GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multi-Center Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in Hematopoietic Cell Transplant (HCT) Recipients with Respiratory Syncytial Virus (RSV) Infection of the Upper Respiratory Tract	
Sponsor:	Gilead Sciences, Inc. 199 E Blaine St Seattle, WA 98102	
IND Number:	114498	
EudraCT Number:	2014-002474-36	
Clinical Trials.gov Identifier:	NCT02254408	
Indication:	Respiratory Syncytial Virus (RSV)	
Protocol ID:	GS-US-218-0108	
Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile:	Timothy R. Watkins, MD, MSc PPD PPD PPD
Protocol Version/Date:	Original Amendment 1 Amendment 2 Amendment 3 Amendment 4 Amendment 5 Amendment 6	13 May 2014 31 July 2014 22 September 2014 21 October 2014 04 February 2015 30 June 2015 20 November 2015

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
199 E Blaine St
Seattle, WA 98102

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IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	114498 2014-002474-36 NCT02254408
Study Centers Planned:	Approximately 60 centers in Asia Pacific, Australia, Canada, Europe, South America, and the United States
Objectives:	The primary objective of this study is as follows: • To evaluate the effect of presatovir (GS-5806) on RSV viral load in RSV-positive autologous or allogeneic HCT recipients with acute upper respiratory tract infection (URTI) symptoms The secondary objectives of this study are as follows: • To evaluate the effect of presatovir on development of lower respiratory tract complication (LRTC), progression to respiratory failure, and all-cause mortality • 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 HCT recipients with RSV URTI. All subjects will be permitted to receive the standard of care therapy for RSV infection per their local medical practices, in addition to the investigational medicinal product (IMP). Subjects will be randomized in a 1:1 ratio to receive IMP (presatovir or placebo) and will be stratified by 2 factors: 1) Presence or absence of lymphopenia, defined as a lymphocyte count < 200 cells/μL versus ≥ 200 cells/μL of blood 2) Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)

Number of Subjects Planned:	Approximately 200 RSV-positive subjects
Target Population:	Males and females 18 to 75 years of age who have had an allogeneic or autologous HCT and have documented acute RSV-related URTI symptoms
Duration of Treatment:	5 doses over 17 days
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Section 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 to 75 years of age
2) Received an autologous or allogeneic HCT using any conditioning regimen
3) Documented to be RSV-positive as determined by local testing (eg, polymerase chain reaction [PCR], direct fluorescence antibody [DFA], respiratory viral panel (RVP) assay, or culture) using an upper respiratory tract sample collected ≤ 6 days prior to Day 1
4) New onset of at least 1 of the following respiratory symptoms for ≤ 7 days prior to Day 1: nasal congestion, runny nose, cough, or sore throat, or worsening of one of these chronic (associated with a previously existing diagnosis, eg, chronic rhinorrhea, seasonal allergies, chronic lung disease) respiratory symptoms ≤ 7 days prior to Day 1
5) No evidence of new abnormalities consistent with LRTI on a chest X-ray relative to the most recent chest X-ray, as determined by the local radiologist. If a chest X-ray is not available or was not obtained during standard care < 48 hours prior to Screening, a chest X-ray must be obtained for Screening
6) Oxygen saturation ≥ 92% on room air
7) An informed consent document signed and dated by the subject or a legal guardian of the subject and the investigator or his/her designee
8) A negative urine or serum pregnancy test is required for female subjects (unless surgically sterile or greater than two years post-menopausal)

9) Male and female subjects of childbearing potential must agree to contraceptive requirements as described in Appendix 5
10) Willingness to complete necessary study procedures and have available a working telephone or email

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 non-marketed (according to region) 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 investigational RSV vaccines after HCT
2) Use of a moderate or strong 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 medical history:

3) Admitted to the hospital primarily for a lower respiratory tract disease of any cause as determined by the investigator
4) Pregnant, breastfeeding, or lactating females
5) Unable to tolerate nasal sampling required for this study, as determined by the investigator
6) Known history of HIV/AIDS with a CD4 count <200 cells/μL within the last month
7) History of drug and/or alcohol abuse that, in the opinion of the investigator, may prevent adherence to study activities

Related to medical condition at Screening:

8) Documented to be positive for other respiratory viruses (limited to influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus, or coronavirus) within 7 days prior to the Screening visit, as determined by local testing (additional testing is not required)
9) Clinically significant bacteremia or fungemia within 7 days prior to Screening that has not been adequately treated, as determined by the investigator

10) Clinically significant bacterial, fungal, or viral pneumonia within 2 weeks prior to Screening that has not been adequately treated, as determined by the investigator

11) Excessive nausea/vomiting at Screening, as determined by the investigator, or an inability to swallow pills that precludes oral administration of the IMP (for subjects without an NG tube in place)

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

Related to allergies:

13) 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)

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

Related to laboratory results:

15) Creatinine clearance < 30 mL/min (calculated using the Cockcroft-Gault method)

16) Clinically significant ALT/AST, as determined by the investigator

17) Clinically significant total bilirubin (TB), as determined by the investigator

Study Procedures/ Frequency:

For a complete overview of study procedures and visits, please refer to Section 6 and Appendix 2.

Study Procedures

Questionnaire: The FLU-PRO questionnaire will be completed by the subject at Visits 2, 4, and 6.

Vital signs (VS): Vital signs will be measured at all study visits, with the exception of Visits 3 and 5 if conducted as home visits, PPD

O_2 saturation: O_2 saturation will be recorded at all study visits, with the exception of Visits 3 and 5 if conducted as home visits, PPD while breathing room air. If the subject is dependent on supplemental O_2, it should be removed for testing, if possible. Subjects requiring invasive mechanical ventilation will not have O_2 saturation measured while ventilated. Refer to Section 6.11.5 for procedure instructions.

Supplemental O_2: The need for supplemental O_2 and the mode of delivery will be assessed at all study visits through Day 28 conducted at the hospital or in clinic.

Laboratory tests: When available, existing laboratory values ≤ 6 days prior to Screening (Visit 1) may be used for eligibility assessment. Study staff will perform urine or serum pregnancy tests on site at Screening and at each dosing visit (Visits 2, 4, 6, 7, and 8) prior to administration of IMP (as necessary). Blood specimens for safety (Visits 2, 4, 6, 7, 8, 9, and 10) and RSV viremia evaluation (using quantitative real time polymerase chain reaction [RT-qPCR] - Visits 2, 4, 6, 7, 8, 9 and 10) will be collected prior to dosing and for serum antibody titers to RSV at Visits 2 and 10 (Days 1 and 28). Blood specimens for serum creatinine will be collected 2 hours post-dose at Visits 2 and 6 (Days 1 and 9) from subjects participating in the PK subgroup only. Blood will also be drawn to monitor troponin levels at the site's local laboratory pre-dose at Visits 2, 8, and 10.

PK blood draws: Pharmacokinetic (PK) samples will be collected from all subjects (excluding subjects in the PK subgroup) at the following time points: pre-dose at Visit 4 (Day 5), pre-dose and 2 hours post-dose at Visit 6 (Day 9), and anytime at Visit 9 (Day 22).

Subjects will have the option of participating in the PK subgroup, until 30 subjects have enrolled into the subgroup. PK samples will be collected in the PK subgroup at the following time points: 1, 2, 4, and 6 hours post-dose at Visit 2 (Day 1), anytime at Visit 3 (Day 3), pre-dose at Visit 4 (Day 5), pre-dose and 2 hours post-dose at Visit 6 (Day 9), and anytime at Visit 9 (Day 22).

Nasal sampling: Nasal sampling will be performed at all study visits (both scheduled and unscheduled, PPD with the exception of Screening (Visit 1), and stored and shipped to a central laboratory for testing according to specifications in the study procedures manual. All samples must be collected prior to dosing. Two nasal samples will be obtained, 1 from each nostril, each time nasal sampling is performed. At any time during the study, if a bronchoscopy is planned for the same day as nasal sampling, nasal samples should be obtained, if possible, prior to application of any topical anesthetic (eg, lidocaine) in the nostrils.

Nasal samples will be used for RSV sequencing to evaluate development of resistance and a multiplex assay to identify co-infections.

RSV testing: All subjects must be documented to be RSV-positive as determined by local testing (eg, PCR, DFA, RVP assay, or culture) prior to Screening using an upper respiratory tract sample collected ≤ 6 days prior to Day 1. 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.

Electrocardiogram (ECG): A baseline ECG will be performed at Visit 2, prior to dosing. ECGs will also be obtained pre-dose at Visit 8, and anytime at Visit 10. ECG results should be verified before the subject leaves the clinical site in case further medical care is advised.

Optional Extended Viral Monitoring: PPD

Study Visits

Visit 1: Screening (Day -1)

This visit must be performed in the clinic or in hospital. Potential subjects must be documented RSV positive in the upper respiratory tract prior to being approached for informed consent. The following Screening procedures/labs are required:

- Obtain written informed consent
- Collection of medical history and demographics
- Review of concomitant medications
- Vital Signs, including O_2 saturation
- Height and weight
- Blood draw for Screening labs for local laboratory analyses, unless existing laboratory values collected ≤ 6 days prior to Screening can be obtained for review
- Chest X-ray (chest X-rays obtained < 48 hours prior to Screening may be used)
- Urine or serum pregnancy test in women unable to confirm menopause, hysterectomy, and/or bilateral oophorectomy
- Review of any adverse events (AEs) occurring after signing of the consent form

Visit 2: Baseline Assessments, Randomization, and IMP Administration (Day 1)

If the subject meets all eligibility criteria, Visit 1 and Visit 2 may occur on the same day. The IMP must be administered under supervision by the study staff. Visit 2 should occur in clinic or in hospital. Visit 2 assessments should be performed in the following order:

- FLU-PRO questionnaire (must be performed prior to all other assessments)
- Vital Signs, including O_2 saturation
- Weight
- Pre-dose blood draw (for safety labs, serum antibody titer to RSV, RSV viremia, and local troponin testing)
- Obtain 2 nasal samples
- Urine or serum pregnancy test in women unable to confirm menopause, hysterectomy, and/or bilateral oophorectomy

- 12-lead Pre-dose ECG
- Randomization via IXRS
- Investigational medicinal product administration
- Pharmacokinetic blood draw (PK subgroup only): 1 (±15 min), 2 (±15 min), 4 (±30 min), and 6 hours (±30 min) post-dose
- Blood draw for serum creatinine (PK subgroup only): 2 hours post-dose (±15 min)
- Assessment of AEs, concomitant medications, hospitalizations, intensive care unit (ICU) admissions or utilization of ICU care for > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for > 24 hours)

Visit 3: Day 3 (± 24 hours)

For subjects in the PK subgroup, this visit must be performed in clinic or in hospital. For all other subjects, this visit may be performed in clinic, in hospital, or at home by the study coordinator or designee, or a home nursing vendor.

- Pharmacokinetic blood draw (PK subgroup only)
- Obtain 2 nasal samples
- Vital Signs, including O_2 saturation (unless conducted as a home visit)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care for > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for > 24 hours). Review of procedure-related AEs only, if home visit.

Visits 4: Days 5 (± 24 hours)

This visit must be performed in clinic or in hospital. Visit 4 assessments should be performed in the following order:

- FLU-PRO questionnaire (must be performed prior to all other assessments)
- Vital signs, including O_2 saturation
- Weight

- Pharmacokinetic blood draw (for all subjects): pre-dose
- Pre-dose blood draw (for safety labs and RSV viremia)
- Obtain 2 nasal samples
- Urine or serum pregnancy test in women unable to confirm menopause, hysterectomy, and/or bilateral oophorectomy
- Investigational medicinal product administration
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, admission to intensive care unit (ICU) or utilization of ICU care for > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for > 24 hours)

Visit 5: Day 7 (± 24 hours)

This visit may be performed in clinic, in hospital, or at home by the study coordinator or designee, or a home nursing vendor.

- Obtain 2 nasal samples
- Vital Signs, including O_2 saturation (unless conducted as a home visit)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care for > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for > 24 hours). Review of procedure-related AEs only, if home visit.

Visits 6 – 8: Days 9, 13, and 17 (± 24 hours)

These visits must be performed in clinic or in hospital. Visit 6-8 assessments should be performed in the following order:

- FLU-PRO questionnaire (Day 9 only, must be performed prior to all other assessments)
- Vital signs, including O_2 saturation
- Weight
- Pharmacokinetic blood draw (for all subjects): pre-dose and 2 hours post-dose (±15 min) (Day 9 only)

- Pre-dose blood draw (for safety labs and RSV viremia at all visits, and local troponin testing on Day 17 only)
- Obtain 2 nasal samples
- 12-lead Pre-dose ECG (Day 17 only)
- Urine or serum pregnancy test in women unable to confirm menopause, hysterectomy, and/or bilateral oophorectomy
- Investigational medicinal product administration
- Blood draw for serum creatinine (PK subgroup only): 2 hours post-dose (±15 min) (Day 9 only)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care for > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for > 24 hours)

Visits 9 and 10: Day 22 (± 24 hours) and End of Study/Day 28 (+ 3 days)

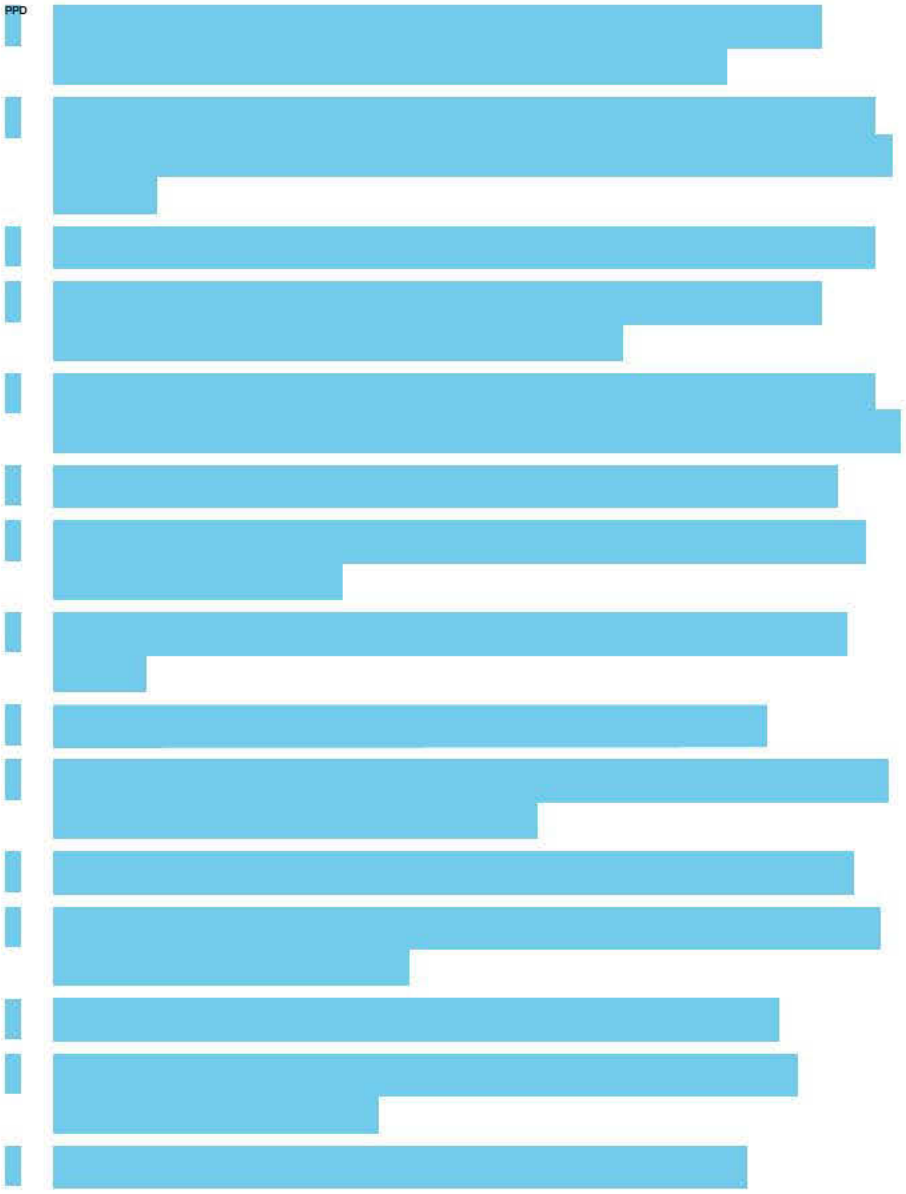
These visits must be performed in clinic or in hospital. Visit 10 may occur no earlier than Day 28 and no later than Day 31. Visit 9 and 10 assessments should be performed in the following order:

- Vital signs, including O_2 saturation
- Weight
- Pharmacokinetic blood draw (for all subjects, Day 22 only)
- Blood draw for safety labs (Days 22 and 28), for serum antibody titer to RSV (Day 28 only), RSV viremia (Days 22 and 28), and local troponin testing (Day 28 only)
- Obtain 2 nasal samples
- Obtain sample for local RSV testing* (Day 22 only) (refer to Section 6.11.11)
- 12-lead ECG (Day 28 only)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care for > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for > 24 hours)

	PPD **Visits 11 - 14*: Days 35, 42, 49 and 56 (±48 hours)** Visit 11 - 14 assessments may be performed in clinic, in hospital, or at the subject's home by the study coordinator or designee, or a home nursing vendor. • Obtain 2 nasal samples • Assessment of procedure-related AEs PPD
Test Product, Dose, and Mode of Administration:	200mg presatovir (GS-5806) (four 50 mg tablets) administered orally or via nasogastric (NG) tube on Study Days 1, 5, 9, 13, and 17 The entire dose must be taken within 1 hour. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should receive a second dose.
Reference Therapy, Dose, and Mode of Administration:	Placebo to Match tablets administered orally or via NG tube. Administration is the same as for presatovir.
Criteria for Evaluation:	
Safety:	Safety will be assessed by the reporting of AEs and serious adverse events (SAEs) throughout the study, clinical laboratory tests, ECGs and VS at various time points during the study.
Efficacy:	The primary endpoint is the time-weighted average change in RSV nasal viral load (log_{10} copies/ml) from Baseline (Day 1) to Day 9 as measured by RT-qPCR. The key secondary endpoints are: • Proportion of subjects who develop a LRTC through Day 28, defined as one of the below, as determined by the adjudication committee: — Primary RSV lower respiratory tract infection (LRTI) — Secondary bacterial LRTI — Lower respiratory tract infection due to unusual pathogens — Lower respiratory tract infection, noninfectious or of unknown etiology

- Proportion of subjects who develop respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) through Day 28
- Proportion of all-cause mortality through Day 28

The exploratory endpoints are:



Pharmacokinetics: Presatovir concentrations in plasma will be summarized by time point for all subjects.

The plasma PK parameters of presatovir (eg, C_{max} and AUC) will be calculated for all subjects in the PK subgroup (as appropriate).

Statistical Methods:

The full analysis set (FAS) will include subjects who have an RSV $\log_{10}$ viral load greater than or equal to the lower limit of quantification (LLOQ) of the RT-qPCR assay in the pre-dose Day 1 nasal sample, as determined by RT-qPCR at the central lab, and have received at least 1 full dose of IMP. The evaluable subjects for the primary endpoint will include those in the FAS with evaluable nasal samples for RSV viral load by Day 9 (including Baseline).

The primary efficacy analysis of time-weighted average change in RSV $\log_{10}$ viral load from Day 1 through Day 9 will be performed on subjects included in the efficacy evaluable analysis set. To test the null hypothesis that there is no difference between the presatovir and placebo treatment groups in the time-weighted average change in RSV viral load, a parametric analysis of covariance (ANCOVA) model with corresponding baseline RSV viral load and randomization stratification factors as covariates will be used, with a 2-sided 0.05 alpha level. Adjusted means and 95% confidence intervals (CIs) will also be presented.

The FAS analysis set will be used for all summaries and analyses of secondary endpoints. All secondary and other endpoints will be analyzed using 2-sided tests for treatment differences. The proportion of subjects who develop LRTC, the proportion of subjects who develop respiratory failure requiring mechanical ventilation, and the proportion of all-cause mortality among all subjects through Day 28 will be analyzed using Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. Analyses of exploratory endpoints are discussed in Section 8.5.3.

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.

Safety analyses will be performed on all subjects who received IMP. Safety data will be collected and summarized from Screening through Day 28. 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.

Concentrations of presatovir in plasma will be determined using a validated bioanalytical assay(s). 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. For subjects in the PK subgroup, plasma concentrations of presatovir over time will be plotted in semi-logarithmic and linear formats as mean $\pm$ SD, and plasma concentration-time data for each subject will be analyzed using standard non-compartmental methods. Pharmacokinetic/pharmacodynamic (PK/PD) relationship may be explored as appropriate.

Sample size calculations are based on results observed in a study that evaluated the efficacy of oral and aerosolized ribavirin treatment for preventing progression from upper to lower respiratory tract infection in HCT recipients with RSV infections (unpublished data from Dr. PPD). The sample size calculation assumes the time-weighted average change in RSV $\log_{10}$ viral load from Day 1 to Day 9 in the placebo group will be -1 $\log_{10}$ copies/mL with a corresponding standard deviation (SD) of 2 and that 85% of the subjects will be evaluable. Based on these assumptions, with 85 evaluable subjects per group there is over 85% power to detect a 1 log difference in time-weighted average change in $\log_{10}$ viral load between treatment groups using a 2-sided 0.05-level test. Given an evaluable rate of 85%, a total of 200 subjects will need to be randomized into the study.

All safety data will be monitored by a Data Monitoring Committee (DMC). An Adjudication Committee will review relevant clinical data to determine whether a LRTC has developed.

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
AE	adverse event
AhR	aryl hydrocarbon
AIDS	auto-immune deficiency syndrome
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
BCRP	breast cancer resistance protein
BID	twice a day
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CCM	cell culture medium
CI	confidence interval
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report
CT	computerized tomography
CYPxx	cytochrome P450 enzyme xx
DAVG	time-weighted average change
DDI	drug-drug interactions
DFA	direct fluorescence antibody
DMC	Data Monitoring Committee
DSPH	Drug Safety and Public Health
EC	ethics committee
EC_{50}	concentration of drug to reach 50% inhibition of virus replication
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
ELF	epithelial lining fluid
EMR	electronic medical records

EudraCT	European clinical trials database
FAS	full analysis set
FIH	first in human
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (Guidelines)
GD	gestational day
GI	gastrointestinal
GLP	good laboratory practice
GSI	Gilead Sciences, Inc.
hr	hour
HCT	hematopoietic cell transplant
HDPE	high-density polyethylene
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HLGT	high level group term
HLT	high level term
HSP	hysterosalpingogram
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
IXRS	interactive voice/web response system
kg	kilogram
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	lower level term
LRTC	lower respiratory tract complication
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters mercury
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
PD	pharmacodynamic
PFUe	plaque forming unite equivalents
Pgp	P glycoprotein
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
PXR	pregnane x receptor
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
RNA	ribonucleic acid
ROW	rest of world
RSV	respiratory syncytial virus
RT-qPCR	quantitative real time polymerase chain reaction
RVP	respiratory viral panel
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	total bilirubin
TBD	to be determined
TEM	treatment emergent mutation
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
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.

Respiratory syncytial virus infection is the most common cause of admissions to pediatric general inpatient units in the United States (US) and Western Europe {20222}. Unfortunately, the rate of hospitalization among RSV-infected children has remained unchanged in the US over the last decade. From 1997 to 2006, RSV-coded hospitalizations accounted for 24% of an estimated 5.5 million lower respiratory tract infection (LRTI) hospitalizations among children < 5 years of age. During this period, it was estimated that approximately 172,000 hospitalizations each year were caused by RSV infection among children < 5 years of age; approximately 73% of these hospitalizations occur among children < 12 months of age {20227}.

RSV infection is also a cause of respiratory disease in the adult population. Adult recipients of autologous or allogeneic hematopoietic cell transplants (HCT) are at high risk for RSV infection related morbidity and mortality. Based upon retrospective epidemiologic data, 2-17% of HCT recipients will develop RSV infection of the respiratory tract {28652}, {26908}, {28657}, {28645}, {28650}, {28653}, {20233}. Progression from upper respiratory tract infection (URTI) to LRTI may occur in 17-84% of these RSV-infected patients {28641}, {26937}, {28657}, {28650}, {28653}, {20233}, {28646}, {28724}, {28654}, {28648}. Once RSV progresses from URTI to LRTI, the morbidity and mortality is high. Progression to LRTI often requires hospitalization and at times, intensive care unit admission for supportive care (eg oxygenation, mechanical ventilation, intravenous fluids, vasopressors). Lower respiratory tract infection is associated with high mortality rates, ranging from 6.5-26.7% {28647}, {28646}, {28656}, {28641}, {28725}, {28643}, {28644}, {28652}, {28650}. A long term sequelae seen among survivors of RSV LRTI is airflow decline documented at 1 year after the initial infection {28643}.

Currently, there are no effective vaccines or approved prophylactic treatment options for RSV infection in the HCT population. Once hospitalized, treatment for RSV infection in HCT patients is supportive, with intravenous hydration, supplemental oxygen, and mechanical ventilation. Although treatment options such as antiviral agents, corticosteroids, and immunoglobulin are frequently used, there is no definitive treatment for RSV infection in the HCT 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 HCT population. A recent retrospective analysis suggests that palivizumab is not effective for treatment of RSV LRTI in

the HCT population {28654}. Virazole® (ribavirin), an inhaled antiviral agent, is approved for treatment of RSV infection in the pediatric population but is not used in general pediatric practice because of concerns regarding its efficacy and tolerability, as well as the complexity of the specialized aerosol delivery system that is required {19902}. A randomized study of inhaled ribavirin has been attempted in the HCT population; however, due to the aforementioned concerns, only 14 subjects were recruited over a 5-year period {28640}. A recent review of published epidemiologic studies suggests that ribavirin-based therapy, oral or aerosolized, had variable success rates for preventing RSV-associated morbidity or mortality in high risk HCT patients {28655}. A single center retrospective analysis also suggested that ribavirin treatment, when administered during the URTI phase, resulted in lower rates of progression to LRTI in treated versus untreated patients (16% versus 45%) and mortality (35% versus 70%) {26937}. Taking into account the limited available efficacy data from controlled clinical trials, the current guidelines for diagnosis and treatment of RSV infection do not provide recommendations regarding whether patients should be treated with any treatments other than supportive care at the LRTI versus URTI phase {28723}. Therefore, variability in standard practices for treatment of RSV infection in HCT patients exists around the world.

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 lung 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. Based on in vitro and nonclinical pharmacokinetic studies, presatovir did not demonstrate a potential for significant drug-drug interactions (DDI).

Additional details regarding nonclinical pharmacokinetics, 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. 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,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 (IC_{50} values of 0.50 and 3.8 μM, respectively) so clinical drug interactions with substrates of these transporters are possible.

Additional details regarding nonclinical pharmacokinetics 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 to100 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 can be found in the presatovir (GS-5806) IB.

1.2.4. Clinical Trials of Presatovir

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 to up to 70 unique 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 300mg and multiple dose regimen of 75mg 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 multiple 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. 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. 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-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 pharmacokinetics of presatovir is not expected to be meaningfully altered in the setting of renal impairment (e.g, mild to moderate).

1.2.4.3. 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.

1.2.4.4. 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-218-1502 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-218-1797 is a Phase 2b, randomized, controlled trial evaluating prestovir in lung transplant recipients with RSV infection. The study will enroll approximately 60 RSV-positive subjects between 18 and 75 years of age who have had a lung transplant and who have documented RSV infection. Subjects will be randomized in a 2:1 ratio to receive presatovir or placebo. This is an ongoing global study.

Additional details regarding clinical trials of presatovir can be found in the presatovir (GS-5806) IB.

1.3. Rationale for This Study

There is a significant unmet medical need for a safe, convenient, and effective treatment for RSV infection. The only approved antiviral therapy for RSV, ribavirin, is approved for use in pediatric populations only, but is rarely used in clinical practice due to its limited efficacy and concerning safety profile. There is no approved antiviral therapy for RSV infection among HCT recipients, where the current standard of care is supportive.

This study follows a Phase 1 FIH study (GS-US-218-0101) and a Phase 2a RSV challenge study (GS-US-218-0103), which evaluated the safety, tolerability, and PK of single and multiple doses of presatovir in 140 healthy adult volunteers. In Study GS-US-218-0103, presatovir was shown to be efficacious in reducing RSV viral load and clinical symptoms in healthy adult subjects experimentally infected with RSV.

Given these results from healthy adult volunteers studied in a controlled setting, the current study is designed to evaluate the safety, tolerability, PK, and efficacy of presatovir among HCT patients with an RSV related URTI. 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 pediatric and 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 Days 1, 5, 9, 13, and 17. 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 was able to achieve presatovir trough concentrations ~4-5 fold of $paEC_{95}$ (52 ng/mL) for up to 120 hours following dose initiation for the virus used in the challenge study, the M37 strain of RSV.

In selecting the dose for the current study, the goal was to achieve presatovir trough concentrations above 4-fold of $paEC_{95}$ for 95% of of the clinical RSV isolates for the duration of RSV shedding in HCT patients. Longitudinal viral dynamics data from investigators at an academic HCT center also indicate that the majority of HCT patients shed RSV for 15 days, but some may shed for as long as 21 days (unpublished). In addition, recent studies indicate that the mean time to progression of URTI to LRTI is 7 days, with 90% of subjects progressing within 15 days after presenting with a URTI {26937}, {28648}. Therefore, a total of 5 doses of presatovir (200 mg each dose, every 4 days) is expected to provide > 4-fold $paEC_{95}$ coverage for ~95% of 75 wild-type clinical RSV isolates through Day 22, which is expected to result in significant durable antiviral effect.

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:

- To evaluate the effect of presatovir on RSV viral load in RSV-positive autologous or allogeneic HCT recipients with acute URTI symptoms

The secondary objectives of this study are:

- To evaluate the effect of presatovir on development of LRTC, progression to respiratory failure, and all-cause mortality

- To evaluate the PK, safety, and tolerability of presatovir

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- Time-weighted average change in nasal RSV viral load (log_{10} copies/mL) from Baseline (Day 1) to Day 9 as measured by RT-qPCR

The key secondary endpoints of this study are:

- Proportion of subjects who develop a LRTC through Day 28, defined as one of the below, as determined by the adjudication committee:
  - Primary RSV LRTI
  - Secondary bacterial LRTI
  - Lower respiratory tract infection due to unusual pathogens
  - Lower respiratory tract infection, noninfectious or of unknown etiology
- Proportion of subjects developing respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) through Day 28
- Proportion of all-cause mortality through Day 28

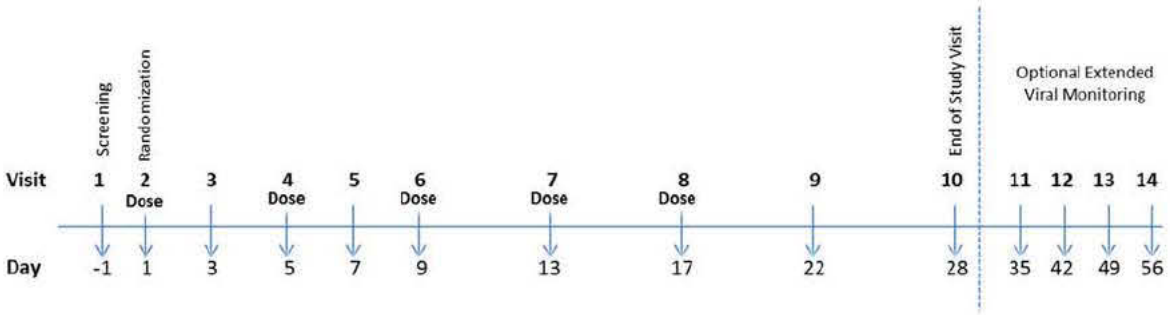
The exploratory endpoints of this study are:

PPD

[redacted]

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 HCT recipients with RSV URTI. This study will enroll approximately 200 subjects from approximately 50 international HCT centers.
RSV positive subjects with URTI symptoms and no evidence of LRTI will be randomized 1:1 to receive presatovir or placebo administered as 200 mg every 4 days for 5 doses. Subjects will be followed for a total of 28 days, during which a total of 10 Study visits will be performed to follow safety, tolerability, PK, and viral loads in nasal samples and the blood. [redacted]



3.3. Study Treatments

Approximately 200 subjects will be randomized 1:1 to receive 200 mg (four 50 mg tablets) of IMP (presatovir or placebo) as a single dose on Days 1, 5, 9, 13, and 17. The IMP will be administered orally or via NG tube. The entire dose must be taken within 1 hour. Investigational medicinal product should be dispensed with gloves.

Subjects will remain in the clinic for 30 minutes post-dose for observation. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should receive another dose. If another dose is administered, the subject should remain in the clinic for an additional 30 minutes post-dose for observation.

Presatovir will be provided as white, plain-faced, film-coated, round tablets containing 50 mg presatovir (61 mg GS-5806-02, bis-hydrochloride salt dihydrate form of presatovir). Placebo to Match will be provided as white, plain-faced, film-coated, round tablets containing no presatovir.

The expected duration of subject participation is approximately 1 month, to include Screening through the final visit on Day 28.

3.4. Duration of Treatment

The treatment portion of the study is 17 days (a total of 5 doses administered as single doses on Days 1, 5, 9, 13, and 17).

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, AST > 5 × ULN and rising
- ALT, AST remains > 5 × ULN with no change in TB for more than 2 weeks
- A 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; and
  - — Evidence of dysfunction: elevation of the TB by > 2 × ULN without an elevation of the alkaline phosphatase (ALP) by > 2 × ULN; and
  - — 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 6.11.6 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 Visits and assessments, with the exception of IMP dosing.

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 6.9.2 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 (ie, diagnostic machines that transcribe data directly to a database, or data entered directly into an Electronic Medical Record 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 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 URTI symptoms, recruited from approximately 60 centers in Asia Pacific, Australia, Canada, Europe, South America, and the United States.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Males and females 18 to 75 years of age

2) Received an autologous or allogeneic HCT using any conditioning regimen

3) Documented to be RSV-positive as determined by local testing (eg, PCR, DFA, RVP assay, or culture) using an upper respiratory tract sample collected ≤ 6 days prior to Day 1

4) New onset of at least 1 of the following respiratory symptoms for ≤ 7 days prior to Day 1: nasal congestion, runny nose, cough, or sore throat, or worsening of one of these chronic (associated with a previously existing diagnosis, eg, chronic rhinorrhea, seasonal allergies, chronic lung disease) respiratory symptoms ≤ 7 days prior to Day 1

5) No evidence of new abnormalities consistent with LRTI on a chest X-ray relative to the most recent chest X-ray, as determined by the local radiologist. If a chest X-ray is not available or was not obtained during standard care < 48 hours prior to Screening, a chest X-ray must be obtained for Screening

6) O_2 saturation ≥ 92% on room air

7) An informed consent document signed and dated by the subject or a legal guardian of the subject and the investigator or his/her designee

8) A negative urine or serum pregnancy test is required for female subjects (unless surgically sterile or greater than two years post-menopausal)

9) Male and female subjects of childbearing potential must agree to contraceptive requirements as described in Appendix 5

10) Willingness to complete necessary study procedures and have available a working telephone or email

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 non-marketed (according to region) 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 investigational RSV vaccines after HCT.

2) Use of a moderate or strong 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 medical history:

3) Admitted to the hospital primarily for a lower respiratory tract disease of any cause as determined by the investigator

4) Pregnant, breastfeeding, or lactating females

5) Unable to tolerate nasal sampling required for this study, as determined by the investigator

6) Known history of HIV/AIDS with a CD4 count <200 cells/μL within the last month

7) History of drug and/or alcohol abuse that, in the opinion of the investigator, may prevent adherence to study activities

Related to medical condition at Screening:

8) Documented to be positive for other respiratory viruses (limited to influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus, or coronavirus) within 7 days prior to the Screening visit, as determined by local testing (additional testing is not required)

9) Clinically significant bacteremia or fungemia within 7 days prior to Screening that has not been adequately treated, as determined by the investigator

10) Clinically significant bacterial, fungal, or viral pneumonia within 2 weeks prior to Screening that has not been adequately treated, as determined by the investigator

11) Excessive nausea/vomiting at Screening, as determined by the investigator, or an inability to swallow pills that precludes oral administration of the IMP (for subjects without an NG tube in place)

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

Related to allergies:

13) 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)

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

Related to laboratory results:

15) Creatinine clearance < 30 mL/min (calculated using the Cockcroft-Gault method)

16) Clinically significant ALT/AST, as determined by the investigator

17) Clinically significant 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:

1) Presence or absence of lymphopenia, defined as a lymphocyte count < 200 cells/μL versus ≥ 200 cells/μL of blood

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

When available, the most recent laboratory value for lymphocyte count (obtained ≤ 6 days prior to Screening [Visit 1]) may be used for randomization. If an existing laboratory value is not available, the test will be performed at Screening using the local hospital laboratory.

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 1:1 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. Interim analyses will be conducted and reviewed by delegated personnel not involved in the study conduct.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where 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 (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 matching placebo 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 matching placebo are packaged in white, high density polyethylene (HDPE) bottles with desiccant and polyester fiber coil. Each bottle contains 4 tablets and is capped with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

All labels for IMP distributed to investigative sites in the US and the rest of world (ROW) will meet all applicable requirements of the US Food and Drug Administration (FDA), the EU Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010), and/or other local regulations, as applicable.

5.2.3. Storage and Handling

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

Presatovir 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 IMP should be stored in a securely locked area, accessible only to authorized site personnel. The study center will be required to maintain a log of daily temperature readings in the storage area for the duration of the study, with the exception of weekends and/or holidays per site written procedure. To ensure the stability and proper identification, the drug products will be stored in the containers in which they were supplied until units are dispensed to individual subjects at the site.

5.3. Dosage and Administration of Presatovir

Eligible subjects will receive a single dose of 200 mg presatovir or placebo on Days 1, 5, 9, 13, and 17. Doses will be administered orally or via NG tube. The entire dose must be taken within 1 hour. Investigational medicinal product should be dispensed with gloves.

Subjects will remain in the clinic for 30 minutes post-dose for observation. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should receive another dose. If another dose is administered, the subject should remain in the clinic for an additional 30 minutes post-dose for observation.

5.4. Prior and Concomitant Medications

Strong and moderate inducers of CYP enzymes may reduce the exposure of presatovir. Preliminary PK results from a clinical drug-drug-interaction (DDI) 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 C_{max} and 26.1% increase in AUC_{inf}). 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 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. Additional information is provided in the study procedures manual.

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. Visit 1: Screening Visit (Day -1)

Visit 1 must be performed in clinic or in hospital. Potential subjects must be documented RSV positive in the upper respiratory tract prior to being approached for informed consent. 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 (Visit 1) 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
- Collection of Medical History and Demographics
- Review of concomitant medications
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- Height and weight
- O_2 saturation (on room air)
- Chest X-ray (chest X-rays obtained < 48 hours prior to Screening may be used)
- Blood draw for screening labs (labs obtained ≤ 6 days prior to Screening may be used)
  - Creatinine clearance (calculated using the Cockroft-Gault method)
  - AST and ALT
  - Total bilirubin

- 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 consent form

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 Visit 2 (Day 1) 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. Visit 2: Baseline Assessments, Randomization, and Treatment Assessments (Day 1)

6.1.2.1. Baseline Assessments

Visit 2 must be performed in clinic or in hospital and should occur within 24 hours of confirmation of the subject's eligibility. Samples and assessments performed at Screening (Visit 1) may not be used as Visit 2 Baseline assessments. Baseline (Visit 2) assessments should be performed in the following order and documented on Day 1 prior to IMP administration:

- FLU-PRO questionnaire

- Review of concomitant medications, mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for >24 hours)

- Weight

- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)

- O_2 saturation (on room air)

- Pre-dose blood draw for central and local laboratory analysis:

  — Safety Labs (hematology and serum chemistry to include to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB)

  — Serum antibody titer to RSV

  — Respiratory syncytial virus viremia

- Local troponin testing
- Local testing for lymphocyte count (if not obtained ≤ 6 days prior to Screening [Visit 1])

- Nasal samples (2 total, 1 from each nostril)
- Urine or serum pregnancy test (for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy)
- 12-lead Pre-dose ECG

6.1.2.2. Randomization and Treatment Assessments (Day 1)

After all Baseline assessments are complete, eligible subjects will be randomized via Interactive Voice/Web Response System (IXRS) 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:

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

When available, the most recent laboratory value for lymphocyte count (obtained ≤ 6 days prior to Screening [Visit 1]) may be used for randomization. If an existing laboratory value is not available, the test will be performed at Screening using the local hospital laboratory.

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 1:1 ratio to receive IMP (presatovir or matching placebo).

Subjects will receive a dose of 200 mg (four 50 mg tablets) of presatovir or matching placebo at Day 1. All IMP will be administered orally or via NG tube. The entire dose must be taken within 1 hour. Investigational medicinal product should be dispensed with gloves. Subjects will remain in the clinic for 30 minutes post-dose for observation. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should receive another dose. If another dose is administered, the subject should remain in the clinic for an additional 30 minutes post-dose for observation. Details of IMP administration are included in the Study Procedures Manual.

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

- Pharmacokinetic sampling at 1 (±15 min), 2 (±15 min), 4 (±30 min), and 6 hours (±30 min) post-dose for PK subgroup subjects
- Blood draw for serum creatinine at 2 hours (±15 min) post-dose for PK subgroup subjects
- Assessment of AEs, concomitant medications, hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for >24 hours)

6.2. Visit 3: Day 3 (±24 hours)

For subjects in the PK subgroup Visit 3 assessments must be performed in the clinic or in hospital. For all other subjects Visit 3 assessments may be performed at the clinic, in hospital, or at the subject's home by the study coordinator or designee, or a home nursing vendor.

- Nasal samples (2 total, 1 from each nostril)
- Pharmacokinetic sampling (for PK subgroup subjects only)
- Vital signs, including O_2 saturation (unless conducted as a home visit)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for >24 hours). Review of procedure-related AEs only, if home visit.

6.3. Visit 4: Day 5 (±24 hours)

Visit 4 assessments must be performed in clinic or in hospital and should be performed in the following order and documented (also refer to Appendix 2, Study Procedures Table):

- FLU-PRO questionnaire
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- O_2 saturation (on room air)
- Weight
- Pre-dose blood draw for central laboratory analysis:
  - Safety Labs (hematology and serum chemistry to include to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB)

  - Pharmacokinetic sampling for all subjects: pre-dose
  - Respiratory syncytial virus viremia
- Nasal samples (2 total, 1 from each nostril)
- Urine or serum pregnancy test (for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy)
- Investigational medicinal product administration*
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for >24 hours)

* Subjects will receive a single dose of 200 mg (four 50 mg tablets) of presatovir or matching placebo at Days 5, 9, 13, and 17. All IMP will be administered orally or via NG tube. The entire dose must be taken within 1 hour. Investigational medicinal product should be dispensed with gloves. Subjects will remain in the clinic for 30 minutes post-dose for observation. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should receive another dose. If another dose is administered, the subject should remain in the clinic for an additional 30 minutes post-dose for observation. Details of IMP administration are included in the Study Procedures Manual.

6.4. Visit 5: Day 7 (±24 hours)

Visit 5 assessments may be performed in clinic, in hospital, or at the subject's home by the study coordinator or designee, or a home nursing vendor.

- Nasal samples (2 total, 1 from each nostril)
- Vital signs, including O_2 saturation (unless conducted as a home visit)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use (≥ 2 L/min for >24 hours). Review of procedure-related AEs only, if home visit.

6.5. Visits 6-8: Days 9, 13, and 17 (±24 hours)

Visit 6-8 assessments must be performed in clinic or in hospital and should be performed in the following order and documented at these visits (also refer to Appendix 2, Study Procedures Table):

- FLU-PRO questionnaire (Day 9 only)
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)

- O_2 saturation (on room air)
- Weight
- Pre-dose blood draw for central and local laboratory analysis:
  - Safety Labs (hematology and serum chemistry to include to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB)
  - Pharmacokinetic sampling for all subjects: pre-dose (Day 9 only)
  - Respiratory syncytial virus viremia
  - Local troponin testing (Day 17 only)
- Nasal samples (2 total, 1 from each nostril)
- 12-lead Pre-Dose ECG (Day 17 only)
- Urine or serum pregnancy test (for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy)
- Investigational medicinal product administration*
- Pharmacokinetic sampling for all subjects: 2 hours post-dose (±15 min) (Day 9 only)
- Blood draw for serum creatinine at 2 hours (±15 min) post-dose for PK subgroup subjects (Day 9 only)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for >24 hours)

* Subjects will receive a single dose of 200 mg (four 50 mg tablets) of presatovir or matching placebo at Days 5, 9, 13, and 17. All IMP will be administered orally or via NG tube. The entire dose must be taken within 1 hour. Investigational medicinal product should be dispensed with gloves. Subjects will remain in the clinic for 30 minutes post-dose for observation. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should receive another dose. If another dose is administered, the subject should remain in the clinic for an additional 30 minutes post-dose for observation. Details of IMP administration are included in the Study Procedures Manual.

6.6. Visit 9: Day 22 (±24 hours)

Visit 9 assessments must be performed in clinic or in hospital and should be performed in the following order and documented (also refer to Appendix 2, Study Procedures Table):

- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- O_2 saturation (on room air)
- Weight
- Blood draw for central laboratory analysis:
  - Safety Labs (hematology and serum chemistry to include to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB)
  - Pharmacokinetic sampling for all subjects
  - Respiratory syncytial virus viremia
- Nasal samples (2 total, 1 from each nostril)
- Obtain sample for local RSV testing* (refer to Section 6.11.11)
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care >24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for > 24 hours)

PPD

6.7. Visit 10: End of Study/Day 28 (+3 days)

Visit 10 assessments must be performed in clinic or in hospital. The visit will occur no earlier than Day 28 and no later than Day 31. Visit 10 assessments should be performed in the following order and documented (also refer to Appendix 2, Study Procedures Table):

- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- O_2 saturation (on room air)
- Weight
- Blood draw for central and local laboratory analysis:
  - Safety Labs (hematology and serum chemistry to include to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB,)

- Serum antibody titer to RSV
- Respiratory syncytial virus viremia
- Local troponin testing

- Nasal samples (2 total, 1 from each nostril)
- 12-lead ECG
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours , standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for > 24 hours)

6.8. Visits 11 – 14*: Days 35, 42, 49 and 56 (±48 hours)

Visit 11 - 14 assessments may be performed in clinic, in hospital, or at the subject's home by the study coordinator or designee, or a home nursing vendor.

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

PPD

6.9. 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.

6.9.1. 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 Visit 10, Day 28/End of Study Visit, with the exception of IMP administration.

6.9.2. 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 (see Sections 6.2 through 6.7). 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 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 (only if the subject withdraws prior to Visit 6 [Day 9])
- Vital Signs (body temperature, heart rate, respiratory rate, and blood pressure)
- O_2 saturation (on room air)
- Weight
- Blood sample collection for central and local laboratory analysis:
  - Safety Labs (hematology and serum chemistry to include to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB)
  - Serum antibody titer to RSV
  - Respiratory syncytial virus viremia
  - Pharmacokinetic sampling (only if the subject withdrawals prior to Visit 9 [Day 22])
  - Local troponin testing
- Nasal samples (2 total, 1 from each nostril)
- 12-lead ECG
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for > 24 hours)

6.10. 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 Visit 6 [Day 9])
- Vital signs, including O_2 saturation (on room air)
- Weight

- Collection of nasal samples (2 total, 1 from each nostril) for analysis at the central lab
- Assessment of AEs, concomitant medications, hospitalizations, re-hospitalizations, ICU admissions or utilization of ICU care > 24 hours, standard of care test results (ie, chest radiographs, microbiology, echocardiograms), mechanical ventilation (invasive and non-invasive of any duration), and supplemental O_2 use ($\geq$ 2 L/min for > 24 hours)

6.11. Study Assessments

6.11.1. Nasal Samples, Virology, and Antibody Titer

Prior to Screening (Visit 1), all subjects should be documented as RSV positive, as determined by the local laboratory test methods (eg, PCR, DFA, RVP assay, or culture) using an upper respiratory tract sample collected ≤6 days prior to Day 1.

Nasal samples will be obtained at each study visit, with the exception of Screening (Visit 1), for analysis at the central laboratory, and should be collected prior to dosing at all dosing visits. Two samples will be collected at each time point, 1 from each naris. At any time during the study, if a bronchoscopy is planned for the same day as nasal sampling, nasal samples should be obtained, if possible, prior to application of any topical anesthetic (eg, lidocaine) in the nostrils. If it is not possible to collect nasal samples from both nares (eg, subject has an NG tube in place), 2 samples should be taken from the same naris and the tube for the second sample should be marked as "back-up." PPD

Nasal samples will be analyzed using RT-qPCR to determine RSV viral load, RSV sequencing to evaluate development of resistance (see Section 6.11.2), and a multiplex assay to identify co-infections. PPD ll nasal samples for central laboratory analysis will be collected, placed in individual tubes, and stored/shipped to the central laboratory as per instructions outlined in the Laboratory Manual.

Blood samples will be collected for RSV viremia evaluation (RT-qPCR) at Visits 2, 4, 6, 7, 8, 9, and 10 (Days 1, 5, 9, 13, 17, 22 and 28) prior to dosing, and RSV antibody titers at Visits 2 and 10 (Days 1 and 28). Samples will be processed, stored and shipped to the central laboratory as per instructions outlined in the Laboratory Manual.

6.11.2. 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 Resistance Analysis Plan. In addition, all samples obtained from subjects who had quantifiable RSV RNA by RT-qPCR at the end of the study 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.

6.11.3. FLU-PRO Questionnaire

The FLU-PRO questionnaire will be completed at Visits 2, 4, and 6 (Days 1, 5, and 9). The FLU-PRO should be administered prior to all other study procedures, however, if the FLU-PRO cannot be administered first it should be administered consistently at the required visits (ie, always after the same study procedure[s]). The FLU-PRO is currently being validated for evaluation of symptoms in patients who are infected with influenza. Due to the lack of validated tools for 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. A copy of the FLU-PRO questionnaire may be found in the Study Procedures Manual.

6.11.4. 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 all study visits, with the exception of Visits 3 and 5 if they are performed as home visits, PPD .

6.11.5. Oxygen Saturation

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, even if the subject is dependent on O_2 supplementation. If the subject is receiving supplemental O_2, the O_2 source must be removed for a period of 30 seconds prior to this assessment. This 30 second period may be conducted while the subject is sitting quietly. The O_2 saturation will be documented in the source documentation at regular intervals during a 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 $\leq 88\%$, whichever is achieved first. The lowest O_2 saturation recorded over the 2-minute interval will be captured in the eCRF. Oxygen saturation will be collected at all study visits, with the exception of Visits 3 and 5 if they are performed as home visits, PPD .

Subjects requiring invasive mechanical ventilation will **not** have O_2 saturation measured while ventilated, and it should be recorded in the source documentation as not assessed and the reason should be documented. If it is determined by the investigator that it is unsafe to remove the subject's supplemental O_2 for assessment of O_2 saturation (eg, subject is on high-flow mask), then it should be recorded in the source documentation as not assessed and the reason should be documented.

6.11.6. Safety Labs

When available, the most recent laboratory values (obtained ≤ 6 days prior to Screening [Visit 1]) 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 blood samples will be collected pre-dose at all visits where IMP is administered.

Central laboratory testing of blood specimens for safety analysis will include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB at Visits 2, 4, 6, 7, 8, 9, and 10 (Days 1 , 5, 9, 13, 17, 22, and 28).

Any test showing an increase of serum ALT or AST > 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, immediate close observation is required. If close monitoring is not possible, IMP will be discontinued.

Blood will also be drawn to monitor troponin levels pre-dose at Visits 2 and 8 (Days 1 and 17), and anytime at Visit 10 (Day 28). At each visit, the sample 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. However, 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.

Blood specimens for serum creatinine will be collected 2 hours post-dose at Visits 2 and 6 (Days 1 and 9) from subjects participating in the PK subgroup only.

Urine or serum pregnancy tests will occur for all females of childbearing potential at Screening and at each dosing visit (Visits 2, 4, 6, 7, and 8) prior to administration of IMP.

6.11.7. Chest X-ray

Given the potential for a poor outcome once progression to lower respiratory tract disease occurs in this population, a chest X-ray is generally performed as part of standard clinical evaluation of a new URTI. For this study, evaluation of a chest X-ray is required at Screening. A chest X-ray obtained <48 hours prior to Screening may be used. Otherwise, a chest X-ray will need to be obtained at Screening.

6.11.8. Electrocardiogram (ECG)

As part of safety testing, at Visit 2 (Day 1) a pre-dose 12-lead ECG will be performed on the institution's equipment. A 12-lead ECG will also be performed pre-dose at Visit 8 (Day 17) and anytime at Visit 10 (Day 28). ECG results should be verified before the subject leaves the

clinical site in case further medical care is advised. 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. Any additional ECG measures obtained for the purposes of patient care also require collection.

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

6.11.9.1. LRTC Source Documentation for Adjudication Committee Review

During the course of the study, it is anticipated that Investigators will perform chest X-rays and/or CT scans as part of standard of care if there is any concern of a lower respiratory tract complication. Images and results for chest X-rays used for screening and eligibility, including the comparison chest X-ray, and all scans done as part of standard of care (to include CT and chest X-rays) while subjects are on study, will be collected and stored electronically for review by the Adjudication Committee and a possible central read. Additionally, the following results from any confirmatory testing will be collected:

- Results of all local microbiology tests performed while on study through Visit 10 or early termination before Visit 10 (All bacterial, viral, fungal, parasite, or other results from samples obtained from any respiratory specimen [eg, bronchoalveolar lavage, sputum, pleural fluid, lung tissue] and from blood specimens, including bacterial culture, viral PCR, and serology studies).
- Echocardiogram tracings and reports of any ECG performed in relation to a potential LRTC event
- Temperature
- Clinical notes (with range of dates)
- Daily body weights
- Autopsy reports (if performed)
- Other supporting documentation, as requested

6.11.9.2. 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

6.11.10. Plasma PK

Pharmacokinetic blood sampling will be performed using the site's local procedures and analyzed at a central laboratory. Pharmacokinetic blood samples will be processed, placed in individual tubes, and stored/shipped to the central laboratory as per instructions outlined in the Laboratory Manual. These plasma PK samples may also be used to evaluate the plasma PK of co-administered agents (eg, ganciclovir, acyclovir).

Extensive PK sampling will occur on a subset of subjects (up to 30 subjects) to adequately characterize presatovir PK in this patient population. Subjects will have the option to elect to participate in extensive PK sampling at the time of informed consent. Pharmacokinetic samples will be obtained at the following time points, depending on whether the subject is part of the PK subset:

Table 6-1. PK Timepoints

	Visit 2 (Day 1) 1hr post-dose (±15 min)	**Visit 2 (Day 1) 2hrs post-dose (±15 min)**	**Visit 2 (Day 1) 4hrs post-dose (±30 min)**	**Visit 2 (Day 1) 6hrs post-dose (±30 min)**	**Visit 3 (Day 3) anytime**	**Visit 4 (Day 5) pre-dose**	**Visit 6 (Day 9) pre-dose**	**Visit 6 (Day 9) 2hrs post-dose (±15 min)**	**Visit 9 (Day 22) anytime**
PK samples						X	X	X	X
PK subgroup samples	X	X	X	X	X	X	X	X	X

6.11.11. Optional Extended Viral Monitoring

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

Protocol-specific SAE reporting exemptions: In this study, death related to clinical progression of underlying disease requiring HCT, or graft failure will not need to be reported as an SAE. Death related to clinical progression of underlying disease requiring HCT, or graft failure should only be reported as SAEs on the eCRF, unless there is evidence suggesting a causal relationship between the IMP or study procedure and the event. In that case, the investigator must immediately report the event as an SAE in accordance with the procedure in Section 7.3 below. Such clinical progression or graft failure (which is assessed as not related to IMP/procedure) will be exempt from global expedited reporting requirements for the duration of the study. The events will be collected and evaluated by Gilead and reported as appropriate in any relevant aggregate safety report, as well as the final clinical study report.

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 subinvestigator 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 subinvestigator 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 after the post treatment follow-up visit but within 30 days or 4 weeks of the last dose of study IMP, 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 4. 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 3.

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 5 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:

- To evaluate the effect of presatovir on RSV viral load in RSV-positive autologous or allogeneic HCT recipients with acute URTI symptoms

The secondary objectives of this study are:

- To evaluate the effect of presatovir on development of LRTC, progression to respiratory failure, and all-cause mortality
- To evaluate the PK, safety, and tolerability of presatovir

8.1.2. Primary Endpoint

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

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

where Y_i is the change from Baseline in RSV $\log_{10}$ viral load at *Visit i*, t is the time at the specified timepoint, a is the baseline assessment at Day 1 and b is the last assessment at or prior to Day 9. The time-weighted average change, often referred to as the DAVG, provides the average viral burden in change from baseline during the time period of interest.

8.1.3. Secondary Endpoint

Secondary endpoints are:

- Proportion of subjects who develop a LRTC through Day 28, defined as one of the below, as determined by the adjudication committee:
  - Primary RSV LRTI
  - Secondary bacterial LRTI
  - Lower respiratory tract infection due to unusual pathogens

— Lower respiratory tract infection, noninfectious or of unknown etiology

- Proportion of subjects who develop respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) through Day 28
- Proportion of all-cause mortality through Day 28

8.1.4. Exploratory Endpoints

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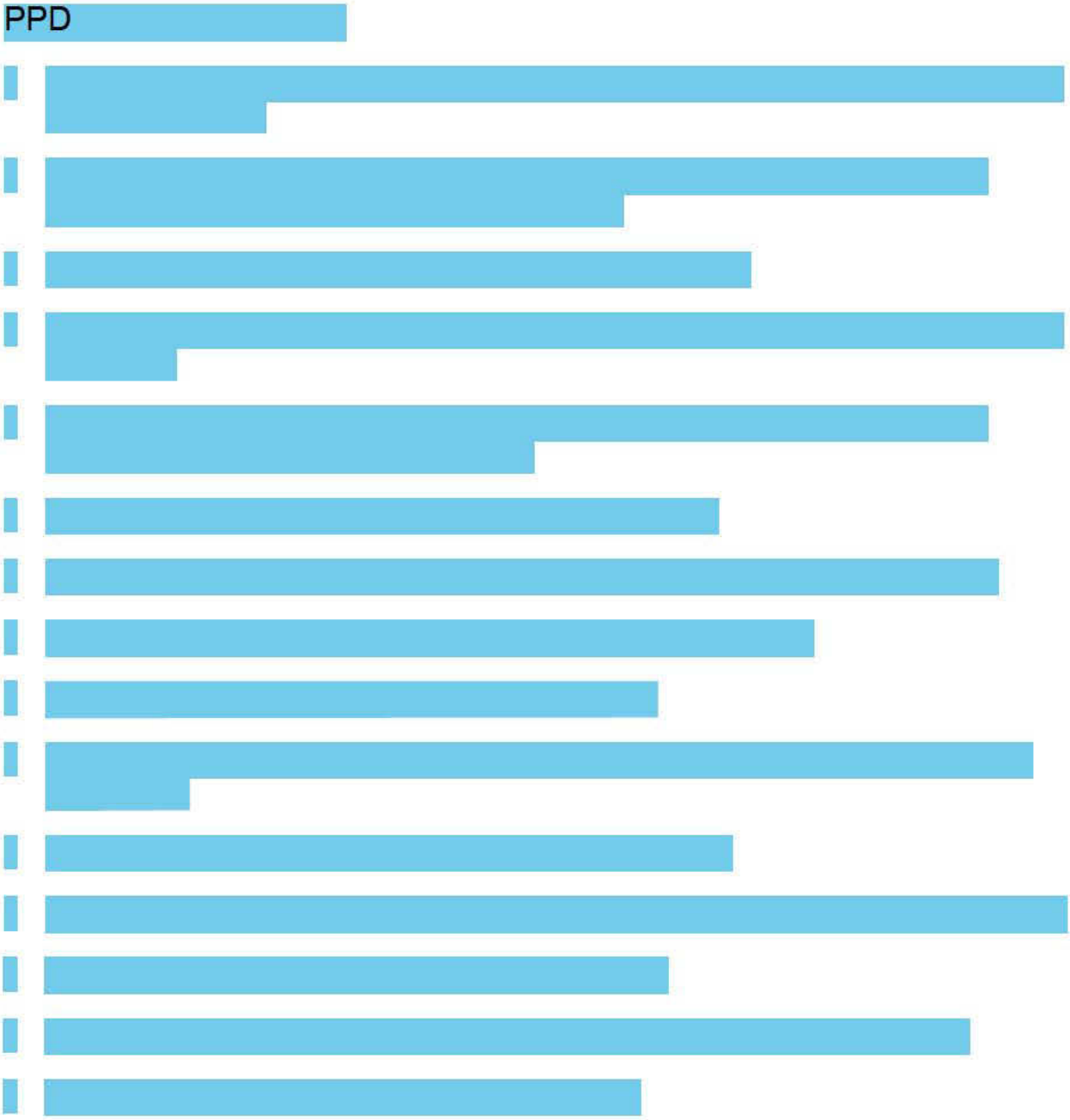

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The full analysis set (FAS) will include subjects who have an RSV $\log_{10}$ viral load greater than or equal to the LLOQ of the RT-qPCR assay in the pre-dose Day 1 nasal sample, as determined by RT-qPCR at the central lab, and have received at least 1 full dose of IMP. The primary analysis set for efficacy analysis will be the evaluable analysis set which will include those in the FAS with evaluable nasal samples for RSV viral load by Day 9 (including Baseline).

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 (eg, specimen hemolyzed).

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 summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, randomization stratification group, and age.

Baseline data will include a summary of body weight, height, BMI, and baseline disease characteristics.

For categorical demographic and Baseline characteristics, a Fisher's exact test will be used to compare treatment groups. For continuous demographic and Baseline characteristics, a Wilcoxon rank sum test will be used to compare treatment groups.

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 to Day 9. The primary analysis will be performed on subjects included in the efficacy evaluable population. To test the null hypothesis that there is no difference between the presatovir and placebo treatment groups in the time-weighted average change in viral load, a parametric analysis of covariance (ANCOVA) model with corresponding baseline viral load and randomization stratification factors as covariates will be used, with a 2-sided 0.05 level. Adjusted means and 95% confidence intervals (CIs) will also be presented. If stratification leads to small cell sizes, a modification to the stratification, which will be described in the SAP, will be implemented.

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 proportion of subjects who develop LRTC through Day 28, the proportion of subjects who develop respiratory failure requiring mechanical ventilation through Day 28, and the proportion of all-cause mortality among subjects through Day 28will each be analyzed using a Cochran-Mantel-Haenszel test stratified by randomization stratification factors. If stratification leads to small cell sizes, a modification to the stratification, which will be described in the SAP, will be implemented.

In order to account for multiple hypothesis testing of endpoints, a family alpha spending rule will be used to control the Type 1 error rate of 0.05 across the primary and secondary endpoints, testing for differences between treatment groups. The primary endpoint analysis will serve as the gatekeeper for the secondary analyses. If the primary null hypothesis is rejected, then the following secondary endpoints will be tested sequentially at $\alpha = 0.05$ based upon the closed testing procedure {11631}.

- Proportion of subjects who develop a LRTC through Day 28
- Proportion of subjects who develop respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) through Day 28
- Proportion of all-cause mortality through Day 28

8.5.3. Exploratory Analyses

8.6. Safety Analysis

All safety data collected on or after the date that IMP was first dispensed up to the date of last dose of IMP through Day 28 will be summarized by treatment group (according to the IMP received). 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 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 the date of last dose of IMP through 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.

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 4. 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 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 using descriptive statistics 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

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.

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

PK/PD relationship may be explored as appropriate.

8.9. Sample Size

Sample size calculations are based on results observed in a study that evaluated the efficacy of oral and aerosolized ribavirin treatment for preventing progression from upper to lower respiratory tract infection in hematopoietic cell transplant recipients with RSV infections (unpublished data from Dr. PPD). The sample size calculation assumes the time-weighted average change in RSV $\log_{10}$ viral load from Day 1 to Day 9 in the placebo group will be -1 $\log_{10}$ copies/mL with a corresponding standard deviation (SD) of 2 and that 85% of the subjects will be evaluable. Based on these assumptions, with 85 evaluable subjects per group there is over 85% power to detect a 1 log difference in time-weighted average change in $\log_{10}$ viral load between treatment groups using a 2-sided 0.05-level test. Given an evaluable rate of 85%, a total of 200 subjects will need to be randomized into the study.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of 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

Blinded reviewers will review related clinical data to determine whether a lower respiratory tract complication has developed. These clinical data (ie, vital signs, clinical notes, radiology reports [including echocardiograms], and microbiology results) will be used to determine if one of the following has occurred, excluding other causes such as pulmonary embolism, cardiogenic shock, heart failure, and fluid overload:

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

Detailed definitions for each of the above diagnoses will be provided to the adjudication committee 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, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, 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 or the subject's legally authorized representative 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 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 (e.g. 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, e.g. 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.
199 E BLAINE ST
SEATTLE, WA 98102

STUDY ACKNOWLEDGEMENT

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

GS-US-218-0108, Protocol Amendment 6, 20 November 2015

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

Timothy Watkins
Name (Printed)
Author

PPD

11/20/2015
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

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

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

a Chest X-ray obtained < 48 hours prior to Screening may be used

b Existing values collected ≤ 6 days prior to Screening may be used

c Required for women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy

d On room air

e Central laboratory testing: hematology and serum chemistry to include WBC with differential, Hgb, platelets, BUN, creatinine, serum albumin, AST, ALT, ALP, and TB

f 2 samples total, 1 from each nostril – collected prior to dosing on dosing days

g For subjects in the PK subgroup only: Collected 1 (±15 min), 2 (±15 min), 4 (±30 min) and 6 hours (±30 min) post-dose

h For all subjects: collected pre-dose on Day 5, pre-dose and 2 hours (±15 min) post-dose on Day 9, and anytime on Day 22

i For subjects in the PK subgroup only: PK is collected anytime during Visit 3 and Visit 3 must occur in clinic.

j For subjects in the PK subgroup only. Subjects not participating in the PK subgroup can have this visit completed at home by a home nursing vendor or by the study coordinator or designee.

k For subjects in the PK subgroup only: Blood draw for serum creatinine 2 hours (±15 min) post dose on Day 1 and Day 9 (Visit 2 and Visit 6)

l Only for subjects who agree to the optional extended viral monitoring at the time of consent.

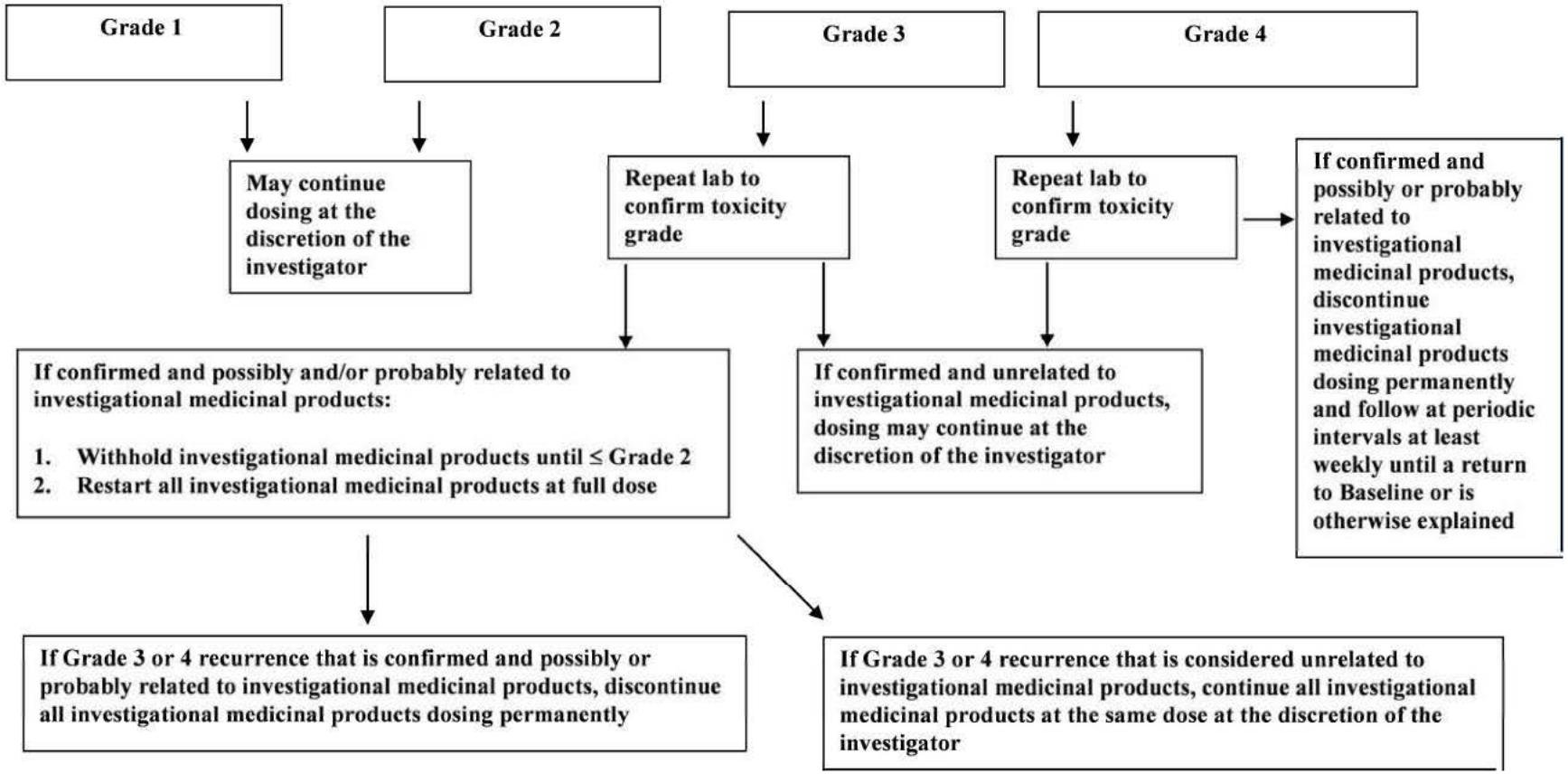
m Only for subjects who agree to the optional extended viral monitoring at the time of consent and test positive (or inconclusive) for RSV at Visit 9 (Day 22)

n Assessment of procedure-related AEs only, if home visit

o Not required if home visit

p Local troponin testing will be done pre-dose in accordance with the standard assay available and used at the site. Point-of-care “rapid” troponin tests are not acceptable for protocol-mandated troponin testing.

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days** **Infant, 2 – ≤ 7 Days** **Infant, 1 Day**	1000 to 1300/mm^3 1.00 to 1.30 GI/L 1250 to 1500/mm^3 1.25 to 1.50 GI/L 4000 to 5000/mm^3 4.00 to 5.00 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L 1000 to < 1250/mm^3 1.00 to < 1.25 GI/L 3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L 750 to < 1000/mm^3 0.75 to < 1.00 GI/L 1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 500/mm^3 < 0.50 GI/L < 750/mm^3 < 0.75 GI/L < 1500/mm^3 < 1.50 GI/L
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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%

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	146 to 150 mEq/L 146 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	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 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	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
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
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 ≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
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** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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	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
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	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
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) **Pediatric >2 to <18 years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L >130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L > 190 mg/dL >4.92 mmol/L	NA NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA 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

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	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 (e.g., 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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated 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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	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)
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 5. 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 the screening visit and at each dosing visit (Visits 2, 4, 6, 7, and 8) prior to administration of study drug to ensure pregnant women are not included or treated with study drug in the trial. Please refer to the latest version of the Investigator's Brochure 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.

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 at screening and at each dosing visit (Visits 2, 4, 6, 7, and 8) prior to receiving study drug.

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, with spermicide, 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.