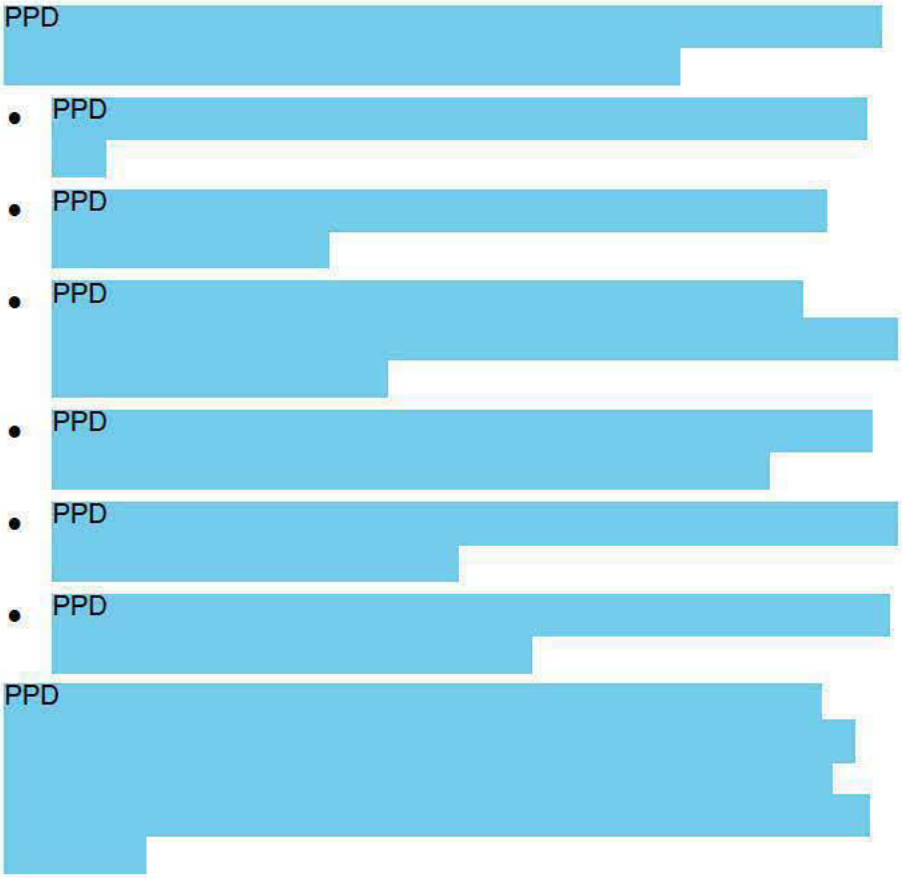
Optional Extended Viral Monitoring: PPD

Optional Registry: PPD

- PPD
- PPD

  - PPD

Clinical data collection for optional Registry:



Test Product, Dose, and Mode of Administration:	200-mg presatovir (GS-5806) (four 50 mg tablets) administered orally on study Day 1/Baseline, followed by 100-mg presatovir (2 x 50 mg tablets) administered orally daily on Days 2 through 14. Refer to Section 5.3 for IMP administration details.
Reference Therapy, Dose, and Mode of Administration:	PTM tablets self-administered orally will be provided to subjects randomized to receive placebo. Four placebo tablets will be administered orally on Day 1/Baseline, followed by 2 tablets administered orally daily on Days 2 through 14. Refer to Section 5.3 for IMP administration details.
Criteria for Evaluation:	
Safety:	Safety will be assessed by the reporting of AEs and serious adverse events (SAEs) throughout the study, clinical laboratory tests, and VS at various time points during the study.

Efficacy:

The co-primary efficacy endpoints are:

- Time-weighted average change in $\log_{10}$ viral load from Day 1/Baseline through Day 7 ($DAVG_7$) as measured in nasal samples by RT-qPCR among subjects in the Full Analysis Set (FAS)
- Time-weighted average change in $\log_{10}$ viral load from Day 1/Baseline through Day 7 ($DAVG_7$) as measured in nasal samples by RT-qPCR in a subset of FAS subjects whose duration of RSV symptoms prior to the first dose of study medication is $\leq$ median

The secondary endpoints are:

- Time-weighted average change in FLU-PRO score from Day 1/Baseline through Day 7
- Percent change from study Day1/Baseline in FEV_1% predicted value at Day 28/End of Study

The exploratory endpoints are:

PPD

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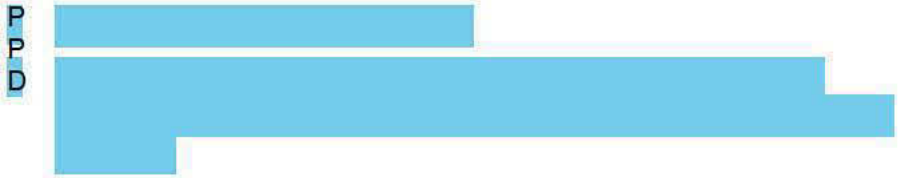
P
D

The following exploratory endpoints will be considered for examination using data collected as part of the optional Registry:

P
P
D



Pharmacokinetics: Presatovir concentrations in plasma will be analyzed for all subjects receiving presatovir treatment.

Statistical Methods:

Safety

Safety analyses will be performed on all subjects who received at least 1 dose of IMP. Safety data will be listed by subject and summarized by treatment (active or placebo) using the number (percent) of subjects with events/abnormalities for categorical data and using descriptive statistics for continuous data.

Efficacy

The FAS will include all randomized subjects who take at least 1 full dose of study drug and have a RSV viral load greater than or equal to the lower limit of quantification (LLOQ) in the pre-dose Day 1/Baseline nasal sample, as determined by RT-qPCR conducted at the central lab. The subgroup analysis set includes subjects in the FAS whose duration of RSV symptoms prior to the first dose of study medication is ≤ median. The FAS and the subgroup analysis set will be used for all summaries and analyses of the primary and secondary efficacy endpoints. All primary and other endpoints will be analyzed using 2-sided tests for treatment differences.

The primary efficacy analysis of time-weighted average change in RSV $\log_{10}$ viral load from Day 1/Baseline through Day 7 will be performed on subjects included in the FAS and subjects included in the FAS subgroup with ≤ median duration of symptoms prior to first dose of study medication. To test these two co-primary null hypotheses of no difference between the presatovir and placebo treatment groups in the time-weighted average change in RSV viral load, parametric analysis of covariance (ANCOVA) models with corresponding baseline RSV viral load as a continuous variable and stratification factors included as covariates will be used. Adjusted means and 95% confidence intervals (CIs) will be presented. The co-primary analyses will be controlled at an overall type I error rate at the 2-sided 0.05 level in which the alpha level for the overall population will be 0.04 and the alpha level for the subgroup population (subjects in the FAS with duration of RSV symptoms prior to first dose of study medication ≤ median) will be 0.017, as determined by a grid search accounting for the known correlation of the populations.

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

The percent change in FEV_1% predicted values from Day 1/Baseline through Day 28/End of Study will be analyzed using an ANCOVA model with study baseline FEV_1% predicted value and stratification factors as covariates. The percent change in FEV_1% predicted values will be calculated as the difference of FEV_1% predicted values at Day 1/Baseline through Day 28/End of Study, divided by study baseline FEV_1% predicted value and multiplied by 100. In order to account for the multiple hypotheses testing across the primary and secondary endpoints, a sequential testing procedure will be used to control the overall Type 1 error rate of 0.05. The co-primary endpoint analyses will serve as the gatekeeper for the secondary analyses conducted within each population.

Analyses of exploratory endpoints are discussed in Section 8.5.3. Continuous endpoints will be analyzed using an ANCOVA model with corresponding baseline value and stratification factor as covariates. Categorical endpoints will be analyzed by Cochran-Mantel-Haenszel test adjusted for stratification factors. Continuous endpoints with repeated measures may also be analyzed based on a linear mixed-effects model with repeated measures (MMRM).

All endpoints will be summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percent of subjects for categorical data.

Data from the optional Registry portion of the study will be summarized descriptively. Statistical hypothesis testing will not be conducted. Nominal significance will be cited for descriptive purposes only. All continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, and median, Q1, Q3, minimum, maximum) by visit. All categorical variables will be summarized by number and percentage of subjects in each categorical definition.

Pharmacokinetic

Concentrations of presatovir in plasma will be determined using a validated bioanalytical assay. Descriptive statistics (eg, n, mean, standard deviation, %CV, median, and range) will be calculated for each sampling time. The pharmacokinetic/pharmacodynamic (PK/PD) relationship may be explored as appropriate.

Power and sample size

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. PPD)
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 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 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 $\leq$ median duration of symptoms prior to first dose of study medication 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.

DMC

An independent data monitoring committee (DMC) will monitor the safety and welfare of the study subjects. The DMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Gilead retains final decision-making authority on all aspects of the study.

Endpoint Adjudication Committee

Based on enrollment and data collection into the study registry, an Adjudication Committee may be formed to review relevant clinical data in order to confirm episodes of CLAD, BOS, and acute rejection.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
ADD	Attention Deficit Disorder
ADLs	Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BAL	bronchoalveolar lavage
BALF	BAL fluid
BCRP	breast cancer resistance protein
BMD	bone mineral density
BMI	body mass index
BOS	bronchiolitis obliterans syndrome
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CLAD	chronic lung allograft dysfunction
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CO_2	carbon dioxide
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report
CT	computerized tomography
CVA	cerebral vascular accident
CYP	cytochrome P450 enzyme
DAVG	time-weighted average change
DDI	drug-drug interactions
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health

E2	depressed estradiol
EC	ethics committee
EC50	concentration of drug to reach 50% inhibition of virus replication
ECG	Electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELF	epithelial lining fluid
EMR	electronic medical records
ER	emergency department
EudraCT	European clinical trials database
FAS	full analysis set
FIH	first-in-human
FDA	(United States) Food and Drug Administration
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
GCP	Good Clinical Practice (Guidelines)
GD	gestation day
GI	gastrointestinal
GSI	Gilead Sciences, Inc.
hCG	human chorionic gonadotropin
Hr	hour
hrs	hours
HCT	hematopoietic cell transplant
HDPE	high-density polyethylene
hERG	human ether-à-go-go-related gene
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLGT	high level group term
HLT	high level term
HSP	hysterosalpingogram
iADLs	instrumental activities of daily living
IB	Investigator's Brochure
IC_{50}	concentration of drug to reach 50% inhibition
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	independent ethics committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)

IRB	institutional review board
IUD	intrauterine device
IVIG	Intravenous Immunoglobulin
IWRS	interactive voice response system
kg	kilogram
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	lower level term
LRTI	lower respiratory tract infection
LT	lung transplant
MATE1	Multidrug and toxin extrusion protein 1
MATE2	Multidrug and toxin extrusion protein 2
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mEq/L	milliequivalents per liter
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters mercury
mmol/L	millimoles/liter
MMRM	mixed-effect model repeated measures
NA	not applicable
ND	not detectable
NG	nasogastric
nM	nanomolar
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
O_2	oxygen
OATP	organic anion transporter proteins
PCR	polymerase chain reaction
PD	pharmacodynamic
PFUe	plaque forming unite equivalents
Pgp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic
PO	oral administration (per os, by mouth)
PR	the interval between the beginning of the P wave and the beginning of the QRS complex on ECG
PT	preferred term
PTM	placebo-to-match

Q1	first quartile
Q3	third quartile
QA	quality assurance
QRS	part of electrocardiographic wave representing ventricular depolarization
QT	interval between the start of the Q wave and the end of the T wave on ECG
QTc	corrected QT
QTcF	QT interval corrected for heart rate using the Fridericia formula
rCLAD	restrictive chronic lung allograft dysfunction
RBC/HPF	red blood cells per high power field
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-qPCR	reverse transcription quantitative polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
sec	second
SF-12	Short Form 12
SOC	system organ class
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	total bilirubin
TBD	to be determined
TEM	treatment emergent mutation
TEN	toxic epidermal necrolysis
t_{max}	the time (observed time point) of C_{max}
$t_{½}$	an estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC
µL	microliter
ULN	upper limit of the normal range
URTI	upper respiratory tract infection
US	United States
UV	ultraviolet
VS	vital signs
V_{ss}	apparent volume of distribution at steady state
v/v	volume/volume
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Respiratory syncytial virus (RSV), a member of the family *Paramyxoviridae*, is an enveloped virus with a negative single-strand ribonucleic acid (RNA) genome. The RSV genome encodes 11 proteins, including 3 surface glycoproteins (F, G, and SH) and several proteins that comprise the viral RNA polymerase complex (N, P, L, and M2-1). Two major antigenic subgroups of RSV are known, RSV A and RSV B, that differ primarily in the genetic sequence of the G glycoprotein while maintaining a higher degree of homology across other parts of the genome. Both subgroups show comparable pathogenicity and can co-circulate in the same community during a seasonal epidemic, but their individual prevalence usually varies from season to season.

While RSV infection is commonly recognized as an important virus affecting pediatric patients, it is also an important cause of respiratory disease in the adult population. Those at particular risk include immunosuppressed adults, such as recipients of a solid organ transplant, especially those with a lung transplant (LT). Each winter, up to 12% of LT patients are infected with RSV {4871},{34873} resulting in a mortality rate as high as 10% to 20% {34809}, {34810}, {34811}. Respiratory viral infections, including RSV, are associated with the development of chronic lung allograft dysfunction (CLAD), the most recognized form being bronchiolitis obliterans syndrome (BOS){34804}, {34805}. Multiple studies suggest the incidence of BOS is higher after a respiratory viral infection, with RSV specifically implicated{4871}, {34805}, {34806}, {34809}, {34872},{34811}. It is hypothesized that these viral infections lead to graft rejection through the triggering of an alloreactive immune response against tissue antigens {34807}. BOS is of particular concern as it carries a substantial associated morbidity and mortality in LT patients.

Given the strong association between RSV infection and adverse clinical outcomes in LT patients, 2 clinical trials were recently conducted to test an experimental therapeutic in this patient population. Alnylam Pharmaceuticals sought to evaluate whether ALN-RSV01, a small interfering RNA targeting RSV replication, would be suitable for the treatment of RSV infection. A Phase 2a study enrolled 24 RSV infected LT patients to evaluate the safety, tolerability, and efficacy of treatment with ALN-RSV01 {34808}. The primary endpoint was safety and tolerability; viral load and development of BOS were included as secondary endpoints. Although treatment with ALN-RSV01 did not result in a significant reduction in viral load (6.6 +/-6.1 vs 13.6 +/- 10.1 log10PFUe/ml*day, p=0.067), treatment with ALN-RSV01 was associated with a lower incidence of new or progressive BOS at Day 90 (6.3% [n=1] vs. 50% [n=4], p=0.027). Based on this finding, a Phase 2b study enrolled 87 subjects with a primary endpoint of new-onset BOS at Day 180. Although the BOS observations at Day 90 were similar to the previous study, the primary endpoint was not met (13.6% [n=10] vs. 30.3% [n=6], p=0.058) {34818}, {34819}. While they were small in number, these studies revealed that the mean duration of viral shedding was just over 5 days after enrollment, with shedding completed by 7 days for the majority of subjects. Notably however, the studies enrolled patients well after symptom onset.

1.2. Presatovir (GS-5806)

1.2.1. General Information

Presatovir is an oral RSV fusion inhibitor with potent and selective anti-RSV activity in vitro. When tested in vitro against 75 diverse clinical isolates of RSV type A and B, the EC_{50} values (concentration of drug to reach 50% inhibition of virus replication) ranged from 0.15 to 1.09 nM, with a mean EC_{50} value of 0.43 ± 0.22 nM. In vivo efficacy data from cotton rats infected with human RSV demonstrated that administration of presatovir at 0.3 to 30 mg/kg resulted in a dose-dependent reduction in viral load in both the upper respiratory tract and lungs. The steady-state volume of distribution (V_{ss}) of presatovir in all nonclinical species tested was 2- to10-fold higher than the volume of total body water and the oral bioavailability was moderate to high. The exposure to presatovir in the lung and epithelial lining fluid (ELF) was also assessed in Sprague-Dawley rats and yielded lung tissue/plasma and ELF/plasma ratios of approximately 30 and 9, respectively. Concentrations in lung tissue and ELF declined approximately in parallel to those in plasma indicating rapid equilibration between the lung and plasma compartments. Presatovir exhibited low cytotoxicity in cell culture and did not interact with pharmacologically relevant receptors that are predictive of off-target toxicity.

Additional details regarding nonclinical PK, pharmacology, and toxicology can be found in the current presatovir (GS-5806) Investigator's Brochure (IB).

1.2.2. Nonclinical Pharmacokinetics

Consistent with the high, concentration-independent forward permeability across Caco-2 monolayers and low, concentration-independent efflux, presatovir exhibited moderate to high bioavailability in nonclinical species. Although presatovir is a substrate for Pgp and BCRP, there was no evidence for these transporters limiting the bioavailability of the compound. Systemic clearance of presatovir in nonclinical species is well predicted from the rates of metabolism by hepatic microsomal fractions and primary hepatocytes. Biliary excretion is likely to be the major route of elimination of presatovir and its metabolites as < 2% of radiolabel dosed orally to rats was recovered in urine. Presatovir exhibited high metabolic stability in human hepatocytes and with human hepatic microsomal fraction and with recombinant human cytochromes P450. The predominant identified routes of metabolism of presatovir are N-acetylation (in rats) and oxidative deamination. In humans, the only CYP enzymes yielding detectable metabolism of presatovir are CYP3A4 and CYP3A5.

Inducers and inhibitors of CYP3A enzymes may affect the human pharmacokinetics of presatovir. Drug interactions of presatovir with drugs that are substrates of major human CYP enzymes, UGT1A1, or major drug transporters (OATP1B1, OATP1B3, Pgp, OCT1, OCT2, BSEP, OAT1, and OAT3) are unlikely in the expected clinically relevant concentration range. Presatovir inhibits the renal transporters MATE1 and MATE2-K (IC50 values of 0.50 and 3.8 μM, respectively) so clinical drug interactions with substrates of these transporters are possible.

Additional details regarding nonclinical PK can be found in the presatovir (GS-5806) IB.

1.2.3. Nonclinical Pharmacology and Toxicology

The IC_{50} for the inhibitory effect of presatovir on hERG potassium current was 7.8 μM. Cardiovascular effects of presatovir were evaluated in dogs at doses up to 75 mg/kg. The principal hemodynamic findings were lower heart rate values, and higher arterial pulse and systolic pressure values. All hemodynamic effects dissipated by 22 hours post-dose. All electrocardiograms (ECGs) were qualitatively within normal limits, and no presatovir-related arrhythmias or abnormal waveforms were detected. Slight presatovir-related higher PR and QTc interval values were expected physiological responses secondary to concomitant presatovir-related lower heart rate values. These changes were not considered physiologically important in the context of this study.

In a repeat dose study, presatovir was administered by oral gavage for 4 weeks to young adult rats once daily at doses up to 100 mg/kg/day. Two animals administered 100 mg/kg/day were found dead during the dosing phase. Although the cause of death for these 2 animals was undetermined, an association with presatovir cannot be excluded. Based on the results of this study, the NOAEL for presatovir is 70 mg/kg/day, which corresponded to mean AUC_{0-t} and C_{max} values on Day 23 of the dosing phase of 96, 316 ng.h/mL, and 6028 ng/mL, respectively. In a repeat-dose study conducted in young adult dogs, presatovir was administered by oral gavage for 4 weeks at doses up to 20 mg/kg/day. The NOAEL for this study is 20 mg/kg/day, which corresponded to mean AUC_{0-t} and C_{max} values on Day 27 of the dosing phase of 129,831 ng·h/mL and 8081 ng/mL, respectively.

Presatovir was negative in the rat micronucleus study and did not cause mutations in the Ames assay or induce chromosomal damage in vitro with or without S9 metabolic activation. Thus, the potential for genetic toxicity is considered low.

In a definitive embryo-fetal developmental toxicity study in rats, time-mated females were administered presatovir via oral gavage at the dose levels of 30, 70, and 100 mg/kg/day during the period of organogenesis (gestation day [GD] 6-17). Presatovir treatment resulted in dose-dependent reduction in mean maternal body weight, body weight gain, and food consumption during the dosing period when compared to the control group at doses ≥ 70 mg/kg/day. A significant reduction (>10% decrease) in mean maternal body weight was noted in the 100 mg/kg/day group during the dosing period. Therefore, the NOAEL for maternal toxicity is 70 mg/kg/day (GD 17 C_{max} and AUC_{0-24} of 3590 ng/mL and 60,200 ng·hr/mL, respectively). With the exception of slightly lower fetal adjusted body weight at 100 mg/kg/day, presatovir administration had no effects on any of the embryo/fetal developmental parameters. No fetal anomalies were related to presatovir administration and the NOAEL for developmental toxicity is 100 mg/kg/day (GD 17 C_{max} and AUC_{0-24} of 4420 ng/mL and 91,700 ng·hr/mL, respectively).

In a definitive embryo-fetal developmental toxicity study in rabbits, time-mated females were administered presatovir via oral gavage at 0, 10, 30, and 50 mg/kg/day during the period of organogenesis (GD 7-19). During the dosing period, presatovir administration resulted in significant reductions in mean maternal body weight gain and food consumption at 50 mg/kg/day. Therefore, the NOAEL for maternal toxicity is 30 mg/kg/day (GD 19 C_{max} and

AUC_{0-24} of 3150 ng/mL and 47,500 ng·hr/mL, respectively). There were no presatovir-related effects on embryo/fetal viability and growth and no fetal anomalies, and the NOEL for developmental toxicity is 50 mg/kg/day (GD 19 C_{max} and AUC_{0-24} of 4800 ng/mL and 88,200 ng·hr/mL, respectively).

Additional details regarding nonclinical pharmacology and toxicology studies can be found in the presatovir IB.

1.2.4. Clinical Trials of Presatovir

For additional information regarding completed clinical trials of presatovir, refer to the presatovir IB.

1.2.4.1. GS-US-218-0101

This Phase 1, placebo-controlled, single- and multiple-dose ranging, first-in-human (FIH) study was conducted to evaluate safety, tolerability, and PK following oral administration of presatovir in up to 70 unique healthy subjects. The study included 3 stages (Parts A, B, and C) with 8 total staggered cohorts (7 pre-specified, 1 adaptive). Within each cohort of Parts A and B, 8 unique subjects were randomized to receive blinded investigational medicinal product (IMP), either presatovir (n = 6) or placebo (n = 2). Within each cohort of Part C, 10 unique subjects were randomized to receive blinded IMP, either presatovir (n = 8) or placebo (n = 2). A maximum single dose of 300 mg and multiple dose regimen of 75 mg once daily for 7 days was achieved. Presatovir PK was evaluated under fasting and fed states.

No deaths or serious adverse events (SAEs) were reported, and there were no dose-limiting toxicities. In the presatovir-treated subjects, there were no discontinuations due to AEs. Among the 23 subjects who received single doses of presatovir, 5 subjects (21.7%) experienced a total of 11 AEs, with the most common AEs being presyncope and dermatitis (reported by 2 subjects each). Both incidents of presyncope, and 1 of the 2 events of dermatitis, were judged by the investigator to be related to study procedures; 1 event of dermatitis was inflammation of the skin of the right antecubital and 1 event was nonspecific dermatitis on the chest. Among the 52 subjects receiving multip le doses of presatovir, 20 subjects (38.4%) experienced a total of 45 AEs, with diarrhea and nausea reported by 4 subjects and headache and contact dermatitis reported by 3 subjects. All other AEs experienced by subjects receiving multiple doses of presatovir were reported by ≤ 2 subjects each.

Twelve-lead ECGs were obtained at Baseline and Days 1, 15, and 21. Analysis of these ECGs demonstrated no clinically significant increase in the PR, QRS, QT, and QTcF intervals, and no clinically significant arrhythmias associated with administration of presatovir.

Presatovir exposures increased in an approximately dose-proportional manner over the dose range tested following single and multiple oral administrations under fasted conditions. Presatovir terminal half-lives ranged from 30 to 33 hours following single oral administration and approximately 36 hours following multiple oral administrations. Overall, the variability of the PK parameters was relatively low, with the majority of the PK parameters displaying CV%

of 30% or lower. In addition, the food effect on presatovir PK following single or multiple oral administration has been evaluated. Following single administration of presatovir at 25, 50, or 75 mg, C_{max} under fed conditions decreased approximately 20% to 40% compared to fasted conditions, but this effect was less pronounced following once daily dosing at the higher dose (75 mg) around steady-state.

1.2.4.2. Study GS-US-218-0109

This Phase 1 mass-balance study was conducted to evaluate the PK, metabolism, and excretion of presatovir in healthy subjects. The primary objective of this study was to determine the mass balance of presatovir following administration of a single, oral dose of radiolabeled [^{14}C]-presatovir. The secondary objectives of this study were to evaluate the PK of presatovir and metabolites, where possible and to determine the metabolite profile of presatovir in humans following administration of a single, oral dose of radiolabeled [^{14}C]-presatovir.

Eight subjects were enrolled and assessed for a period of a minimum of 10 days and a maximum of 21 days with a 7-day follow-up period. Following a single oral radiolabeled dose of presatovir (50 mg), the maximum mean concentrations of drug-derived radioactivity in blood and plasma were observed at 2 hours post-dose for both matrices. The overall recovery of radioactivity was 89.9%, with recovery primarily in feces (72.3%) versus urine (17.6%). Mean blood to plasma concentration ratios ranged from 0.450 to 0.591 through 120 hours post-dose, indicating that radioactivity was primarily in the plasma, relative to the cellular components of the blood.

The circulating radioactivity consisted mainly of presatovir (88%) and low levels of minor metabolites 5-chloro-2-amino (*N*-methanesulfonyl) benzamide (M58; 7%), oxy-presatovir-glucuronide (M47; 3%), and GS-557855 (M30B; 1%)).

The major component excreted in feces was unchanged parent presatovir (18.5% of the dose; coeluted with dioxy-presatovir-2 [M63]), along with other minor metabolites (dioxy-GS-presatovir-3 [M64; 5.42% of the dose] and dioxy-GS-557855-2 [M70; 3.51% of the dose]). The remaining identified 8 metabolites detected in feces each accounted for less than a mean of 2.5% of the dose. In urine, unchanged parent presatovir was the main species (~10.0% of the dose), and metabolite M47 represented ~3.59% of the dose.

In summary, [^{14}C] presatovir was primarily eliminated in the feces after oral administration to healthy subjects. Low levels of various metabolites were observed indicating the likely absence of a single dominant pathway. Radioactivity was eliminated as a combination of metabolites and unchanged parent drug. Overall, the PK of presatovir is not expected to be meaningfully altered in the setting of renal impairment (eg, mild to moderate).

1.2.4.3. Study GS-US-218-1010

Study GS-US-218-1010 was a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of presatovir on the QT/QTc interval in healthy subjects, with a lead-in, open-label, dose-ranging pilot phase to determine the supratherapeutic dose of presatovir.

This study was a 2-stage study. Stage I was a lead-in, open-label, 3-cohort, single-dose ranging pilot study to determine the supratherapeutic dose of presatovir. Stage II was a partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose crossover study evaluating the effect of presatovir on the QT/QTc interval in healthy subjects. For Stage I and Stage II, a total of up to 24 (for 18 evaluable) and 48 (for 40 evaluable) subjects, respectively, were planned to be enrolled, with an approximately even distribution of healthy male and non-pregnant, non-lactating female subjects 18 to 45 years of age, inclusive.

In Stage I of the study, all 19 randomized subjects completed the study. In Stage II of the study, of 48 randomized subjects, 47 completed the study. One subject was withdrawn from the study due to investigator discretion. Demographic and baseline characteristics were balanced between Stage I and Stage II. Overall, subjects in the Safety Analysis Set (which combined Stage I and Stage II safety data) had a mean age of 34 years (range 20 to 45 years); most were predominantly white (80.6%), and of Hispanic/Latino ethnicity (95.5%), with slightly more males (59.7%) than females (40.3%). The mean (SD) BMI and estimated glomerular filtration rate (eGFR) values were 26.2 (2.62) kg/m2 and 120.9 (15.34) mL/min, respectively.

Study GS-US-218-1010 showed that presatovir displayed approximately dose-proportional PK between 200 and 800 mg, with median terminal half-life ranging from 27 to 40 hours.

Presatovir, administered at doses of 200 and 800 mg, did not lead to changes in the QTc interval in healthy adults. Thus, this is a negative thorough QT study as defined by ICH guidance. Neither of the 2 doses of presatovir was associated with significant changes in ECG or wave morphology**.** There were no clinically relevant relationships between time-matched, baseline-adjusted, placebo-corrected QTcF or QTcI and plasma concentrations of presatovir.

Presatovir was generally well tolerated at doses of 200 and 800 mg.

1.2.4.4. Study GS-US-218-1532

Study GS-US-218-1532 was a single-center, single-dose, open-label Phase 1 study evaluating the PK of presatovir in healthy adult Japanese and Caucasian subjects. Eligible Japanese subjects received a single dose of 200 mg presatovir in the morning on Day 1 (fasted). Eligible Caucasian subjects received a single dose of 200 mg presatovir in the morning on Day 1 (fasted) and Day 13 (following a high-fat breakfast).

All subjects (15 Japanese, 16 Caucasian) who were enrolled in the study completed their assigned treatment and completed the study. Adverse events were noted in 1 Japanese subject (6.7%), 2 fasted Caucasian subjects (12.5%), and 1 fed Caucasian subject (6.7%). All events reported in this study were Grade 1; there were no SAEs, deaths, or discontinuations due to AEs. No event type was reported in more than one subject.

Following a single oral dose of 200 mg presatovir, the plasma exposures (C_{max} and AUC_{inf}), time to peak concentrations, and half-life were similar between Japanese and Caucasian subjects, and between subjects who were fed and fasted. These data suggest there were no differences for presatovir PK between Japanese and Caucasian subjects and no dose modifications are needed for presatovir dosing in Japanese subjects. Due to the lack of a food effect on presatovir PK, presatovir can be taken without regard to food.

1.2.4.5. Study GS-US-218-0103

This Phase 2a, randomized, double-blind, placebo-controlled study was conducted to evaluate the safety, tolerability, and efficacy of presatovir in healthy adult volunteers infected with an RSV challenge virus (RSV-A Memphis 37b strain). The study included 7 quarantines, each comprising approximately 20 subjects. Each subject was admitted to the Quarantine Unit and inoculated with RSV on Study Day 0. Subjects were randomized and treated with presatovir or placebo when infection was documented in the nasal wash, or by the fifth day after inoculation, whichever occurred first.

For Quarantines 1 through 4 (pre-specified quarantines), subjects were randomized 1:1 to receive presatovir or placebo, administered as a 50 mg single dose on Dose Day 1, followed by 25 mg once daily on Dose Days 2 through 5.

For Quarantines 5 through 7 (adaptive quarantines), subjects were randomized 4:1 to receive presatovir or placebo. Subjects in Quarantine 5 were administered a 50 mg single dose on Dose Day 1, followed by 25 mg once daily on Dose Days 2 and 3. Subjects in Quarantine 6 were administered a 100 mg single dose. Subjects in Quarantine 7 were administered a 10 mg single dose on Dose Day 1, followed by 5 mg once daily on Dose Days 2 through 5.

A total of 140 subjects were randomized into this study. All subjects completed study drug and 1 placebo subject discontinued the study due to investigator's discretion. Baseline demographics and characteristics were similar between treatment groups across all dose cohorts.
Seventy-eight (78) subjects received the pre-specified dose in quarantines 1-4 (presatovir n=39, placebo n=39). Of these, 54 subjects (69%) were documented to be RSV positive prior to randomization and were included in the primary and secondary analyses (presatovir n=27, placebo n=27). A total of 87 subjects received presatovir across all quarantines.

Treatment with presatovir resulted in the following:

Primary Endpoint:

- Treatment with presatovir resulted in lower mean AUC viral load from initial dose through end of quarantine. Viral load was assessed twice daily using nasal washes. The mean AUC of viral load as measured by the RT-qPCR assay from first viral load measurement post initial dose of study drug through Day 12 was significantly lower in presatovir subjects compared to placebo subjects (Δ= 506.9 $\log_{10}$ PFUe*hour/mL, p<0.001).

Secondary Endpoints:

- Treatment with presatovir resulted in lower mean AUC viral load during the entire quarantine period. The mean AUC of viral load post challenge through Study Day 12 as measured by the RT-qPCR assay was significantly lower in presatovir subjects compared to placebo subjects (Δ= 531.0 $\log_{10}$ PFUe*hour/mL, p=<0.001).

- Treatment with presatovir resulted in lower mean total mucus weight during dosing. The average weight of each unused tissue was determined prior to start of study. The daily mucus weight was calculated by first counting the number of tissues used each day, then subtracting the total weight of these tissues, unused, from the daily total weight of used tissues. The mean total weight of mucus produced post-initial dose of study drug through the dose was significantly lower in the presatovir subjects compared to placebo subjects (Δ= 8.2 g, p=0.028).

- Treatment with presatovir resulted in a lower mean AUC of change from Baseline in total symptom score during the entire quarantine period. Ten symptoms (runny nose, stuffy nose, sneezing, sore throat, earache, malaise [tiredness], cough, shortness of breath, headache, and muscle and/or joint ache) were each scored from 0 (no symptoms) to 3 (quite bothersome most/all of the time). Total symptom scores (0-30) were the average score of questions answered by each subject, multiplied by 10. The mean AUC of change from Baseline in total symptom score post initial dose of study drug through Study Day 12 was significantly lower in the presatovir subjects compared to placebo subjects (Δ= 225.1 score*hour, p=0.005). The total symptoms score AUC was also significantly lower for presatovir treated subjects.

In each of the adaptive quarantines statistically significant results were also achieved in the primary endpoint and each of the secondary endpoints described above with the exception of a reduction in mean total mucus weight in Quarantine 7. In addition, an exposure response effect was noted.

No subject experienced a serious AE. All AEs were mild or moderate (Grade 1 or 2) in severity, except for three Grade 3 AEs experienced by 1 placebo-treated subject (increased blood lactate dehydrogenase, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]). Grade 1 pulmonary function decrease (<10% change) was the only treatment-related AE experienced by >2 subjects in either treatment group (presatovir: 4.6%, n=4/87; placebo: 3.8%, n=2/53). Changes in clinical laboratory values were Grade 1 or 2 in severity, except for one Grade 4 value (increased AST; reported for placebo-treated subject described above). Elevated ALT was more commonly reported among presatovir-treated subjects (presatovir: 14.9%; placebo: 9.4%), but elevated AST was less commonly reported (presatovir: 5.7%; placebo: 15.1%). Low neutrophil count was reported as Grade 1 in 11 subjects (2 received placebo) and Grade 2 in 2 subjects (1 received placebo). Among the 9 subjects who experienced a Grade 1 low neutrophil count and received presatovir, 2 had a Grade 1 low neutrophil count at Screening. Clinically relevant changes in vital signs or ECGs were not observed.

1.2.4.6. Ongoing Studies

Study GS-US-218-1227 is a Phase 2b, randomized, double blind, placebo-controlled, single dose study evaluating the antiviral effects, PK, safety, and tolerability of presatovir in hospitalized adults with RSV infection. Approximately 200 RSV-positive subjects will be randomized 1:1 to receive either presatovir or placebo as a single, 200-mg dose on Day 1, and stratified into 1 of the following categories: no chronic airways or lung disease, COPD, asthma, or other chronic airways or lung disease. These stratifications will augment the probability of similar baseline RSV viral loads and duration of RSV viral shedding in the active and placebo groups. This is an ongoing global study.

Study GS-US-218-0108 is a Phase 2b, randomized, double-blind, placebo-controlled multi-center study evaluating antiviral effects, PK, safety, and tolerability of presatovir in HCT recipients with RSV infection of the upper respiratory tract. The study will enroll approximately 200 RSV-positive males and females 18 to 75 years of age who have had an allogeneic or autologous HCT and have documented acute RSV-related upper respiratory tract infection (URTI) symptoms. Subjects will be randomized in a 1:1 ratio to receive presatovir or placebo. This is an ongoing global study.

Study GS-US-218-1502 is a Phase 2b, randomized, double-blind, placebo-controlled multi-center study evaluating antiviral effects, safety, PK, and tolerability of presatovir in HCT recipients with RSV infection of the lower respiratory tract. The study will enroll approximately 60 RSV-positive males and females 18 to 75 years of age who have had an allogeneic or autologous HCT and have documented acute RSV-related lower respiratory tract infection symptoms. Subjects will be randomized in a 1:1 ratio to receive presatovir or placebo. This is an ongoing global study.

Study GS-US-218-1409 is a Phase 1 study to evaluate the effect of inhibitors of p-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), Organic Anion Transporer Proteins (OATP) 1B1 and 1B3 and cytochrome P450 inducers on presatovir PK in healthy subjects. Forty-nine healthy males and females of non-childbearing potential who are 18-55 years of age were enrolled. All subjects have completed dosing; analysis of this study is ongoing.

For additional information on ongoing trials of presatovir, please refer to the presatovir (GS-5806) Investigator Brochure (IB).

1.3. Rationale for This Study

There is a significant unmet medical need for a safe, convenient, and effective treatment for RSV infection. Currently, there are no effective vaccines or approved prophylactic treatment options for RSV infection in the LT population. Treatment for RSV infection in LT patients is supportive, with use of intravenous hydration, supplemental oxygen, and mechanical ventilation as required. Although treatment options such as antiviral agents, corticosteroids, and immunoglobulin are frequently used, there is no approved treatment for RSV infection in the LT population. Synagis® (palivizumab), a monoclonal antibody against RSV approved for prophylaxis against RSV infection among high risk infants, has never been evaluated in a randomized controlled study for treatment of RSV infection in the LT population. Likewise, Virazole® (ribavirin for inhalation) is approved for treatment of RSV infection in the pediatric population but is not used in general practice in-part because of concerns regarding its efficacy and tolerability, as well as the complexity of the specialized aerosol delivery system that is required {19902}. Importantly, current guidelines for the diagnosis and treatment of RSV infection do not provide recommendations regarding whether patients should be treated with anything other than supportive care {28723}. As a result, variability in standard practices for treatment of RSV infection in LT patients exists around the world.

This study follows 4 completed Phase 1 studies of presatovir in healthy adult volunteers, a completed Phase 2a study of presatovir in healthy adult volunteers infected with a RSV challenge virus, and 3 ongoing Phase 2b studies of RSV infected adults. In total, 245 unique

healthy adult subjects were enrolled in the completed studies described above (Studies GS-US-218-0101, -0103, -0109, -1010, and -1532). No subjects treated with presatovir experienced a SAE, a ≥ Grade 3 AE, or an AE leading to discontinuation. The Phase 2a study demonstrated that presatovir has potent antiviral activity against RSV and that in the challenge setting was able to reduce both viral load and clinical symptoms in healthy adults experimentally infected with RSV. Given the findings to date, presatovir may have the potential for clinical benefit in LT patients infected with RSV.

The current study is designed to evaluate the safety, tolerability, PK, and efficacy of presatovir among LT patients with RSV related acute respiratory symptoms. Safety and efficacy data generated from this study, taken together with currently available data, will be used to support further clinical development of presatovir in adult patients infected with RSV.

1.4. Dose Rationale

The dose and administration schedule selected for this study is a single dose of 200 mg presatovir administered orally or via NG tube on Day 1/Baseline, followed by 100 mg once daily on Days 2 through 14. This regimen was selected based upon the PK characteristics of presatovir and the pharmacokinetic/pharmacodynamic (PK/PD) relationship established in the antiviral effect study with different doses/regimens in Study GS-US-218-0103.

In Study GS-US-218-0103, a 5-day treatment regimen of presatovir (50 mg single dose on Dose Day 1, followed by 25 mg once daily on Dose Days 2 through 5) resulted in a significant reduction in RSV viral load. The mean AUC of RSV viral load as measured by the RT-qPCR assay from first viral load measurement post initial dose of study drug through end of quarantine (Day 12) was significantly lower in presatovir subjects compared to placebo subjects (Δ= 506.9 $\log_{10}$ PFUe*hour/mL, $p<0.001$). This 5-day regimen achieved presatovir trough concentrations ~4-5 fold higher than the $paEC_{95}$ (52 ng/mL) for up to 120 hours following dose initiation for RSV M37 (virus strain used in GS-US-218-0103 study).

The dose for the current study was selected with the goal to maintain the plasma trough concentration of presatovir at least 5-fold above the $paEC_{95}$ (25 ng/mL) of the clinical RSV isolates for the duration of RSV shedding in LT patients. Longitudinal viral dynamics data in LT patients with RSV is limited and is reported as a part of randomized trials and epidemiologic studies. Two trials indicate the majority of patients shed RSV for an average of 5.5 days {34808} {34818} {34819}; however, the time of enrollment from onset of symptoms was variable and in some cases substantial. Moreover, immunosuppressed patients with RSV infection are demonstrated to shed virus for 21 days or longer {34949} {34950} {34957}. The dose and schedule in the current study, 200 mg on Day 1/Baseline followed by 100 mg daily on Days 2 through 14, will maintain plasma levels of presatovir greater than 5-fold above $paEC_{95}$ for at least 18 days after the first dose.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the effect of presatovir on nasal RSV viral load in RSV-positive 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 PK, safety, and tolerability of presatovir

3. STUDY DESIGN

3.1. Endpoints

The co-primary efficacy endpoints are:

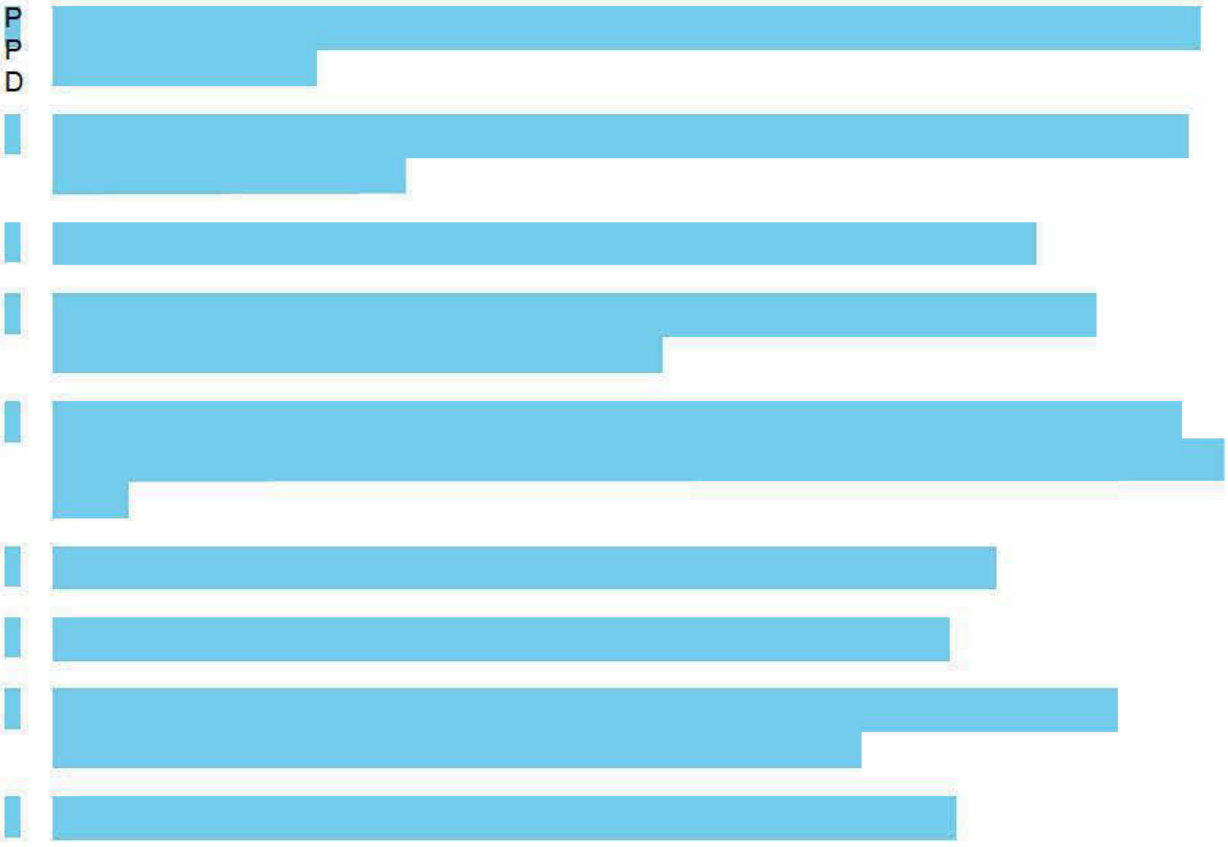
- Time-weighted average change in $\log_{10}$ viral load from Day 1/Baseline through Day 7 ($DAVG_7$) as measured in nasal samples by RT-qPCR among subjects in the FAS
- Time-weighted average change in $\log_{10}$ viral load from Day 1/Baseline through Day 7 ($DAVG_7$) as measured in nasal samples by RT-qPCR in a subset of FAS subjects whose duration of RSV symptoms prior to the first dose of study medication is ≤ median

The secondary endpoints of the main study portion (Day 1/Baseline through Day 28/End of Study) are:

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

The exploratory endpoints for the main study portion are:

P
P
D



PPD

The exploratory endpoints for the optional Registry portion (Day 28/End of Study through Week 48) are:

PPD

3.2. Study Design

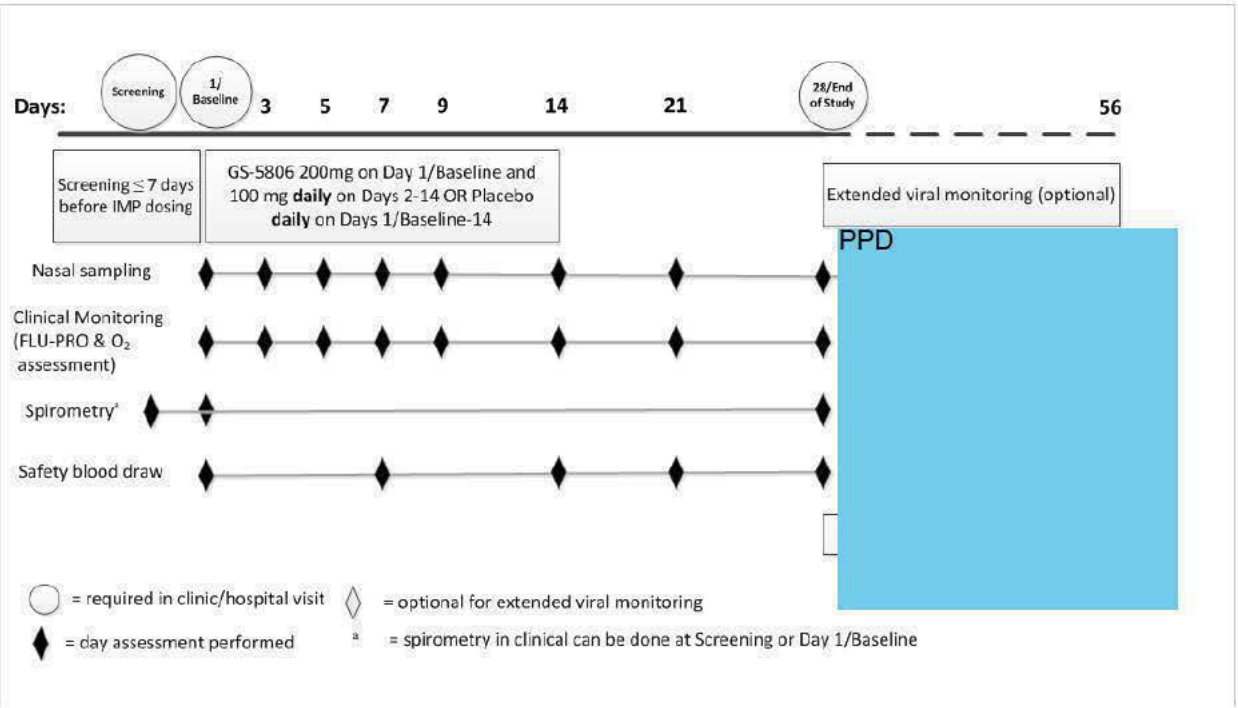
This is a randomized, double-blind, placebo-controlled study evaluating the effect of presatovir on efficacy, PK, safety, and tolerability in LT recipients with RSV infection.

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).

This study will enroll approximately 60 subjects from approximately 40 centers. RSV positive subjects with acute respiratory symptoms will be randomized in a 2:1 ratio to receive presatovir administered as a 200-mg dose on Day 1/Baseline, followed by daily 100-mg dose 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: use of any treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized) (yes or no) and 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 3-1. Study Design



3.3. Study Treatments

Sixty subjects will be randomized in a 2:1 ratio to receive presatovir administered as a 200-mg dose on Day 1/Baseline, followed by daily 100-mg dose on Days 2 through 14 or PTM once daily for a total of 14 days. Refer to section 5.3 for IMP administration details.

3.4. Study Duration

Subjects will participate in the main study portion for a total of 28 days; the duration of treatment is 14 days for a total of 14 doses.

3.5. Discontinuation Criteria

Reasons for potential premature discontinuation from IMP dosing include:

- Any Grade 3 or 4 AE or SAE
- Intercurrent illness that would, in the judgment of the investigator, affect the subject's ability to receive IMP (eg, unable to ingest oral dose)
- ALT or AST > 5× ULN
- Worsening of clinical symptoms with no other acceptable explanation
- Hy's Law criteria are met:
  - — Evidence of injury: elevation of the ALT or AST by > 3× ULN
  - — Evidence of dysfunction: elevation of the total bilirubin (TB) by > 2× ULN without an elevation of the alkaline phosphatase (ALP) by > 2× ULN
  - — Clinical verification to ensure effect is health product-induced and not induced by disease or another cause of injury

In the event that any of the above criteria are met, the Principal Investigator (PI) will review the case in detail and discuss with the Gilead Medical Monitor whether the subject should be discontinued from IMP. If close monitoring of ALT, AST, ALP, and TB per Section 6.7.6 is not possible, IMP will be discontinued.

Reasons for premature discontinuation from the study include:

- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.7.2
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

If a subject prematurely discontinues from IMP dosing, he/she will remain on study and will continue with all subsequent study Day visits and assessments, with the exception of IMP administration.

If a subject prematurely discontinues from the study, every attempt should be made to bring the subject back for the Early Termination procedures. See Section 6.5.2 for more information.

3.6. Source Data

For the purposes of this study, study specific questionnaires (ie, respiratory symptom assessments) are considered source documents and are to be filed with the subject's medical or study records. Electronic data (eg, diagnostic machines that transcribe data directly to a database, or data entered directly into an Electronic Medical Record (EMR) system) is considered source data, provided the data is not recorded directly on the CRF/eCRF, and provided there is a clear audit trail in the electronic record(s). Template source document worksheets will be prepared by Gilead and provided to sites to use at their discretion. If source document worksheets are used, they are to be kept with the subject's medical or study records as original source documents. No data will be recorded directly on the CRF/eCRF, and any data recorded directly on the CRF/eCRF will not be considered source data.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

The subject population will consist of approximately 60 RSV-positive subjects who received a LT (single or double) or heart/lung transplant and have acute respiratory symptoms, recruited from approximately 40 centers in North America, Australia, and Europe.

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria at the time of randomization to be eligible for participation in this study:

1) Males and females ≥ 18 years of age who have received a LT (single or double) or heart/lung transplant > 90 days prior to Screening

1) Confirmed to be RSV-positive by local polymerase chain reaction (PCR) testing (starting from when the upper or lower respiratory tract sample is obtained) ≤ 7 days prior to IMP administration on Day 1/Baseline

2) New onset or acute worsening, if the symptom is chronic, of at least 1 of the following respiratory symptoms ≤ 7 days prior to IMP administration on Day 1/Baseline: nasal congestion, earache, runny nose, cough, sore throat, shortness of breath, or wheezing

3) An informed consent document signed and dated by the subject

4) A negative urine or serum pregnancy test for female subjects of childbearing potential (unless surgically sterile or greater than 2 years post-menopause) at Screening or prior to Randomization on Day 1/Baseline

5) Agreement from male and female subjects of childbearing potential who engage in heterosexual intercourse to use protocol specified method(s) of contraception as described in Appendix 6

6) Ability and willingness to complete necessary study procedures

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

Related to concomitant or previous medication use:

1) Use of any investigational agents within 30 days, **OR** use of any investigational monoclonal anti-RSV antibodies within 4 months or 5 half-lives of Screening, whichever is longer, **OR** use of any prior investigational RSV vaccines

2) Use of a strong or moderate cytochrome P450 enzyme (CYP) inducer including but not limited to rifampin, St. John's Wort, carbamazepine, phenytoin, efavirenz, bosentan, etravirine, modafinil, and nafcillin, within 2 weeks prior to the first dose of IMP

3) Use of any of the following lympholytic treatment within the stated time frame: anti-thymocyte globulin (ATG), < 3 months; anti-lymphoblast globulin (ALG), < 3 months; muronomab-CD3 (OKT3), < 3 months; rituximab < 6 months; alemtuzumab < 9 months

Related to transplant history:

4) Recipient of any other organ transplant prior to Screening, with the exception of a LT (single or double) or heart/lung transplant

5) Recipient of a hematopoietic cell transplant at any time

6) Presence of BOS Stage 3 at Screening defined as a FEV_1 of 50% or less of baseline

Related to medical condition at Screening:

7) Respiratory failure requiring invasive mechanical ventilation

8) Evidence of shock requiring vasopressors

9) Known viral coinfection (including but not limited to influenza, metapneumovirus, human rhinovirus, parainfluenza, cytomegalovirus, or coronavirus) in the upper or lower respiratory tract ≤ 14 days prior to Screening unless discussed with the medical monitor and deemed acceptable

10) Active systemic infection or infectious pneumonia of any etiology (ie, bacterial, viral [other than RSV] or fungal), including aspiration pneumonia, that is considered clinically significant by the investigator unless discussed with the medical monitor and deemed acceptable

11) Pregnant or lactating females

12) Evidence of recent and rapidly deteriorating lung function, occurring before the onset of the current viral respiratory infection, including but not limited to: acute lung allograft rejection, rapidly-progressive CLAD, and rCLAD (as determined by the investigator)

13) Any condition which, in the opinion of the investigator, would prevent full participation in this study or would interfere with the evaluation of the trial endpoints

Related to allergies:

14) Known hypersensitivity or allergy to the IMP**,** its metabolites, or formulation excipients (microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc)

15) History of hypersensitivity, anaphylactic reaction, Stevens-Johnson Syndrome, or toxic epidermal necroylsis response to sulfa drugs

Related to laboratory values:

16) Clinically significant kidney dysfunction as defined by:

An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) study 4 parameter equation obtained from screening laboratory measurements or via local laboratory measurements obtained $\leq$ 7 days prior to Screening. The eGFR may be manually calculated or the reported eGFR value may be used, but any automatically calculated eGFR must be calculated using the MDRD equation.

17) Clinically significant liver function test abnormalities as defined by a ALT or AST > 5 times the ULN obtained in screening laboratory measurements or via local laboratory measurements obtained $\leq$ 7 days prior to Screening

18) Clinically significant elevations in total bilirubin (TB), as determined by the investigator

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is a randomized, double-blind, placebo-controlled multi-center study. Eligible subjects will be stratified by the following factors:

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

Treatment of current RSV infection with ribavirin will be defined as ≥1 dose of ribavirin (oral, intravenous, or aerosolized) prior to randomization or with written orders for the initiation of therapy at the time of randomization. Subjects will be randomized in a 2:1 ratio to receive IMP (presatovir or matching placebo).

Assignment to study treatment will be blinded to the study subjects, investigational site personnel, study vendors, and the Sponsor study team, except for the delegated personnel who will review and check the randomization and drug allocation for accuracy.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency in which breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. In the event of technology failure, the PI may call the IXRS help line to access treatment codes. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding. Details of unblinding will be provided in the study-specific Unblinding Plan.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Presatovir (GS-5806)

5.2.1. Formulation

Presatovir will be supplied as white, plain-faced, film-coated, round tablets containing 50 mg presatovir (60 mg GS-5806-02, bis-hydrochloride salt dihydrate form of presatovir). In addition to the active ingredient, presatovir tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc, which are common pharmaceutical excipients.

The supplied PTM tablets are identical in physical appearance to the 50 mg presatovir tablets and contain the same inactive ingredients.

5.2.2. Packaging and Labeling

Presatovir tablets and PTM tablets are packaged in white, high density polyethylene (HDPE) bottles with silica gel desiccant and polyester packing material. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

Sufficient quantities of presatovir tablets and PTM tablets will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supply Management (or its designee).

Presatovir tablets and PTM tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied.

5.3. Dosage and Administration of Presatovir

Eligible subjects will receive presatovir administered as a 200-mg dose (4 x 50 mg tablets) on Day 1/Baseline, followed by daily 100-mg dose (2 x 50 mg tablets) on Days 2 through 14, or PTM once daily for a total of 14 days.

All IMP or PTM will be administered orally or via a NG tube if required. The entire dose must be taken within 1 hour. If administration through a NG tube is required, tablets may be crushed and dissolved in water. IMP should be dispensed with gloves. Subjects will remain in the clinic

for 30 minutes post-dose for observation. On any day, if vomiting occurs within 30 minutes after ingesting the last pill and pills or pill fragments are found in the vomitus, the subject may re-dose after contacting designated site staff. If another dose is administered, and site staff or home health agency nurses are present, the subject should be observed for an additional 30 minutes post-dose to record whether the dose was tolerated or if additional vomiting occurred. If no site staff or home health agency nursing staff are present during an approved re-dosing episode, follow-up is required 30 to 60 minutes after re-dosing to record tolerance to the re-dosing attempt as above. The subject may be re-dosed only once per day.

5.4. Prior and Concomitant Medications

Strong and moderate inducers of CYP enzymes may reduce the exposure of presatovir. Pharmacokinetic results from a clinical drug-drug-interaction study (GS-US-218-1409) demonstrated that induction of CYP enzymes with rifampin or efavirenz resulted in an 82% or 56% decrease, respectively, in presatovir AUC_{inf}. Therefore, concomitant administration of strong or moderate CYP inducers {26462} (including but not limited to rifampin, St John's Wort, carbamazepine, phenytoin, efavirenz, bosentan, etravirine, modafinil, and nafcillin) is excluded to avoid potential drug resistance.

Cyclosporine, a weak CYP3A inhibitor and a potent inhibitor of efflux transporters (P glycoprotein [P-gp], breast cancer resistant protein [BCRP]) and the hepatic uptake organic anion transporter proteins (OATP1B1 and OATP1B3), has been associated with a mild increase in presatovir plasma exposure (10.6% increase in Cmax and 26.1% increase in AUCinf). Thus presatovir can be coadministered with inhibitors of P-gp, BCRP, OATP 1B1, or OTAP1B3 without dose modification.

The effect of co-administration with strong and moderate CYP3A inhibitors on presatovir PK is currently being investigated in a clinical drug-drug interaction study.

Presatovir is not expected to significantly alter the PK of concomitant medications that are substrates of major human CYP enzymes or drug transporters. Presatovir is not expected to be an inhibitor of common human CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, and CYP2D6), human UGT1A1, or major drug transporters (OATP1B1/1B3, BCRP, P-gp, OCT1, OCT2, BSEP, OAT1, and OAT3) at clinically relevant concentrations. Presatovir is also not an inducer through AhR or PXR at concentrations up to 50 μM.

Presatovir may cause concentration-dependent inhibition of multidrug and toxin extrusion via transporters MATE1 and MATE2-K with IC_{50} values of 0.50 and 3.8 μM, respectively. When co-administered with renally eliminated concomitant medications (ie, filtration plus secretion), presatovir may increase the exposures of substrates secreted by the MATEs transporters, such as ganciclovir, acyclovir, levofloxacin, metformin, captopril, procainamide, fexofenadine, cimetidine, cephradine, and cephalexin. Dosing and safety monitoring should be consistent with prescribing information, in particular for agents which require dose reductions in the setting of renal impairment.

5.5. Accountability for Presatovir

The investigator is responsible for ensuring adequate accountability of all used and unused IMP bottles. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition).

Presatovir accountability records will be provided to each study site to:

- Record the date and quantity of IMP bottles received
- Record the date, subject number, subject initials, the IMP bottle number dispensed
- Record the date, quantity of used and unused IMP bottles returned, along with the initials of the person recording the information

5.5.1. Investigational Medicinal Product Return or Disposal

At the site initiation visit or first monitoring visit, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for return or destruction of unused IMP supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction (as reviewed and approved by Gilead Sciences, Inc. [GSI]), the site may destroy used and unused IMP supplies performed in accordance with the site's (hospital/pharmacy) SOP after reconciliation has been completed by the site monitor. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and GSI (or GSI representative) for return of unused IMP supplies. A copy of the site's SOP will be obtained for central files. Where possible, IMP will be destroyed at the site.

Upon study completion, a copy of the Investigational Drug Accountability records must be filed at the site. Another copy will be returned to GSI. If drug is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. All IMP records must be maintained at the site and copies must be submitted to GSI at the end of the study.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators must document any deviation or departure from protocol procedures, regardless of causality, and notify the Sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

6.1.1. Screening

Screening must be performed in clinic or in hospital. Potential subjects must have documentation of being RSV- positive by local PCR testing on an upper or lower respiratory tract sample prior to being approached for informed consent if RSV testing is part of standard medical care. In cases where a RSV infection is suspected but either RSV testing is not performed as a part of standard medical care, 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. The Principal Investigator or a medically qualified Sub-Investigator (eg, MD, DO, or nurse practitioner) must review and discuss the study with each subject prior to consent. All Screening assessments must be performed after obtaining written consent. All Screening labs and procedures will be performed locally and results will be reviewed by the investigator prior to IMP administration.

The following procedures will be completed at Screening:

- Obtain written informed consent
- Review and collection of Medical History and Demographics
- Review and collection of concomitant medications
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- Height and weight
- Blood draw for screening labs for local laboratory analyses, unless existing laboratory values collected ≤ 7 days prior to Screening can be obtained for review
  - Creatinine
  - AST and ALT
  - Total bilirubin

- Study spirometry
- Urine or serum pregnancy test (for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy)
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the informed consent form
- Nasal sampling for local PCR testing for subjects suspected of having a RSV infection but either RSV testing is not performed as a part of standard medical care, or an RSV screening test is performed but by a non-PCR-based assay
- If a BAL is performed as a part of standard clinical care at Screening, and a RSV Screening test is required to satisfy inclusion criteria under the condition(s) outlined above, excess BALF may be submitted for local RSV PCR-based testing.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic after screening for randomization into the study. Subjects must continue to meet all inclusion criteria and none of the exclusion criteria at the time of randomization. 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.

From the time of obtaining informed consent through the first administration of IMP, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AE case report form (eCRF). All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.1.2. Day 1/Baseline

6.1.2.1. Baseline Assessments

Day 1/Baseline must be performed in clinic or in hospital and should occur within ≤ 7 days of confirmation of the subject's eligibility. Day 1/Baseline assessments must be completed prior to IMP administration and assessments should be performed in the following order, when possible.

- FLU-PRO questionnaire
- Review of concomitant medications
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- Oxygen requirement assessment
- Blood draw for central laboratory analysis:
  - CBC, sodium, potassium, chloride, CO_2, BUN, creatinine, glucose
  - AST, ALT, and alkaline phosphatase

  - Total bilirubin
  - CK
- Blood draw for local troponin testing
- Blood draw for plasma biomarkers, HLA antibody, and RSV antibody titer
- Study onsite baseline spirometry (if not performed at Screening)
- Self administered handheld spirometry (these handheld spirometry measures will be collected specifically in the presence of study staff at Days 1/Baseline)
- Nasal samples (2 total, 1 from each nostril)
- 12-lead ECG
- PPD
- PPD
- Oxygen saturation assessment

Optional Registry assessments on Day 1/Baseline visit:

PPD

- PPD
- PPD
- PPD

6.1.2.2. Randomization and Treatment Assessments (Day 1/Baseline)

After all Baseline assessments are complete, eligible subjects will be randomized via Interactive Voice/Web Response System (IWRS) and IMP will be administered.

- Randomization to presatovir or placebo will be based on a randomization schedule prepared by Gilead and/or designee before the start of the study. Subjects must continue to satisfy all inclusion/exclusion criteria at the time of randomization. Prior to randomization, eligible subjects will be stratified by the following:

— Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)

— Use of palivizumab or IVIG (yes or no)

Treatment of current RSV infection with ribavirin will be defined as ≥1 dose of ribavirin (oral, intravenous, or aerosolized) prior to randomization or with written orders for the initiation of therapy at the time of randomization. Subjects will be randomized in a 2:1 ratio to receive IMP (presatovir) or placebo.

Subjects will receive a dose of 200-mg (4 x 50 mg tablets) of presatovir or PTM on Day 1/Baseline. All IMP will be administered orally or via a NG tube as described in section 5.3 (Dosage and Administration of presatovir) above. Refer to Section 5.3 for IMP administration details.

The following procedures will be performed and documented on Day 1/Baseline after IMP administration:

- PK sampling at 2-4 hours post-dose
- Assessment of AEs and concomitant medications
- If applicable, clinical data collection for all standard of care cardiac-related tests performed during the study period (see Section 6.7.8)

6.2. Days 2 through 21 (±24 hours window applies to each visit day)

Day 3, 5, 7, 9, 14, and 21 visits may be performed at home or in the local hospital/clinic. Visits are **NOT REQUIRED** on Day 2, 4, 6, 8, 10, 11, 12, 13, 15, 16, 17, 18, 19, and 20. (Refer to Appendix 2, Study Procedures Table)

On required in clinic/hospital/home subject visit days assessments should be performed in the following order whenever possible and documented:

- FLU-PRO questionnaire (Days 3, 5, 7, 9, 14, and 21)
- Oxygen requirement assessment (Days 3, 5, 7, 9, 14, and 21)
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure) (Days 7, 14, 21)
- Urine or serum pregnancy test (for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy) (Days 7 and 14)
- PK blood draw (pre-dose on Days 7 and 14, and any time on Day 21). Subjects must have home visit blood draw completed prior to IMP administration on Days 7 and 14. Refer to Section 5.3 for guidance on IMP administration and relevant observation times.

- Blood draw for safety labs and plasma biomarkers (Days 7, 14, 21)
- Nasal samples (2 total, 1 from each nostril) (Days 3, 5, 7, 9, 14,and 21)
- PPD
- PPD
- IMP daily dosing (100 mg, Days 2 through 14); directly observed IMP administration (Day 7 and 14 only)
- Perform IMP accountability (Days 3, 5, 7, 9, 14, and 21)
- Assessment of AEs and concomitant medications (Days 3, 5, 7, 9, 14, and 21)
- Self administered handheld spirometry (these handheld spirometry measures will be collected specifically in the presence of study staff at Days 3, 5, 7, 9, 14, 21)
- If applicable, clinical data collection for all standard of care cardiac-related tests performed during the study period (see Section 6.7.8)
- If the subject is seen at the site for any reason (eg, hospitalization, clinic, or site visit) between Days 2 to 14, a blood draw for troponin measurement is required. Refer to Section 6.7.6 for additional information.
- 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. Refer to section 6.7.7 for additional information.

6.3. Day 28/End of Study visit: (+2 days)

Day 28/End of Study assessments must be performed in clinic / hospital and should be performed in the following order when possible and documented (also refer to Appendix 2, Study Procedures Table):

- FLU-PRO questionnaire
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- Oxygen requirement assessment
- Blood draw for central laboratory analysis:

  —CBC, sodium, potassium, chloride, CO_2, BUN, creatinine, glucose

—AST and ALT, alkaline phosphatase

—Total bilirubin

—CK

- Blood draw for local troponin testing
- Nasal samples (2 total, 1 from each nostril)
- Spirometry
- Self administered handheld spirometry (these handheld spirometry measures will be collected specifically in the presence of study staff at Day 28/End of Study)
- 12-lead ECG
- Blood draw for HLA antibody and RSV antibody titer
- Assessment of AEs and concomitant medications
- Ensure all BAL, microbiology, and pathology results from Screening through Day 28/End of Study are collected
- If applicable, clinical data collection for all standard of care cardiac-related tests performed during the study period (see Section 6.7.8)
- In addition to the study-specific measures described above, all spirometry and other measurements of pulmonary function obtained at unplanned study times, as part of standard clinical care during the study period, will be collected.
- Oxygen saturation assessment

Optional Registry assessments on Day 28/End of Study visit:

PPD

- PPD
- PPD

- PPD [redacted]

6.4. Days 35, 42 49, and 56 visits (±2 days, applies to each visit day)

PPD [redacted]

- Obtain nasal samples (2 total, 1 from each nostril)
- Assessment of procedure-related AEs

6.5. Assessments for Premature Discontinuation from IMP dosing and Early Withdrawal

Reasons for premature discontinuation from IMP dosing or the study are outlined in Section 3.5.

6.5.1. Assessments for Premature Discontinuation from IMP Administration

If a subject prematurely discontinues IMP dosing, the subject will remain on study and will continue with all subsequent study visits and assessments through Day 28/End of Study Visit, with the exception of IMP administration.

6.5.2. Assessments for Early Termination/Withdrawal

Every attempt should be made to keep subjects in the study and to perform the required study-related and follow-up procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

If a subject withdraws early (prior to Day 28) from the study for any reason, every attempt should be made to bring the subject back to the clinic or hospital for the following early termination assessments:

- FLU-PRO questionnaire
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- Oxygen requirement assessment
- Blood draw for central laboratory analysis:
  - CBC, sodium, potassium, chloride, CO_2, BUN, creatinine, glucose

  - AST, ALT, and alkaline phosphatase
  - Total bilirubin
  - CK
- Blood draw for local troponin testing
- Blood draw for RSV antibody titer
- PK blood draw (only if the subject withdraws prior to Day 21)
- Nasal samples (2 total, 1 from each nostril)
- 12-lead ECG
- Assessment of AEs and concomitant medications
- IMP Accountability (if subject withdraws prior to Day 21)
- If applicable, clinical data collection for all standard of care cardiac-related tests performed during the study period (see Section 6.7.8)
- Self administered handheld spirometry (these handheld spirometry measures will be collected specifically in the presence of study staff)
- Oxygen saturation assessment
- Return of handheld spirometer

6.6. Assessments for Unscheduled Visits

Subjects who return to the clinic or hospital between scheduled study visits will have an unscheduled visit performed. The following procedures will be performed and documented at these visits:

- FLU-PRO Questionnaire, prior to all other study procedures (if unscheduled visit occurs prior to Day 28)
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- Oxygen requirement assessment
- Nasal samples (2 total, 1 from each nostril)
- Assessment of AEs and concomitant medications

- Spirometry and other measures of pulmonary function testing (if completed for standard-of-care)
- Self-administered handheld spirometry performed in the presence of study staff
- If applicable, clinical data collection for all standard of care cardiac-related tests performed during the study period (see Section 6.7.8)
- If the subject is seen at the site for any reason (eg, hospitalization, clinic, or site visit) between Days 2 to 14, a blood draw for troponin measurement is required. Refer to section 6.7.6 for additional information.
- If the subject is seen at the site for any reason (eg, hospitalization, clinic, or site visit) between Days 2 to 14, a 12-kead ECG is required. Refer to section 6.7.7 for additional information.

6.7. Study Assessments

6.7.1. Nasal Samples, Virology, and Antibody Titer

All subjects should be documented as RSV-positive, as determined by the local polymerase chain reaction (PCR) testing using an upper or lower respiratory tract sample collected ≤ 7 days prior to IMP administration on Day 1/Baseline. Nasal samples will be obtained on Days 1/Baseline, 3, 5, 7, 9, 14, 21, and 28/End of Study for analysis at the central laboratory. Nasal sampling may also be done at Screening, per local practice routine, for RSV Screening Testing. Two samples will be collected at each time point, 1 from each naris. If it is not possible to collect nasal samples from both nares (eg, subject has an NG tube in the place), two samples should be taken from the same naris. Nasal samples will be analyzed using RT-qPCR to determine RSV viral load, RSV sequencing to evaluate development of resistance (see Section 6.7.2), and a multiplex assay to identify co-infections. PPD

Blood samples will be collected for plasma biomarkers (Days 1/Baseline, 7, 14, and 21), HLA antibody (Day 1/Baseline and 28/End of Study) and RSV antibody titers (Day 1/Baseline and 28/End of Study). PPD

6.7.2. Virology and Resistance Monitoring

To assess the potential for emergence of resistance to presatovir, population sequencing of the RSV F gene will be conducted on evaluable nasal swab samples collected from presatovir and placebo-treated RSV-infected subjects according to the Virology Analysis Plan. PPD

Population sequencing of the RSV F gene will be conducted on evaluable nasal swab samples from all presatovir-treated RSV-infected subjects in this group. Any mutation in the F gene identified by population sequencing in presatovir-treated subjects relative to the pretreatment baseline sequence will be characterized phenotypically following their introduction into wild-type RSV using an established reverse genetics system. The susceptibility of the F mutant recombinants to presatovir will be assessed in cell-based antiviral susceptibility assays to determine whether each treatment-emergent mutation (TEM) confers reduced susceptibility to the compound.

6.7.3. FLU-PRO Questionnaire

The FLU-PRO will be self-administered after informed consent and prior to all other study procedures. The FLU-PRO is currently being validated for the evaluation of symptoms in patients who are infected with influenza. Due to the lack of validated tools for the evaluation of RSV symptoms, and significant overlap between RSV symptoms and influenza symptoms, this tool will be used to assess change in RSV symptoms in this study. This questionnaire will be completed by subjects on Days 1/Baseline, 3, 5, 7, 9, 14, 21 and 28/End of Study.

6.7.4. Vital Signs

This assessment will include body temperature, heart rate, respiratory rate, and blood pressure. The subject is required to sit quietly for approximately 2 minutes prior to obtaining VS. Vital signs will be collected at Screening and on Days 1/Baseline, 7, 14, 21, and 28/End of Study.

6.7.5. Oxygen Requirement Assessment

The requirement for oxygen will be assessed according to whether the subject requires any supplemental oxygen (yes or no) on Day 1/Baseline and a new home oxygen prescription (yes or no) on Days 3, 5, 7, 9, 14, 21, and 28/End of Study.

6.7.5.1. Oxygen Saturation Assessment

Oxygen saturation assessment will begin by first asking the subject to sit quietly for 1 minute. Oxygen saturation will be recorded while breathing room air. If the subject is prescribed supplemental O_2 for chronic use prior to this current illness (eg, 2L/min via nasal cannula), the prescribed amount should be noted in the eCRF and should be used during the O_2 saturation assessment. Any additional supplemental O_2 being used (ie, above room air or prescribed amount for chronic use prior to this current illness) should be removed for a period of 30 seconds prior to this assessment. The O_2 saturation will be documented in the source at regular intervals during

the 2-minute testing period. Oxygen saturation evaluation will be considered complete when the 2-minute period has elapsed, or when the subject achieves a saturation of ≤ 88%, whichever is achieved first. The lowest O_2 saturation recorded over the 2-minute interval will be captured in the eCRF. If the subject is unable to tolerate removal of supplemental oxygen for this assessment (eg, subject dependent on high dose oxygen or on mechanical ventilation), notation that the oxygen saturation could not be assessed by this protocol should be noted with the reason recorded.

6.7.6. Safety Labs

When available, the most recent laboratory values (obtained ≤ 7 days prior to Screening) may be used for eligibility assessment, with the exception of RSV results and pregnancy testing. If an existing laboratory value is not available for eligibility assessment, the test will be performed using the local hospital laboratory. All testing of samples obtained after the Screening assessments (with the exception of an additional local troponin test on Day 1/Baseline and Day 28/End of Study) will be performed at a central laboratory selected by GSI.

Central laboratory testing of blood specimens for safety analysis will include CBC, sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, AST and ALT, alkaline phosphatase, total bilirubin and CK on Days 1/Baseline, 7, and 14 (pre-dose) and on Days 21and 28/End of Study.

Local laboratory testing of troponin will also be done at Day 1/Baseline and Day 28/End of Study for timely safety evaluation by the investigator. Local troponin testing will be done in accordance with the standard assay available 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 draw 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.

Samples will be sent to the local lab at the clinical site for troponin analysis using the laboratory-based assay specific to the local trial site (eg, troponin I or T). Point-of-care “rapid” troponin tests are not acceptable for protocol-mandated troponin testing. The baseline troponin test must be pre-dose. Troponin testing done for the purposes of patient care on the same day as a protocol-required test day may be used, provided the test is completed at the protocol-directed time and is a laboratory-based assay. Troponin results should be verified before the subject leaves the clinical site in case a troponin value is positive and further medical care is advised. Any additional troponin measures obtained for the purposes of patient care also require collection.

Any test showing an increase of serum AST or ALT > 3 × ULN or TB > 2 × ULN, will be repeated within 48 to 72 hours for ALT, AST, ALP, and TB. If the repeat values are unchanged or are normalizing, monitoring will continue at weekly intervals until the results are acceptable or normalized. If any value has increased further from normal, immediate close observation is required. If close monitoring is not possible, IMP administration will be discontinued.

Urine or serum pregnancy tests will occur for all females of childbearing potential (women unable to confirm greater than 2 years post-menopause, hysterectomy and/or bilateral oophorectomy) at Screening or on Day 1/Baseline prior to Randomization, and on Days 7 and 14 prior to IMP administration.

6.7.7. Electrocardiogram (ECG)

As part of safety testing, at Day 1/Baseline a pre-dose 12-lead ECG will be performed on the clinic or local hospital equipment. A second 12-lead ECG will also be performed at Day 28/End of Study.

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 one 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. ECG testing done for the purposes of patient care on the same day as a protocol-required test day may be used, provided the test is completed at the protocol-directed time. ECG results should be verified before the subject leaves the clinical site in case further medical care is advised. Any additional ECG measures obtained for the purposes of patient care also require collection.

6.7.8. Collection of Standard of Care Clinical Data for Central Review

During the course of the study, it is anticipated that Investigators will perform radiologic images of the chest as part of standard of care if there is any concern of a lower respiratory tract complication. Results from radiologic images of the chest used for screening and eligibility, including the comparison images, and all scans done as part of standard of care (to include CT and chest X-rays) while subjects are on study, as well as results from any confirmatory testing done, such as microbiology or ECGs, will be collected and stored electronically for review by the Adjudication Committee and a possible central read. Autopsy reports will also be collected (if performed).

Additionally, throughout the study period (Baseline/Day 1 through Day 28/End of Study) if any cardiac monitoring procedure is performed as part of standard clinical care, or as part of AE/SAE evaluation and/or follow-up, these results will be collected, including but not limited to the following standard of care procedures:

- ECG tracings and results report of any ECG performed
- Cardiac enzyme testing (eg, all troponin results, CK-MB, etc)
- Cardiac stress testing
- Echocardiographic imaging (resting and stress testing)
- Cardiac perfusion scans

- Cardiac MRIs
- Any additional procedure used to evaluate cardiac conditions

6.7.9. Plasma PK

PK blood sampling will be performed using the site's local procedures and analyzed at a central laboratory. PK blood samples will be processed, placed in individual tubes, and stored/shipped to the central laboratory as per instructions outlined in the laboratory manual.

Table 6-1. PK Timepoints

	Day 1/Baseline: 2-4 hrs post-dose	Days 7 and 14: pre-dose	Day 21: anytime
PK samples	X	X	X

6.7.10. PPD

PPD

6.7.11. Optional Extended Viral Monitoring

PPD

6.7.12. Optional Registry:

PPD

- PPD

- PPD
  - PPD
- PPD

Clinical data collection for Optional Registry:

PPD

- PPD
- PPD
- PPD
- PPD
- PPD
- PPD

6.7.13. Spirometry

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. Subjects will also be issued a handheld spirometer for self-administered spirometry testing. These handheld spirometry measures will be collected specifically in the presence of study staff at Days 1/Baseline, 3, 5, 7, 9, 14, 21, and 28/End of Study.

The study baseline forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) can be obtained as part of the Screening or Day 1 visit, but must be obtained *prior to IMP administration*.

The Day 28/End of Study spirometry measurements by the certified respiratory therapist 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. However, measures from the handheld spirometer must also be obtained in the presence of study staff on the same day as the site-specific Day 28/End of Study spirometry measurements.

In addition to the study-specific measures described above, all spirometry and other measurements of pulmonary function obtained at unplanned study times, as part of standard clinical care during the study period, will be collected. The highest baseline value spirometry tests ascertained after lung transplant (before enrollment into this trail), as well as spirometry values measured within a 3 month period prior to the current active RSV infection will also be collected.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

To minimize the possibility of exposing study subjects to unusual risk, the safety information from the study will also be reviewed by an independent DMC on an ongoing basis. The DMC may have access to partially blinded or unblinded data and will determine if it is safe to continue the study according to the protocol.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or a designated qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for IMP and Procedures

The investigator or a designated qualified sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities For AEs or SAEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to IMP initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events:

Following initiation of study medication, all AEs, regardless of cause or relationship, through the Day 28/End of Study visit must be reported to the CRF/eCRF database as instructed. All AEs should be followed up until resolution or until the adverse event is stable, if possible.
Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period, as determined by the Medical Monitor.

Serious Adverse Events:

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period (the Day 28/End of Study visit), however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH.

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All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process:

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically (ie, the eCRF database is not functioning), record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH:	Fax:	+1-650-522-5477
	E-mail:	Safety_fc@gilead.com

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.
- Site personnel should record all SAE data in the eCRF database for those protocol-specific SAEs which are exempted from expedited reporting requirements (Section 7.1.2.1). They should also transmit the SAE information to Gilead DSPH if the SAEs are assessed by the investigator as related to the IMP or study procedure.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant Independent Ethics Committee (IEC) in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the current presatovir (GS-5806) IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology) independent of the underlying medical condition that require medical or surgical intervention or lead to IMP interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE, respectively, as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities Appendix 5. For AEs or SAEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4.

Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post IMP follow-up period, to the Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is provided in Section 7.3.

Pregnancies of female partners of male study subjects exposed to Gilead or other investigational agents must also be reported and relevant information should be submitted Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Refer to Appendix 6 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported in the eCRFs.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the effect of presatovir on nasal RSV viral load in RSV-positive 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 PK, safety, and tolerability of presatovir

8.1.2. Primary Endpoint

The co-primary efficacy endpoints are

- Time-weighted average change in $\log_{10}$ viral load from Day 1/Baseline through Day 7 ($DAVG_7$) as measured in nasal samples by RT-qPCR among subjects in the FAS
- Time-weighted average change in $\log_{10}$ viral load from Day 1/Baseline through Day 7 ($DAVG_7$) in a subset of FAS subjects whose duration of RSV symptoms prior to the first dose of study medication is $\leqslant$ median

The time-weighted average change in nasal RSV viral load from Day 1 through Day 7 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 Day 1 in RSV $\log_{10}$ viral load at the i^{th} Visit , t is the time at the specified timepoint, a is the baseline assessment at Day 1/Baseline and b is the last assessment at or prior to Day 7. The time-weighted average change (DAVG) provides the average viral burden in change from baseline during the time period of interest.

8.1.3. Secondary Endpoint

Secondary endpoints are:

- 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

8.1.4. Exploratory Endpoints

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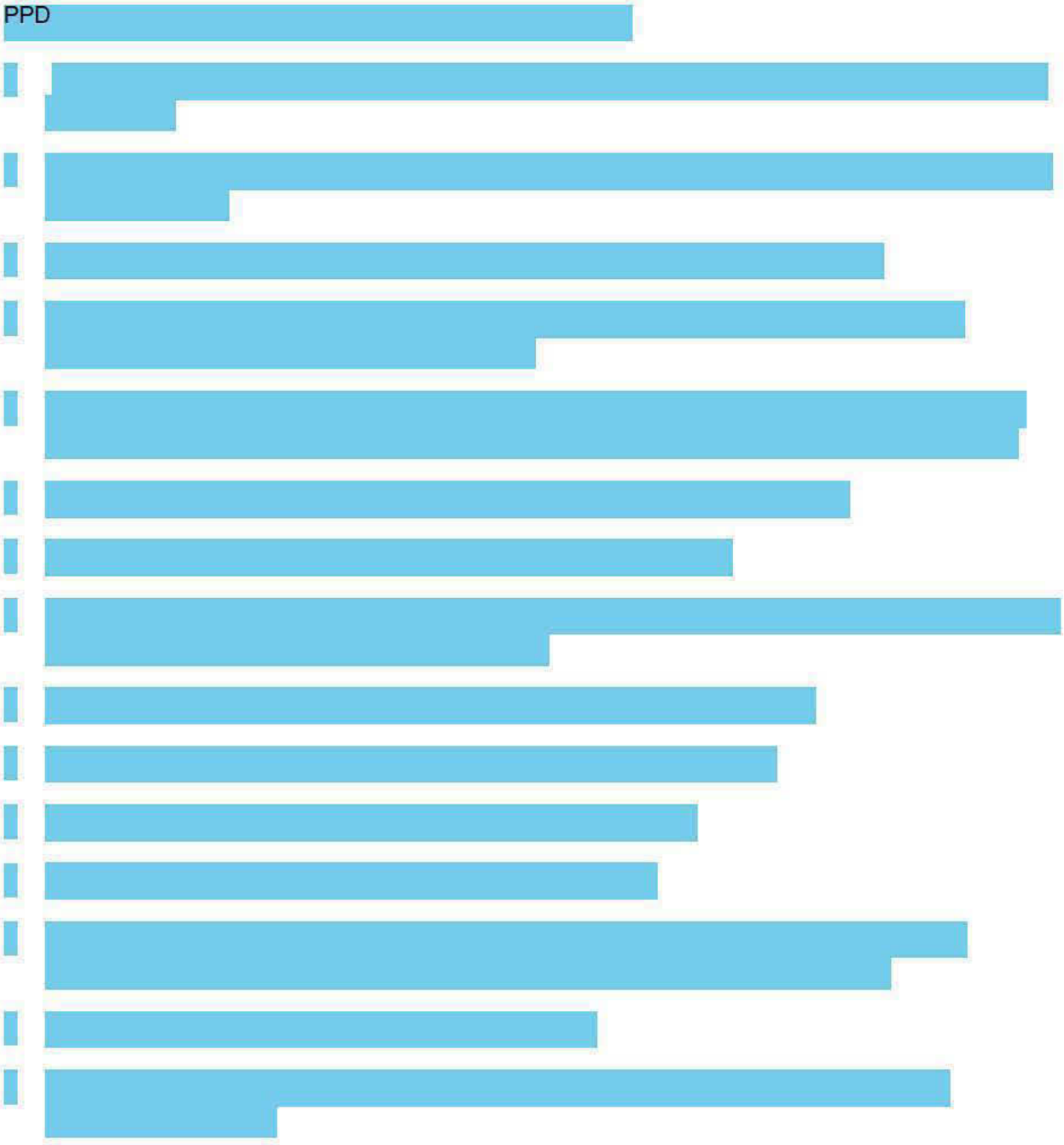
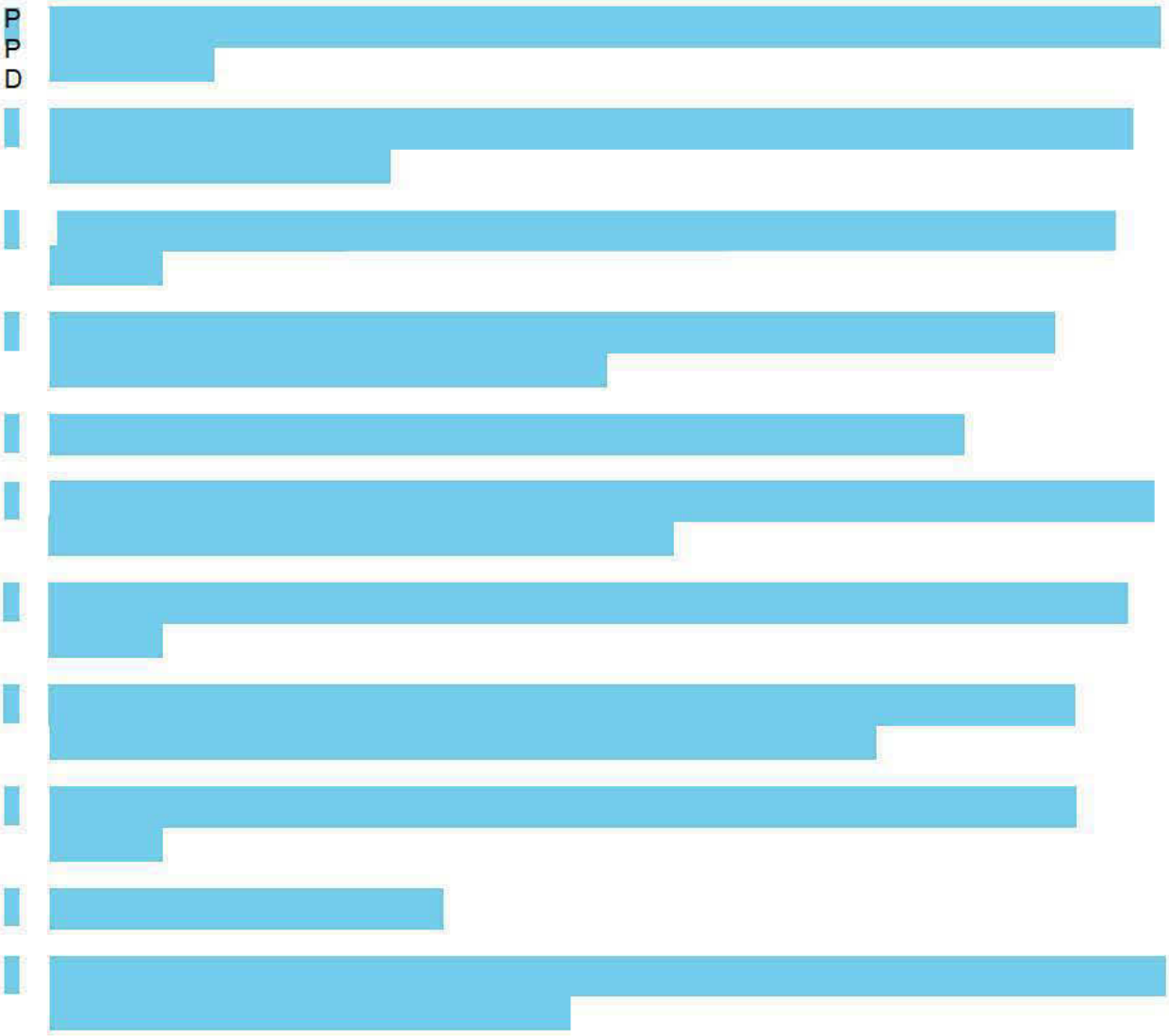


The exploratory endpoints for the optional Registry portion are:

PPD



8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The FAS will include all randomized subjects who take 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 pre-dose Day 1/Baseline nasal sample, as determined by RT-qPCR at the central lab. The subgroup analysis set includes subjects who are in the FAS whose duration of RSV symptoms prior to first dose of study medication is ≤ median. The FAS and the subgroup analysis set will be used as the primary analysis sets for all summaries and analyses of the primary and secondary efficacy endpoints.

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as all subjects who received at least a full dose of IMP.

All data collected during treatment will be included in the safety summaries**.**

8.2.1.3. Pharmacokinetics

The PK Analysis Set will include all subjects in the safety analysis set who have evaluable on-study PK measurements.

8.3. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed. For laboratory data, a missing Baseline value will be replaced with a screening value, if available; otherwise it will be treated as normal (ie, Grade 0; no toxicity grade) for the summary of graded laboratory abnormalities. A retest value may be used if the first test is invalidated.

Values will not be imputed for missing vital sign and other safety data; however, a missing Baseline value will be replaced with a Screening value, if available.

Details for the handling of missing data due to subject discontinuation or other reasons, including unusable and spurious data, and rules for determining major and minor protocol deviations will be described in the SAP.

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

Tables that include both individual subject PK data and summary statistics will present all available data, but only subjects in the PK analysis will be included in the summary statistics.

Viral load data will be log transformed prior to analyses.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be listed by subject and summarized by treatment using standard descriptive summaries or categorical summaries, as appropriate.

Demographic summaries will include but not be limited to sex, race/ethnicity and age. Baseline data will include a summary of body weight, height, BMI, and other baseline characteristics.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is the time-weighted average change in nasal RSV viral load (log_{10} copies/mL) from Day 1/Baseline through Day 7. The primary analysis will be performed on subjects included in the FAS and subjects included in the FAS with ≤ median duration of symptoms prior to the first dose of study medication. To test these two co-primary null hypotheses of no difference between the presatovir and placebo treatment groups in the time-weighted average change in RSV viral load in the FAS and in the subgroup, parametric analysis of covariance (ANCOVA) models with corresponding baseline RSV viral load as a continuous variable and stratification factors included as covariates will be used. Adjusted means and 95% CIs will be provided. If stratification leads to small cell sizes, a modification to the stratification, which will be described in the SAP, will be implemented.

The co-primary analyses will be controlled at an overall type I error rate at the 2-sided 0.05 level in which 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 first dose of study medication ≤ median) will be 0.017, as determined by a grid search accounting for the known correlation of the populations.

8.5.2. Secondary Analyses

The FAS analysis set will be used for all summaries and analyses of secondary endpoints. All secondary endpoints will be analyzed using 2-sided tests to compare treatment differences.

The time-weighted average change in FLU-PRO score from Day 1/Baseline through Day 7 will be analyzed using an ANCOVA model with the baseline FLU-PRO score value and stratification factors as covariates. Adjusted means and a 95% CI will be provided.

The percent change in FEV_1% predicted values from Day 1/Baseline through Day 28/End of Study will be analyzed using an ANCOVA model with study baseline FEV_1% predicted value and stratification factors as covariates. The percent change in FEV_1% predicted values will be calculated as the difference of FEV_1% predicted values at study baseline and Day 28/End of Study, divided by study baseline FEV_1% predicted value and multiplied by 100.

In order to account for multiple hypothesis testing across the primary and secondary endpoints, a family alpha spending rule will be used to control the Type 1 error rate of 0.05. The co-primary endpoint analyses will serve as the gatekeeper for the secondary analyses conducted within each population. If the co-primary null hypothesis is rejected, then the following secondary endpoints will be tested sequentially at the specified alpha-level within each population (ie, $\alpha = 0.04$ and/or $\alpha = 0.017$), respectively, based upon the closed testing procedure {11631}.

- 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

8.5.3. Exploratory Analyses

Main Study portion (Day 1/Baseline through Day 28/End of Study)

PPD

Optional Registry

PPD

8.6. Safety Analysis

All safety data will be listed. Data for the pretreatment and treatment-free follow-up periods will be included in data listings only. Data for the treatment period will be summarized by treatment (active or placebo) using the number of subjects (n and percent) with events/abnormalities for categorical data and using descriptive statistics (n, mean, SD, median, and range) for continuous data.

8.7. Extent of Exposure

A subject's extent of exposure to IMP data will be generated from the IMP administration data. Exposure data will be summarized by treatment group.

8.7.1. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of IMP up to Day 28, or any AEs leading to premature discontinuation of IMP.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by treatment group.

AEs will also be summarized by relationship to treatment (IMP) and severity.

A listing of AEs will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for an SAE.

8.7.2. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from Baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 5. Grading of laboratory abnormalities for analysis purposes will be performed by GSI.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including Day 28/End of Study will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of IMP or after the subject has been discontinued from treatment for at least 28 days will be included in a data listing.

8.7.3. Other Safety Evaluations

Vital signs and ECG data will be summarized by the observed data and by the change from baseline at each time point. In comparison to pre-treatment (either screening or pre-dose on study Day 1) values, vital signs, and ECG measurements will additionally be summarized using pre-determined clinically relevant thresholds.

8.8. Pharmacokinetic Analysis

Concentrations of presatovir will be determined in plasma using a validated Bioanalytical assay. Individual subject presatovir concentration-time data will be displayed using scheduled sampling times. Descriptive statistics (eg, n, mean, standard deviation, %CV, median, and range) will be calculated for each sampling time. The pharmacokinetic/pharmacodynamic (PK/PD) relationship may be explored as appropriate.

8.9. Sample Size

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. PPD)

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 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 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 symptoms prior to first dose of study medication 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.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of accumulated safety data as specified in the DMC charter, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.11. Endpoint Adjudication Committee

Based on enrollment and data collection into the study registry, an Endpoint Adjudication Committee may be formed to review relevant clinical data in order to confirm episodes of CLAD (BOS), and acute rejection. Details will be provided in the Adjudication Committee Charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, and 21 CFR, part 56.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC, depending on region. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

The investigator must use the most current IRB or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a manner as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the presatovir (GS-5806) IB, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that

the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Data Quality Control and Quality Assurance

To insure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Instruct the investigators and study personnel on the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site.
- Be available to consultation and stay in contact with the study site personnel by mail, email, telephone, and/or fax.
- Monitor the subject data recorded in the CRFs against source documents at the study site.
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.

9.1.8. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be destroyed on site if possible. The study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If IMP cannot be destroyed on site, the study monitor will provide instructions for return to Gilead or the shipping facility from which it came for eventual destruction.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.9. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/IECs, or to regulatory authority or health authority inspectors.

9.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2b, Randomized, Controlled Trial Evaluating GS-5806 in Lung Transplant (LT) Recipients with Respiratory Syncytial Virus (RSV) Infection

GS-US-218-1797, Protocol Amendment 1, 2 December 2015

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Timothy R. Watkins

Name (Printed)
Timothy R. Watkins, MD, MSc

PPD

03-December-2015

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Study Procedures Table

	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						
O_2 requirement assessment		X	X	X	X	X	X	X	X	X				
Urine or Serum Pregnancy Test[d]	X	X			X		X							
Screening Labs [c]	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)
Safety Labs[f]		X			X		X	X	X	X	PPD			
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	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				
Collection of Clinical Data for Cardiac-Related tests		X	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)
Spirometry, BAL, Pathology, Microbiology, & Radiology Data Collection[n]									X		PPD			
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, 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 women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy. Must be done at Screening or Day 1/Baseline prior to Randomization and prior to IMP administration on Days 7 and 14

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 baseline FEV_1 can be obtained as part of the Screening or Day 1/Baseline visit, but must be taken *prior to IMP administration*. 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 collected specifically in the presence of study staff at Days 1/Baseline, 3, 5, 7, 9, 14, 21, and 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

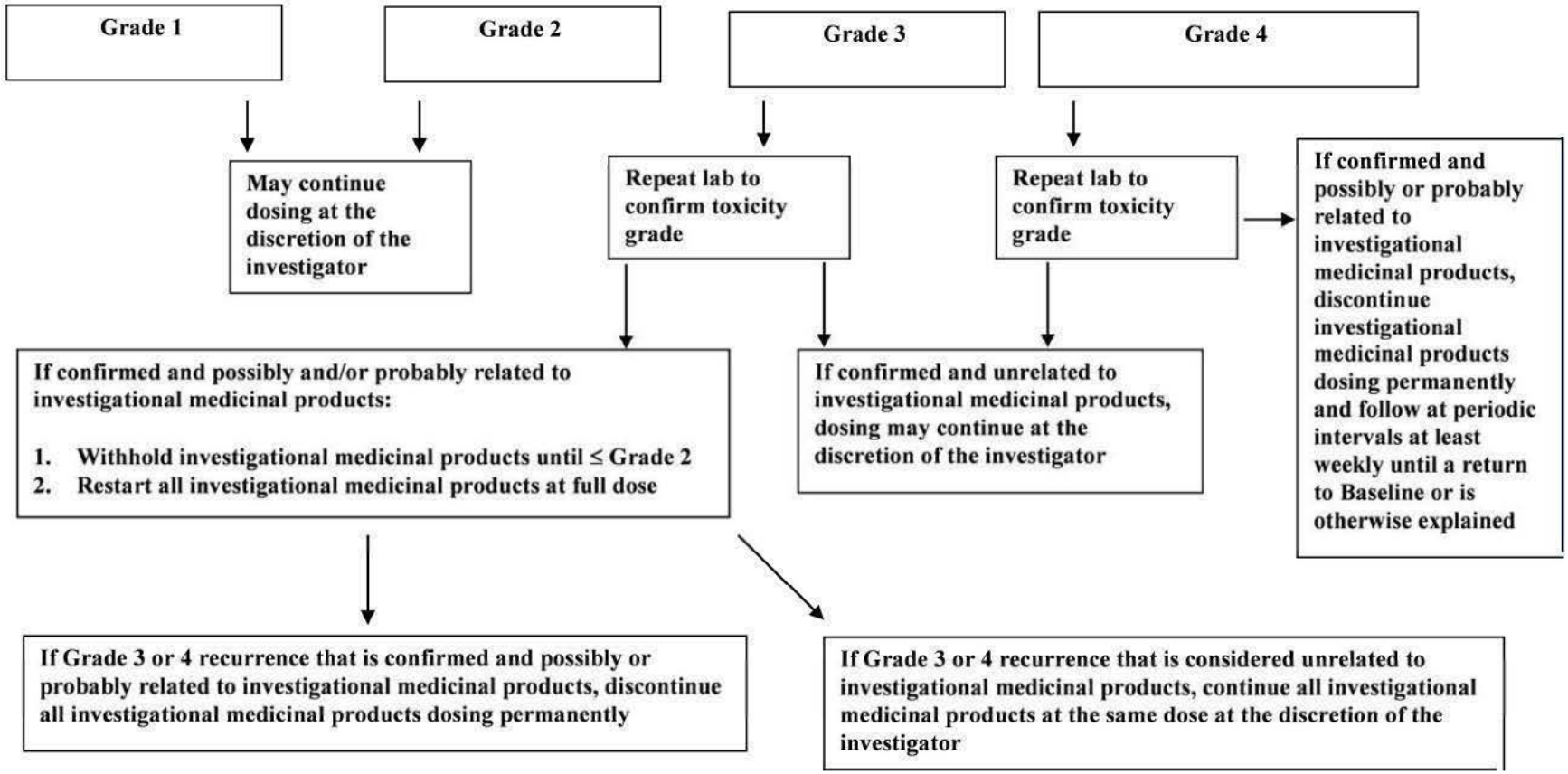
n All the following standard-of-care results available from Screening/Baseline through Day 28/End of Study will be collected by Day 28/End of Study for all subjects: spirometry data, BALF (a 5 mL aliquot of the BAL fluid (BALF) sample from any lobe is requested for this study. This specimen will be stored 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 draw 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.


PPD

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 0.49 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
≥ 16 years	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years**	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. A urine or serum pregnancy test will be performed for all females of childbearing potential at Screening and on Days 7 and 14 prior to Randomization to ensure pregnant women are not included or treated with study drug in the trial. Please refer to the latest version of the IB for additional information about the effects of presatovir.

2) Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a pubertal female who has not yet started menstruating. A woman who has had a tubal sterilization is considered to be of childbearing potential.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (ie, surgical removal of the ovaries and occurring at the age at which the procedure was performed)

- Spontaneous menopause: Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified health care provider. The worldwide mean age of spontaneous menopause is 49.24 (SD 1.73) years

- A hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:

  — If age ≥ 54 years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the postmenopausal range based on the laboratory reference range where the hormonal assay is performed

  — If age < 54 years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the postmenopausal range, depressed estradiol (E2) level in the postmenopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed

3) Contraceptive Requirements

Female subjects of childbearing potential and male subjects must agree to either continue abstinence from sexual intercourse or utilize protocol specified methods of contraception if they choose to engage in intercourse from the screening/enrollment visit throughout the study period and for 30 days following the last dose of study drug (90 days for males). Female study subjects of childbearing potential will undergo regular pregnancy testing while taking presatovir. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

Abstinence is an acceptable method only when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of a trial, and withdrawal (coitus interruptus) are not acceptable methods of contraception.

Protocol specified contraceptive methods are as follows: (1) a combination of one hormonal method and one barrier method; or (2) use of an intrauterine device (IUD) or tubal sterilization; see Appendix Table 1 below. Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm with spermicide, cervical cap with spermicide, and the male condom with spermicide. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy and the male partner should be the sole partner for that subject. For a vasectomy, appropriate post-vasectomy documentation of the absence of sperm in the ejaculate must be available. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

Female subjects of childbearing potential must have a negative urine or serum pregnancy test Screening or Day 1/Baseline prior to Randomization and on Days 7 and 14 prior to IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

<table>
<tr><th rowspan="2">Methods to Use by Themselves</th><th colspan="2">Combination Methods</th></tr>
<tr><th>Hormone Methods
(choose one and use with a barrier method)</th><th>Barrier Methods
(choose one and use with a hormone method)</th></tr>
<tr><td rowspan="2">Intrauterine Devices (IUDs)
• Copper T 380A IUD
• LNg 20 IUD

Tubal Sterilization</td><td>Estrogen and Progesterone
• Oral contraceptives
• Transdermal patch
• Vaginal ring

Progesterone
• Injection
• Implant</td><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Male condom (with spermicide)</td></tr>
<tr><td colspan="2">Partner’s vasectomy must be used with a hormone or barrier method and the male partner should be the sole partner for that subject. For a vasectomy, appropriate post-vasectomy documentation of the absence of sperm in the ejaculate must be available.</td></tr>
</table>

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

4) Additional Requirements for Male Subjects

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 90 days after administration of the last dose of study medication.

Use of condoms has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject’s partner is infected with HIV.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.