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 Hospitalized Adults with Respiratory Syncytial Virus (RSV) Infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	114498	
EudraCT Number:	2014-002137-58	
Clinical Trials.gov Identifier:	NCT02135614	
Indication:	Respiratory Syncytial Virus Infection	
Protocol ID:	GS-US-218-1227	
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Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4:	10 November 2013 13 March 2014 05 August 2014 29 August 2014 17 November 2015

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multi-Center Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in Hospitalized Adults with Respiratory Syncytial Virus (RSV) Infection
IND Number:	114498
EudraCT Number:	2014-002137-58
Clinical Trials.gov Identifier:	NCT02135614
Study Centers Planned:	Approximately 70 centers in Australia, Canada, Europe, Hong Kong, Israel, New Zealand, South Korea, and the United States.
Objectives:	The primary objective of this study is to evaluate the effects of presatovir (GS-5806) on RSV viral load in RSV-positive adults hospitalized with acute respiratory infectious symptoms. The secondary objectives of this study are to evaluate: • The effect of presatovir on change in the FLU-PRO score from Baseline • The effect of presatovir on the length of hospital stay • The effect of presatovir on the rate of unplanned healthcare encounters (clinic visits, emergency room visits, urgent care visits, and rehospitalizations) related to a respiratory illness after discharge • The pharmacokinetics (PK), safety, and tolerability of presatovir
Study Design:	Randomized, double-blind, placebo-controlled study evaluating the effect of presatovir on RSV viral load, PK, safety, and tolerability in hospitalized adults with RSV infection. Subjects will be randomized in a 1:1 ratio to receive presatovir or placebo.

	Subjects will be stratified by the following: 1) No chronic airways or lung disease 2) Chronic obstructive pulmonary disease (COPD) 3) Asthma 4) Other chronic airways or lung disease
Number of Subjects Planned:	Approximately 200 RSV-positive subjects.
Target Population:	Hospitalized women and men ≥ 18 years of age with an acute respiratory illness
Duration of Treatment:	1 day
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3. **Main Inclusion Criteria:** • ≥ 18 years of age at Screening • Willing to adhere to protocol specific requirements for contraception • Subject is a current inpatient • New onset of acute respiratory infectious symtpoms, or acute worsening of chronic symptoms related to ongoing respiratory disease for ≤ 5 days prior to screening: — Upper respiratory tract symptoms: Nasal congestion, runny nose, sore throat, or earache — Lower respiratory tract symptoms: Cough, sputum production, wheezing, dyspnea, or chest tightness • Documented to be RSV-positive as per protocol Section 6.1.1 **Main Exclusion Criteria:** Related to concomitant or previous medication use: • Use of any investigational medicinal products in the 28 days prior to Visit 1, OR use of any investigational monoclonal antibody within 4 months or 5 half-lives of Visit 1 whichever is longer, OR use of any investigational RSV vaccine ever • Chronic use (> 28 days of use) of systemic immunosuppressive agents (see Section 4.3) during the 28 days prior to Screening, or anticipated use during the 28 days following Screening

- Use of oral prednisone or other corticosteroid equivalent to:
  - > 20 mg/day for > 14 days prior to screening is not permitted.
  - > 20 mg/day for ≤ 14 days, including corticosteroids received during current hospitalization (ie, bolus doses), is permitted.
  - ≤ 20 mg/day, regardless of duration, is permitted.
- Subjects taking a moderate or strong cytochrome P450 enzyme (CYP) inducer including but not limited to rifampin, St John's Wort, carbamazepine, phenytoin, efavirenz, bosentan, etracirine, modafinil, and nafcillin within 2 weeks prior to the first dose of IMP

Related to medical condition:

- Influenza positive as determined by a rapid influenza diagnostic test or PCR-based assay for influenza
- Known Middle East Respiratory Syndrome-coronavirus (MERS-CoV) infection or known coinfection with other coronavirus
- Subjects requiring > 50% supplemental oxygen (while subject is awake) at Screening
- Subjects with a Clinical Frailty Score (CFS) > 7 at Baseline
- Requirement for mechanical ventilation, not including noninvasive ventilation
- Clinically significant bacteremia or fungemia that has not been adequately treated prior to Screening, as determined by the investigator
- Inadequate treatment of confirmed bacterial, fungal, or non-RSV pneumonia, as determined by the investigator
- Excessive nausea/vomiting at admission, as determined by investigator, that precludes administration of an orally administered Investigational Medicinal Product (IMP)
- Subjects with an unstable medical condition, as determined by the investigator, that precludes participation in the study

Study Procedures/ Frequency:	For a complete overview of study procedures and visits, please refer to Section 6 and Appendix 2. Hospitalized subjects may undergo a 2-part consent process. **Part 1:** Prospective subjects without an RSV-positive respiratory result during the current hospitalization will be consented for RSV testing of nasal samples. Influenza testing may also be conducted at this time **Part 2:** RSV-positive subjects will be approached to consent for the treatment phase of the study. **Vital Signs (VS):** Vital signs will be measured at Screening, Baseline, Days 2, 3, 5, 7, and 14, and will include temperature, heart rate, respiratory rate, and blood pressure. **O_2 Saturation:** O_2 saturation will be recorded at Screening, Baseline, Days 2, 3, 5, 7, and 14 while breathing room air, even if the subject is dependent on O_2 supplementation. Refer to Section 6.12.7 for procedure. **Supplemental Oxygen Use Diary:** Daily supplemental oxygen use and historical supplemental oxygen use will be collected. A Supplemental Oxygen Use Diary will be dispensed to subjects at randomization. Study coordinators may complete the diary through hospitalization discharge; subjects will complete the diary after discharge. Please refer to Section 6.12.8 for additional details. **Questionnaires:** Questionnaires will be administered by the study coordinator after consent and prior to all other study procedures. The following questionnaires will be utilized in this study: • Clinical Frailty Score (CFS): Baseline • FLU-PRO: Baseline, Days 2, 3, 5, 7, and 14 • European Questionnaire 5 Dimensions (EQ5D-5L): Baseline/Day 1, Days 2, 3, 5, 7, and 14 **Healthcare Utilization Assessment:** Healthcare utilization will be evaluated on Days 7, 14, and 28 to include the use of Intensive Care Unit (ICU), intermediate care facilities, or nursing homes; number of days on supplemental O_2 during the study; use of mechanical ventilation; and number of subsequent unplanned clinic visits, emergency room visits, urgent care visits, and rehospitalizations (for any respiratory illness).

Laboratory tests: When available, the most recent laboratory values from the current hospitalization will be used for eligibility assessment. Urine pregnancy tests will be performed by study staff on site at Screening (as necessary), followed by a serum pregnancy test for all females of child-bearing potential on Day 14. Blood specimens will be collected at Screening (if required), Baseline, and Days 3, 5, and 14.

At Baseline (pre-dose) and Day 5, an additional blood sample will be collected for biomarker analysis. Blood will be drawn to monitor troponin levels at Baseline (pre-dose and 2 hours ± 30 minutes post-dose) and Day 14. Troponin samples will be analyzed using the laboratory-based assay specific to the local trial site (eg, troponin I or T). Additional blood will be collected at Baseline (pre-dose) and Day 14 for serum antibody titer to RSV.

Electrocardiogram (ECG): A pre-dose ECG will be performed at Baseline. A post-dose ECG will be performed 2 hours ± 30 minutes after dosing. A third ECG will be obtained on Day 14.

Clinical Data Collection for Cardiac-Related Tests: Apart 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) when any cardiac-related testing is performed as part of standard clinical care or as part of AE/SAE evaluation and follow-up, results of these tests will be collected. Please refer to Section 6.12.10 for additional details.

PK blood draws: Blood will be drawn for PK at Baseline (Day 1), approximately 2 hours ± 30 minutes after IMP administration, and at any time on Days 3 and 5.

Nasal sampling: Nasal sampling will be performed at Screening per local laboratory methods. Nasal sampling at Baseline, Days 2, 3, 5, 7, and Day 14, will be performed according to specifications in the study manual.

RSV-testing: RSV-testing will be performed at Screening using the local laboratory sampling method and assay. All samples collected from Baseline through Day 14 will be analyzed using an RSV-specific quantitative real-time polymerase chain reaction (RT-qPCR) assay at a central laboratory.

Study Visits

Screening: Day −1

This is a required hospital visit. The following Screening procedures/labs are required:

- Obtain written informed consent for RSV testing
- Collection of 1 or more specimens for RSV- and influenza-testing at the local laboratory, unless results are available from the current admission
- Obtain written informed consent for the treatment portion of the study via the Main Study ICF
- Vital signs, including O_2 saturation
- Blood sample collection for local laboratory analyses, unless results exist from the current admission
- Urine 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

Baseline / Randomization: Day 1

This is a required hospital visit. IMP must be administered in the hospital. The following assessments will be performed at Baseline:

- CFS, FLU-PRO, and EQ5D-5L
- Collection of medical history including:
  - Presence or absence of pleural effusion, if chest X-ray/CT scan was performed during the initial hospitalization
  - Arterial blood pH, if results are available from the initial hospitalization and within 24 hours of Screening
- Height and weight
- Collection of 1 nasal swab sample for analysis at the central lab
- Collection of 1 nasal swab (from the opposite naris) for viral coinfection testing
- Pre-dose blood sample collection
- Pre-dose ECG
- Vital signs, including O_2 saturation, 5 – 10 minutes pre-dose

- Randomization
- IMP administration
- Vital signs, 15 and 30 minutes post-dose
- ECG, blood sample collection, and PK sampling 2 hours ± 30 minutes post-dose
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

Days 1 through 7 will occur 24 hours ± 4 hours apart. There are no procedures on Days 4 and 6.

Days 2 and 3

The Day 2 and 3 visits may occur in the hospital or clinic. Sites preapproved for home visits may conduct these visits at the subject's home. The following assessments will be performed:

- FLU-PRO and EQ5D-5L
- Vital signs, including O_2 saturation
- Collection of 1 nasal swab sample for analysis at the central lab
- PK draw (Day 3 only)
- Blood sample collection (Day 3 only)
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

Day 5

The Day 5 visit may occur in the hospital or clinic. Sites preapproved for home visits may conduct these visits at the subject's home. The following procedures will be performed:

- FLU-PRO and EQ5D-5L
- Vital Signs, including O_2 saturation
- Collection of 1 nasal swab sample for analysis at the central lab
- Blood sample collection

- PK draw
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

Day 7 and Day 14 (± 1 day)

The Day 7 and Day 14 visits may occur in the hospital or clinic. Sites preapproved for home visits may conduct these visits at the subject's home. The following procedures will be performed:

- FLU-PRO and EQ5D-5L
- Healthcare Utilization assessment
- Vital Signs, including O_2 saturation
- Collection of 1 nasal swab sample for analysis at the central lab
- ECG (Day 14 only)
- Blood sample collection (Day 14 only)
- Serum pregnancy test in women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy (Day 14 only)
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

Day 21 (± 1 day)

This visit may be conducted in the hospital or clinic or via telephone:

- Healthcare Utilization assessment
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review

	Day 28 (+ 7 days) This visit may occur no earlier than Day 28 and no later than Day 35. This visit may be conducted in the hospital or clinic or via telephone: • Healthcare Utilization assessment • Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review • If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)
Test Product, Dose, and Mode of Administration:	Presatovir (GS-5806) 50 mg tablets administered orally • Dose Day 1 presatovir: 200 mg (four 50 mg tablets) All IMP will be administered orally with water. The entire dose must be taken within 1 hour. Refer to Section 5.3 for IMP administration details.
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-Match tablets administered orally Administration will be the same as for presatovir. Refer to Section 5.3 for IMP administration details.
Criteria for Evaluation:	
Safety:	Safety will be assessed by the reporting of AEs and serious adverse events (SAEs) throughout the study, clinical laboratory tests, Vital Signs (VS), and ECGs at various time points during the study.
Efficacy:	The primary endpoint is the time-weighted average change in $\log_{10}$ viral load from Baseline (Day 1) to Day 5 as measured by RT-qPCR. The key secondary endpoints are: • Time-weighted average change in the FLU-PRO score from Baseline to Day 5 • Duration of hospital stay following IMP administration • Rate of unplanned medical encounters (clinic visits, emergency room visits, urgent care visits, and rehospitalizations) related to a respiratory illness after initial hospital discharge through Day 28 PPD

Pharmacokinetics:	• Presatovir concentration in plasma at 2 hours ± 30 minutes following IMP administration • Presatovir concentration in plasma at Days 3 and 5 • The following plasma PK parameters will be calculated for presatovir (as appropriate): C_{last}, T_{last}, and AUC_{last}.
Statistical Methods:	Evaluable subjects for efficacy analyses will include those who have an RSV log_{10} viral load greater than the lower limit of quantification (LLOQ) of the RT-qPCR assay in the pre-dose Day 1 nasal swab sample, as determined by RT-qPCR at the central lab, have a minimum of 3 quantifiable nasal swab samples (including Baseline), and have been dosed with IMP. The primary efficacy analysis in time-weighted average change of RSV log_{10} viral load from Day 1 through Day 5 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 of viral load, a parametric analysis of covariance (ANCOVA) model with corresponding baseline viral load and stratification factor as covariates will be used, at a 2-sided 0.05 level. Adjusted means and 95% confidence intervals (CIs) will be presented. The evaluable 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. Time-weighted average change in the FLU-PRO score from Baseline to Day 5 will be analyzed using an ANCOVA model with Baseline FLU-PRO score and the stratification factor as covariates. Adjusted means and 95% CI will be presented for this analysis. Duration of hospital stay following IMP administration will be analyzed using an ANCOVA model with treatment as a fixed effect and stratification factor as a covariate. Adjusted means and 95% CIs will be presented for this analysis. The rate of unplanned medical encounters related to a respiratory illness after initial hospital discharge through Day 28 will be analyzed using a Negative binomial regression method with an offset parameter to account for follow-up time. PPD

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.

Evaluable subjects for PK analysis will include those who are RSV-positive by local assay and dosed with 200 mg of IMP. 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 (Days 1, 3, and 5). Descriptive statistics (n, mean, standard deviation, %CV, median, and range) will be calculated for each sampling time. Plasma concentrations of presatovir over time will be plotted in semi-logarithmic and linear formats as mean ± SD. 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 subjects who received placebo in the GS-US-218-0103 study. The sample size calculation assumes time-weighted average change in $\log_{10}$ viral load from Baseline (Day 1) to Day 5 in the placebo group will be -2.9 $\log_{10}$ copies/ml with a corresponding standard deviation (SD) of 2.3 and that 85% of the subjects will be evaluable. Based on these assumptions, with 85 subjects per group there is approximately 80% power to detect a 1 $\log_{10}$ reduction in time-weighted average change in viral load 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.

Two interim futility analyses of the primary endpoint, time-weighted average change in $\log_{10}$ viral load from Day 1 through Day 5, may be conducted after approximately 25% (n of ~50) and 50% (n of ~100) of the enrollment has been achieved. The results from these interim analyses will be reviewed by the DMC, who may recommend early termination for futility if the conditional power is < 20%. If the DMC recommends early termination for futility, Gilead personnel who are not involved with the study may perform an unblinded review of the interim data, and

the decision may be made to stop the study and unblind treatment assignments. Gilead retains final decision-making authority on all aspects of the study. Further details of the interim analysis and assessment of futility will be described in the SAP, including the computation methods of conditional power such as those proposed by Lachin, 2005 {26904}.

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
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AhR	aryl hydrocarbon
AIDS	auto-immune deficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BID	twice a day
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CC_{50}	50% cytotoxic concentration
CCM	cell culture medium
CFS	Clinical Frailty Scale
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CONMED	concomitant medication
COPD	chronic obstructive pulmonary disease
CRF	case report form(s)
CRO	contract (or clinical) research organization
CTA	clinical trial application
CYP	cytochrome P450 enzyme
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)
ELF	epithelial lining fluid
EMR	electronic medical records

EOS	end of study
ET	early termination
EQ5D-5L	European Quality of Life 5-Dimension utility measure
EU	European Union
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.
h	hour
HAE	human airway epithelial (cells)
Hb	hemoglobin
HCV	hepatitis C virus
Hct	hematocrit
HDPE	high-density polyethylene
HED	human equivalent dose
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HLGT	high level group term
HIV-1	human immunodeficiency virus type 1
HLT	high level term
HPMC	hydroxypropyl methyl cellulose
HRV-10	human rhinovirus serotype 10
IB	Investigator's Brochure
IC_{50}	concentration of drug to reach 50% inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	identification
IEC	independent ethics committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IP	intraperitoneal
IQ	Inhibitory Quotient ratio, calculated as C_{min} plasma concentration/$paEC_{50}$ for presatovir
IRB	institutional review board
ITT	intent-to-treat (analysis or subset)

IV	intravenous
IVRS	interactive voice response system
kg	kilogram
LLN	lower limit of the normal range
LLT	lower level term
m	meter
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MF	male and female combined data
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters mercury
MMRM	mixed-effect model repeated measures
NA	not analyzed
NADPH	nicotinamide adenine dinucleotide phosphate
ND	not detectable
NDA	New Drug Application
nM	nanomolar
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
O_2	oxygen
PEG	polyethylene glycol
PFUe	plaque forming unite equivalents
PK	pharmacokinetic
PND	post-natal day
PO	oral administration (per os, by mouth)
PR	pulse rate
PT	preferred term
PXR	pregnane x receptor
Q1	first quartile
Q3	second quartile
QA	quality assurance
QRS	part of electrocardiographic wave representing ventricular depolarization
RT-qPCR	quantitative real time polymerase chain reaction
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
RO	reverse osmosis

RR	interval between the peak of R waves of 2 consecutive ECG complexes
RSV	Respiratory Syncytial Virus
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SEM	standard error of the mean
SI	selectivity index
SOC	standard of care
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBD	to be determined
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, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of the normal range
US	United States
UV	ultraviolet
VS	vital signs
V_{ss}	apparent volume of distribution at steady state
v/v	volume/volume
WBC	white blood cell count
w/v	weight/volume

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. Respiratory syncytial virus encodes for 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.

RSV 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 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. Among adults, the 2 populations that are at higher risk for RSV infection are the immunocompromised and the elderly. Immunocompromised patients are most commonly represented by those who have received either a bone marrow transplant (BMT) or lung transplant {20233}. RSV is a significant cause of morbidity and mortality in the BMT population, with a reported incidence that ranges from 2% to 17% {26908}. Infection can proceed from the upper to the lower respiratory tract in up to 84% of RSV-infected patients, and the associated mortality rate may be as high as 100% {26908}. In lung transplant populations, it is estimated that approximately ~10% of these patients are diagnosed with an RSV infection each year {20903}. In this population, RSV infection has been associated with development of host versus graft disease, also known as bronchiolitis obliterans syndrome (BOS), which is the most common cause of death after lung transplantation {20903}.

Recently, RSV infection is becoming more recognized in the elderly population {20217}, {20216}. Falsey et al estimates that RSV is responsible for approximately 180,000 admissions each year among the elderly accounting for 10.6%, 11.4%, 5.4% and 7.2% of hospitalizations for pneumonia, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and asthma respectively {20216}. Subsequent epidemiologic data from multiple studies suggest that among all elderly, the prevalence of RSV is likely 7-10% {26905}, {26903}, {26901}, {26906}, {26907}, {26909}, {26908}. The mortality rate is estimated to be 10%, but increases to 40% to50% in patients requiring mechanical ventilation {26902}.

RSV replicates effectively in the upper and lower respiratory tract and can cause respiratory symptoms directly, by damaging the integrity of the small airway epithelium, and indirectly, by inducing strong immune responses in lungs that lead to airway obstruction {20224}. Although the relationship between nasal viral load and clinical disease severity has not been fully explained, there is evidence that higher viral loads are associated with more severe clinical disease in both children and adults. For instance, children up to 36 months of age have nearly 2000-fold higher viral loads in the nasal secretions than adults with COPD hospitalized for RSV-related exacerbations {20210}. Hospitalized children with lower respiratory tract RSV infection have higher nasal viral loads than age-matched controls with less severe disease {20215}, {20213}, {20212}. Among adults, inpatients tend to have higher viral loads than outpatients, and among inpatients, a higher viral load is associated with the development of respiratory failure requiring mechanical ventilation and observed among intensive care unit patients {20214}, {26902}. Higher viral loads may contribute to the severity of disease by causing direct damage to the airway epithelium. A post-mortem study of infants who died of RSV infection revealed that while there was evidence of inflammatory infiltrates centered on bronchial and pulmonary arterioles (ie, T-cells, monocytes, neutrophils), the most prominent feature in all of the cases was airway obstruction attributed to epithelial and inflammatory cell debris, mixed with fibrin, mucus, and edema, suggesting that direct viral cytopathic effect in respiratory epithelium, in conjunction with the host inflammatory response, may contribute to the pathogenesis and severity of RSV infections {20221}.

Currently there are no effective approved prophylactic or therapeutic treatment options for the adult population. Once hospitalized, treatment for RSV infection in adults is supportive, with intravenous hydration, supplemental oxygen, and mechanical ventilation. An RSV vaccine is not available. The only approved antiviral treatment for RSV in pediatric population is Virazole® (ribavirin), an inhaled agent that 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}. Synagis® (palivizumab), a monoclonal antibody against RSV approved for prophylaxis against RSV infection among high risk infants, has been shown to reduce the risk of hospitalization and “medically attended lower respiratory tract infections” {20061}. However, this injectable treatment has only been shown to be cost effective for the prevention of RSV infection in the premature infant population {20232}.

1.2. Presatovir (GS-5806)

1.2.1. General Information

Presatovir is an orally administered 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 pharmacokinetic (PK) volume of distribution (V_{ss}) in all nonclinical species tested was 2- to 10-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.

Four week toxicology studies in 2 species (rat and dog) were conducted. The no-observed-adverse-effect-level (NOAEL) of 70 mg/kg/day in the 4-week rat study and 20 mg/kg/day in the 4-week dog study provided a 1x safety margin based on the exposure levels determined in the Phase 1 study (GS-US-218-0101) at 300 mg presatovir (AUC_{inf} 110,000 ng.hr/mL)

For further information on presatovir, refer to the Investigator's Brochure (IB) for presatovir.

1.2.2. Preclinical Pharmacology and Toxicology

Presatovir was evaluated for the potential to bind physiologically relevant human receptors and ion channels using a radio ligand binding assay. The results showed that, at concentrations up to 10 μM, presatovir did not bind to any of the 68 mammalian ion channels and receptors tested.

Presatovir was studied in a battery of safety pharmacology studies. In a test assessing neurological function, the no-observed-effect-level (NOEL) in rats was 375 mg/kg, the highest dose tested, and in a study of respiratory function, the NOEL in rats was 375 mg/kg, the highest dose tested.

The IC_{50} for the inhibitory effect of presatovir on hERG potassium current was 7.8 μM (Hill coefficient=1.2). Potential cardiovascular effects of presatovir were evaluated in telemetry-instrumented male Beagle dogs at dose levels of 10, 20, and 75 mg/kg. The principal hemodynamic findings were lower heart rate values (−8% at 10 mg/kg, −12% at 20 mg/kg, and −18% at 75 mg/kg) and higher arterial pulse pressure (up to 15%) and systolic pressure values (up to 11%) in dogs administered 20 or 75 mg/kg. 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. Presatovir-related higher PR and QTc interval values (+6% and +3%, respectively) in dogs receiving 75 mg/kg were expected physiological responses secondary to concomitant presatovir-related lower heart rate values. Due to the short duration, reversibility, and dose dependent pattern of small magnitude, these changes were not considered physiologically important in the context of this study.

In a preclinical study, presatovir was administered by oral gavage for 4 weeks to rats once daily at doses of 10, 30, 70, or 100 mg/kg/day. One toxicokinetic group male administered 100 mg/kg/day was found dead on Day 14 of the dosing phase and 1 toxicity group female administered 100 mg/kg/day was found dead on Day 26 of the dosing phase. Although the cause of death for these 2 animals was undetermined, an association with presatovir cannot be excluded. Presatovir administration was associated with minor decreases in body weight gain and food consumption at doses of ≥ 70 mg/kg/day. Minor, nonadverse, reversible

presatovir-related effects on clinical pathology parameters were generally limited to animals administered ≥ 70 mg/kg/day and did not indicate specific target organ toxicity. No presatovir related clinical pathology effects were observed following the 4-week recovery period. At the terminal sacrifice, a presatovir-related microscopic finding of dose dependent, minimal to moderate infiltration of vacuolated macrophages in the lungs of males administered 100 mg/kg/day and females administered ≥ 30 mg/kg/day was observed. At the recovery sacrifice, this finding was seen in three control group animals, but was not observed in presatovir treated animals. Because the lung finding was generally present at minimal to slight severity in presatovir-treated rats at terminal sacrifice as well as in control animals at the recovery necropsy with no evidence of inflammation or fibrosis, it was considered nonadverse. 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 (males and females combined).

Presatovir was administered by oral gavage for 4 weeks to dogs in a GLP-compliant study once daily at doses of 2, 10, or 20 mg/kg/day. Presatovir-related effects were limited to dose dependent increased incidence of emesis, decreased body weight gain, and decreased food consumption. On Day 28, mean heart rate decreases (−20.6%) and mean QT interval increases (+15.3%) for females administered 20 mg/kg/day were observed when compared to the control group. The significant changes in the QT interval were considered unimportant because mean QTc values were not different from the control group at the same time point. No toxicologically important changes were observed in clinical pathology parameters in animals at any dose level. At terminal sacrifice, an increased incidence of minimally increased germinal center tangible-body macrophages was noted in lymph nodes in males administered ≥ 10 mg/kg/day and in females administered 20 mg/kg/day. This finding was considered an exacerbation of a common background finding, and no presatovir-related microscopic observations were noted at the recovery sacrifice. Based on the results of this study, the NOAEL for presatovir administered once daily by oral gavage for 4 weeks to dogs 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 (males and females combined).

Presatovir was negative in the rat micronucleus study at oral doses up to 2000 mg/kg (AUC_{0-t} = 342,413 ng.h/mL) 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 study in time-mated rats, presatovir (GS-5806-02) administered by oral gavage 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. Therefore, the NOAEL for maternal toxicity was 70 mg/kg/day. With the exception of slightly lower fetal adjusted body weight at 100 mg/kg/day, presatovir (GS-5806-02) had no effects on any of the embryo/fetal developmental parameters. No fetal anomalies were related to presatovir (GS-5806-02) administration and the NOEL for developmental toxicity in rats was 100 mg/kg/day.

In a definitive embryo-fetal developmental study in time-mated rabbits, presatovir (GS-5806-02) administered by gavage resulted in significant reductions in mean maternal body weight gain and food consumption at 50 mg/kg/day. Therefore, the NOAEL for maternal toxicity was 30 mg/kg/day. There were no presatovir (GS-5806-02) related effects on embryo/fetal viability and growth and no fetal anomalies. The NOEL for developmental toxicity is 50 mg/kg/day.

Additional details regarding nonclinical pharmacology and toxicology can be found in the GS-5806 IB.

1.2.3. Clinical Trials of Presatovir

1.2.3.1. 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 totalstaggered cohorts (7 pre-specified, 1 adaptive). Within each cohort of Parts A and B, 8 unique subjects were randomized to receive blinded 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). Details of the IMP regimens for each cohort were as follows:

Part A (Single and Multiple Dosing; Pre-specified Cohorts)

- Cohort 1 – 25 mg presatovir or placebo (Day 1) followed by 25 mg presatovir or placebo BID (Days 15-21; 6 presatovir subjects, 2 placebo subjects [Day 1 fasted, Day 15 fed, Days 16-21 fasted])

- Cohort 2 – 75 mg presatovir or placebo (Day 1) followed by 75 mg presatovir or placebo once daily (Days 15-21; 6 presatovir subjects, 2 placebo subjects [Day 1 fasted, Day 15 fed, Days 16-21 fasted])

- Cohort 3 – 150 mg presatovir or placebo (Day 1) followed by 25 mg presatovir or placebo once daily (Days 15-21; 6 presatovir subjects, 2 placebo subjects [Day 1 fasted, Day 15 fed, Days 16-21 fasted])

Part B (Single and Multiple Dosing; Adaptive and Pre-specified Cohorts)

- Cohort 4 – 300 mg presatovir or placebo (Day 1) followed by 10 mg presatovir or placebo once daily (Days 15-21; 6 presatovir subjects, 2 placebo subjects [Day 1 fasted, Day 15 fed, Days 16-21 fasted])

- Cohort 5 – 50 mg presatovir or placebo (Day 1) followed by 25 mg presatovir or placebo once daily (Days 2-7; 6 presatovir subjects, 2 placebo subjects [Days 1-7 fasted])

Part C (Multiple Dosing; Pre-specified Cohorts)

- Cohort 6a – 50 mg presatovir or placebo (Day 1) followed by 25 mg presatovir or placebo once daily (Days 2-7; 8 GS 5806 subjects, 2 placebo subjects [Days 1-7 fed])

- Cohort 6b – 75 mg presatovir or placebo once daily (Days 1-7 [fasted]; 8 presatovir subjects, 2 placebo subjects)

- Cohort 6c – 75 mg presatovir or placebo once daily (Days 1-7 [fed]; 8 presatovir subjects, 2 placebo subjects)

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.

Graphs of plasma concentration-time profiles after administration of a single dose of presatovir (25, 75, 150, or 300 mg) to healthy adult subjects under fasted conditions in Cohorts 1 to 4 demonstrated overall, that the terminal phases for all 4 doses were parallel. The plasma concentrations increased in a dose-proportional manner following single oral administrations at doses ranging from 25 to 300 mg under fasted conditions.

1.2.3.2. 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, target 50-mg (approximately 100-µCi) oral dose of [14C]- presatovir, maximum mean concentrations of drug-derived radioactivity in blood and plasma were observed at 2 hours postdose for both matrices. Levels of

radioactivity in blood and plasma fell below the limit of quantitation for the majority of subjects (n=6) by 120 to 168 hours postdose. Mean blood to plasma concentration ratios ranged from 0.450 to 0.591 through 120 hours postdose, indicating low association of radioactivity with blood cells.

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

The major route of elimination of radioactivity in humans was via feces (~70%), with a major component excreted as unchanged parent presatovir (18.5%; co-eluted with dioxy-presatovir-2 (M63)), along with other minor metabolites (dioxy-presatovir-3 (M64; 5.42%) and dioxy-GS-557855-2 (M70; 3.51%).

Renal elimination was a minor route in humans (~15% of the dose; unchanged parent presatovir ~ 10.0% of the dose; M47 ~3.59% of the dose).

In summary, [^{14}C]-presatovir was extensively metabolized by humans after oral administration. Metabolites were formed through oxidation, deamination, *N*-dealkylation, *N*-acetylation, hydration, and glucuronidation pathways. These results indicate that presatovir was metabolized via multiple metabolic pathways, and eliminated as a combination of metabolites and unchanged parent drug in humans.

1.2.3.3. 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. 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 log10 PFUe*hour/ml, p=<0.001).

- Treatment with presatovir resulted in lower mean total mucus weight during dosing. 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. 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 safety signals were observed across all dose cohorts. In the presatovir pre-specified treatment group, a similar percent of subjects (64%) reported at least 1 AE compared to placebo (56%) with no reported SAEs. The percent of subjects who reported at least 1 drug-related AE was also similar in this presatovir treatment group (20.5%) compared to the placebo group (25.6%). No marked laboratory abnormalities and no clinically relevant ECG values were observed in the presatovir treatment group. A ≥15% change in creatinine clearance was observed in 12.8% of presatovir subjects and 20.5% of placebo subjects.

1.2.3.4. Ongoing Studies

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

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

Study GS-US-218-1797 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.

Please refer to the Investigator's Brochure for additional information regarding ongoing clinical trials.

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, ribavarin, is approved for use in pediatric populations, 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 adults, 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, a single dose of 100 mg 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 antiviral effect of presatovir in adults in a natural infection setting. Efficacy data generated from this study, taken together with currently available safety and efficacy 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 dosing schedule selected for this study is a single dose of 200 mg presatovir administered orally in the fasted state at Visit 2. This regimen was selected based upon 3 main factors: the observed PK profile of presatovir from Studies GS-US-218-0101 and GS-US-218-0103, low/modest food-effect noted in GS-US-218-0101, and the antiviral effect observed with different doses/regimens in GS-US-218-0103.

In 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 significant viral load reduction. 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 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 concentrations ~4-5 fold of $paEC_{95}$ at 120 hours following first dose for the virus used in the challenge study, the M37 strain of RSV.

In selecting the dose for the current study, we took into consideration that presatovir has a half-life of approximately 30 hours and the fact that the $paEC_{95}$ for the wild-type RSV strains is much lower than for the M37 strain; in vitro virological studies of 73 clinical isolates found that the $paEC_{95}$ for the wild-type RSV strains is approximately 25 ng/mL. Based on the PK properties of presatovir, a single dose of 200 mg will achieve a presatovir concentration of > 3- to 5-fold $paEC_{95}$ for wild-type RSV strains through Day 5 post dose, which translates to approximately 8-9 days after symptom onset, assuming most patients present to the hospital 3-4 days after onset of symptoms. We expect this dose to demonstrate significant anti-viral 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 effects of presatovir on RSV viral load in RSV-positive adults hospitalized with acute respiratory infectious symptoms.

The secondary objectives of this study are to evaluate:

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

3. STUDY DESIGN

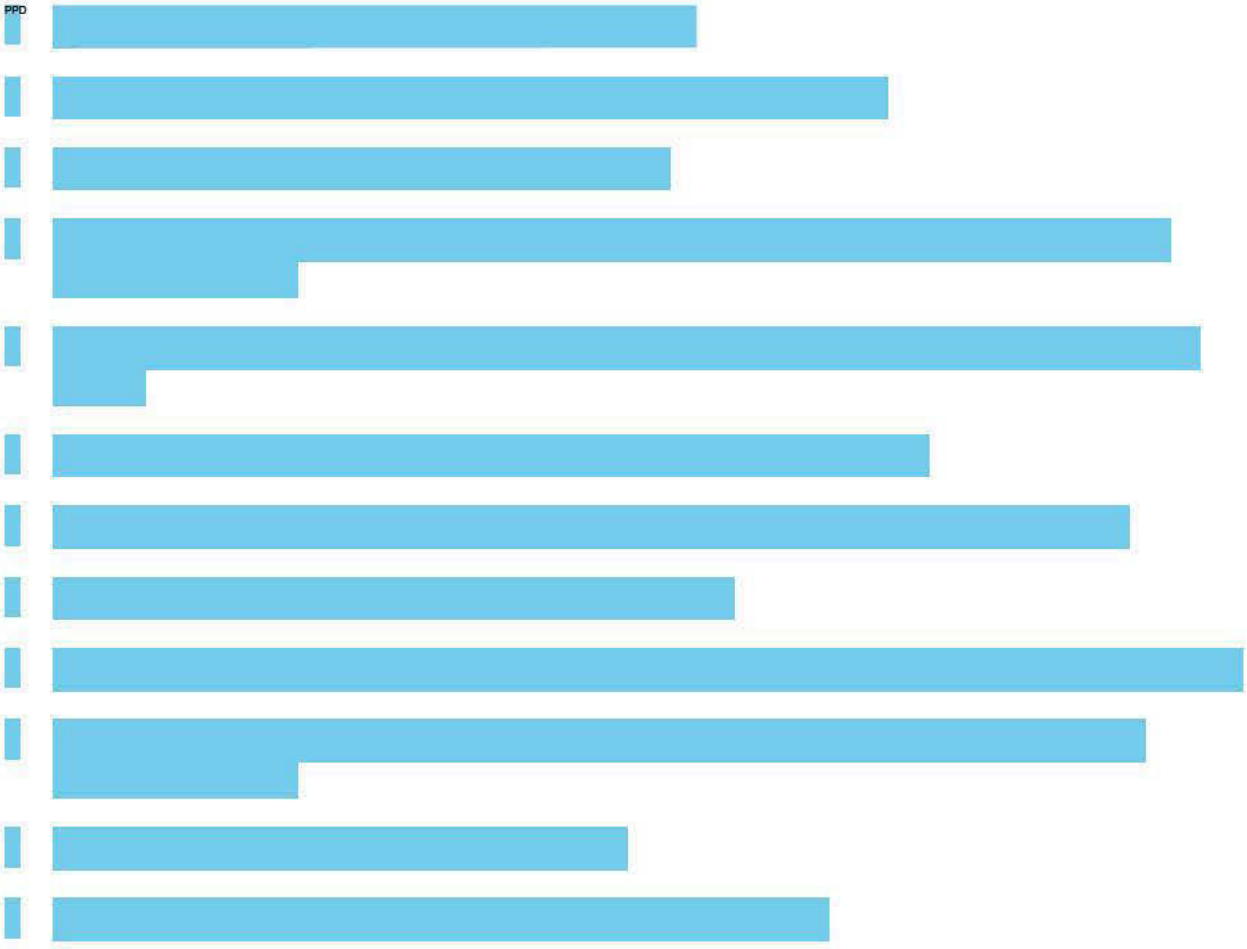
3.1. Endpoints

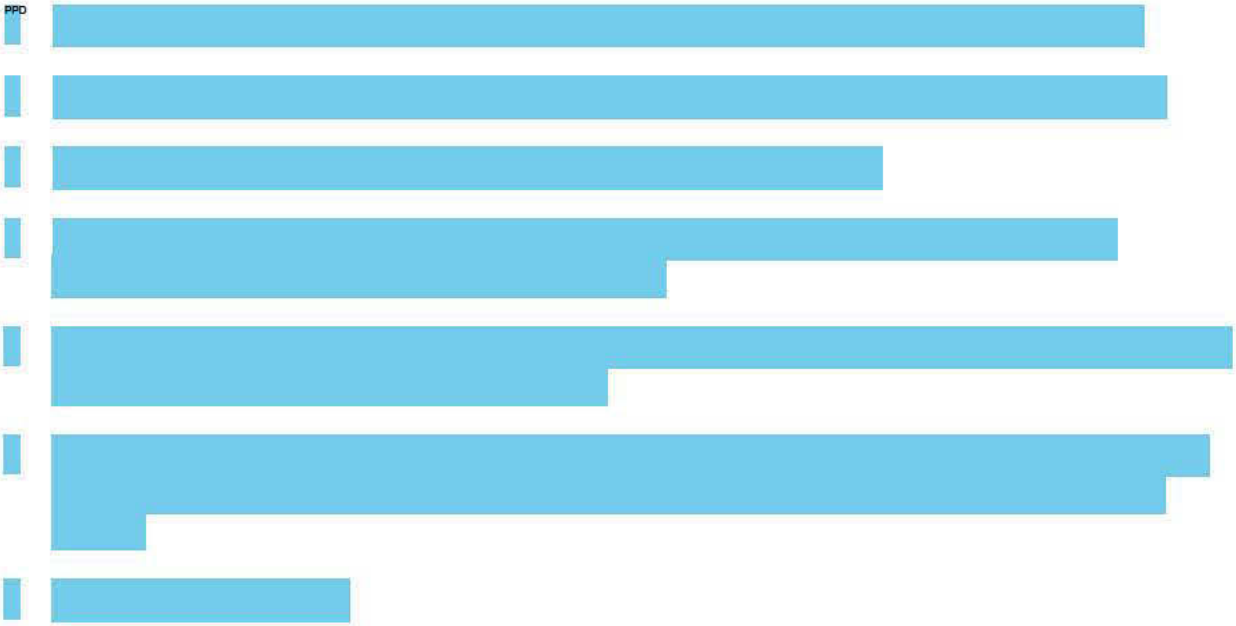
The primary endpoint is the time-weighted average change in $\log_{10}$ viral load from Baseline (Day 1) to Day 5.

The key secondary endpoints are:

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

Exploratory endpoints include:





3.2. Study Design

This is a randomized, double-blind, placebo-controlled multi-center study to be conducted at approximately 70 centers in Australia, Canada, Europe, Hong Kong, Israel, New Zealand, South Korea, and the United States.

The study will enroll 200 hospitalized subjects ≥ 18 years of age with new onset of acute respiratory symptoms or acute worsening of chronic respiratory symptoms related to ongoing respiratory disease. Eligible subjects will be randomized in a 1:1 ratio to receive presatovir or placebo-to-match administered one time as a 200 mg dose at Baseline/Day 1.

Subjects will be stratified as specified in the Statistical Analysis section into one of the following categories:

1) No chronic airways or lung disease

2) COPD

3) Asthma

4) 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. After dosing, subjects will be followed for a total of 28 days, during which a total of 7 study visits will be performed to assess safety, tolerability, PK, RSV viral loads, and other exploratory end points. Subjects will receive a Supplemental Oxygen Use Diary to record their daily oxygen use while on the study, and to record historical oxygen use information as per Section 6.12.8. Safety assessments will include

cardiac monitoring via a pre-dose ECG at Baseline/Day, followed by a post-dose ECG 2 hours ± 30 minutes after dosing. A third and final ECG will be obtained on Day 14. All subjects will undergo local laboratory analysis of pre- and post-dose troponin levels at Baseline/Day 1, followed by local laboratory analysis of troponin on Day 14. Any other troponin result obtained using the site's local laboratory will also be collected.

During the 28-day study period (Baseline through Day 28/End of Study), the results of all cardiac-related tests performed as standard medical care or concurrent to AE/SAE evaluation and follow-up will be collected. These tests will include, but are not limited to, the ECG tracings and results report for any ECG performed outside of the study specific ECG, results of cardiac enzyme testing (eg all troponin results, CK-MB, etc), and any results from stress testing, echocardiographic imaging (resting and stress testing), cardiac perfusions scans, and cardiac MRIs.

Assessment of AEs, SAEs, and concomitant medications will occur continuously throughout the study, from the time of subject consent at Screening (post-consent) through Day 28. AEs and SAEs reporting and follow up will occur as per Section 7 Adverse Events and Toxicity Management.

After approximately 50, 100, and 150 subjects have enrolled, a DMC will meet to review accumulated data and may make recommendations regarding the study conduct. DMC will review unblinded safety data (AEs, VS, safety laboratory results, etc) from all available subjects. Interim futility analyses of the primary endpoint will also be assessed after approximately 50 and 100 subjects have enrolled.

3.3. Study Treatments

Approximately 200 subjects will be randomized 1:1 to receive presatovir or placebo as a single 200 mg dose (four 50 mg tablets) on Day 1. All IMP will be administered orally with water. Tablets are not to be crushed, split, dissolved, or chewed. The entire dose must be taken within 1 hour. Subjects should not be discharged until 30 minutes after dosing.

Presatovir or placebo will be provided as white, plain-faced, film-coated, round tablets containing 50 mg presatovir (61 mg presatovir-02, bis-hydrochloride salt dihydrate form of presatovir).

Presatovir tablets and matching placebo will be 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.

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 1 day, with the only dose administered at the Day 1 visit.

3.5. End of Study

For each subject, end of study occurs when the subject has completed their Day 28 visit.

3.6. Post Study Care

RSV is a transient infectious disease. Presatovir will not be made available to subjects who have completed the study. Subjects will be able to pursue standard of care treatment after study completion.

3.7. 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.

3.8. Biomarker Testing

3.8.1. Biomarker Samples to Address the Study Objectives

Nasal swab samples collected for RSV testing may be used for detection of other respiratory pathogens that may be the cause of infection. All swab samples will be retained for biomarker testing and/or viral analysis.

Blood for biomarkers will be collected on Day 1 (pre-dose) and Day 5. Biomarkers of inflammation and host response (including but not limited to IP-10, CRP, and procalcitonin) may be measured. Serum antibody titers to RSV will be collected on Day 1 (pre-dose) and Day 14 to measure host-response and susceptibility to RSV infection.

3.8.2. Biomarker Samples for Optional Future Research

PPD


PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Subject population will consist of approximately 200 RSV-positive adult subjects from approximately 70 centers in Australia, Canada, Europe, Hong Kong, Israel, New Zealand, South Korea, and the United States.

4.2. Inclusion Criteria

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

- An informed consent document signed and dated by the subject or a legal guardian of the subject and Investigator or his/her designee
- Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5.
- 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.
- All subjects must refrain from blood donation while enrolled in the study and for 30 days after the last dose of IMP.
- ≥ 18 years of age at Screening
- Willing to adhere to protocol specific requirements for contraception
- Subject is a current inpatient
- New onset of acute respiratory infectious symptoms, or acute worsening of chronic symptoms related to ongoing respiratory disease for ≤ 5 days prior to screening:
  - Upper respiratory tract symptoms: Nasal congestion, runny nose, sore throat, or earache
  - Lower respiratory tract symptoms: Cough, sputum production, wheezing, dyspnea, or chest tightness
- Willingness to perform necessary study procedures and have available a working telephone or email
- Documented to be RSV-positive as per protocol Section 6.1.1

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:

- Use of any investigational medicinal product in the 28 days prior to screening, **OR** use of any investigational monoclonal antibody within 4 months or 5 half-lives of screening, whichever is longer, **OR** use of any investigational RSV vaccine ever

- Chronic use (> 28 days of use) of systemic immunosuppressive agents (i.e. alkylating agents, calcineurin inhibitors, immunophilin-binding but not a calcineurin inhibitor, antimetabolites, polyclonal antibodies, monoclonal antibodies) during the 28 days prior to Screening, or anticipated use during the 28 days following Screening

- Use of oral prednisone or other corticosteroid equivalent to:

  — > 20 mg/day for > 14 days prior to screening is not permitted.

  — > 20 mg/day for ≤ 14 days, including corticosteroids received during current hospitalization (ie, bolus doses), is permitted.

  — ≤ 20 mg/day, regardless of duration, is permitted.

- Subjects taking a moderate or strong cytochrome P450 (CYP) enzyme 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:

- Pregnant, breastfeeding, or lactating females

- Subjects requiring > 50% supplemental oxygen (while the subject is awake) at Screening

- Subjects with a CFS > 7 at Baseline

- Known significant abnormality altering the anatomy of the nose or nasopharynx that in, the opinion of the investigator, will preclude obtaining adequate nasal swab sampling in either nasal passage

- Waiting for or recently (within the past 12 months) received a bone marrow, stem cell, or solid organ transplant, or who have received radiation or chemotherapy within 12 months prior to screening

- Subjects with HIV/AIDS and a known CD4 count < 200 cells/μL

- History of severe dementia or Alzheimer's disease
- History of drug and/or alcohol abuse that, in the opinion of the investigator, may prevent adherence to study activities

Related to medical condition:

- Influenza-positive as determined by local diagnostic test
- Known MERS-CoV infection or known coinfection with other coronavirus
- Use of mechanical ventilation during the current admission, not including noninvasive ventilation
- Clinically significant bacteremia or fungemia that has not been adequately treated prior to Screening, as determined by the investigator
- Inadequate treatment of confirmed bacterial, fungal, or non-RSV pneumonia, as determined by the investigator
- Excessive nausea/vomiting at admission, as determined by the investigator, that precludes administration of an orally administered IMP
- Subjects with an unstable medical condition, as determined by the investigator, that precludes participation in the study

Related to allergies:

- Known allergy to components of the IMP (microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc).
- Documented history of acute (anaphylaxis) or delayed (Stevens-Johnson syndrome or epidermal necrolysis) allergy to sulfa drugs

Related to laboratory results at Screening:

- Serum creatinine clearance < 40 ml/min
- AST and ALT > 2 × ULN
- Total bilirubin > 2 × ULN
- Hemoglobin (Hb) < 8 g/dL
- WBC < 2000 cells/μL
- Neutrophil count < 1500 cells/μL
- Platelet count of < 50,000 cells/μL

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: No chronic airways or lung disease, COPD, asthma, or other chronic airways or lung disease. Stratification factors (i.e. diagnosis of asthma, COPD, or other chronic airways or lung disease) will be determined by the investigator. Subjects will be randomized in a 1:1 ratio to receive a single dose of presatovir or matching placebo.

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

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain the treatment assignment for that subject. 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.

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, a deviation will be recorded. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

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

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

5.2.1. Formulation

Presatovir will be supplied as white, plain-faced, film-coated, round tablets containing 50 mg presatovir (61 mg presatovir, 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 study drugs distributed to investigative sites in the USA 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 Materials & Logistics (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). The study center will be required to maintain a log of daily temperature readings in the storage area for the duration of the study. To ensure the stability and proper identification, the drug products will be stored in the containers in which they were supplied until unit dosed for 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 Day 1. All IMP will be administered orally with water. Tablets are not to be crushed, split, dissolved, or chewed. The entire dose must be taken within 1 hour. Subjects should not be discharged until 30 minutes after dosing. IMP is to be handled with gloves.

5.4. Prior and Concomitant Medications

Strong and moderate inducers of CYP enzymes may reduce the exposure of presatovir. Pharmacokinetic (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 moderate or strong 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. CYP3A inhibitors may increase the plasma exposures of presatovir. A clinical drug-drug interaction study to evaluate the effect of CYP3A inhibitors on presatovir PK is ongoing.

Cyclosporine, a weak CYP3A inhibitor and a potent inhibitor of efflux transporters (P glycoprotein [P-gp], breast cancer resistant protein [BCRP]) and the hepatic uptake organic anion transporter proteins (OATP1B1 and OATP1B3), has been associated with a mild increase in presatovir plasma exposure (10.6% increase in Cmax and 26.1% increase in AUCinf). Thus

presatovir can be coadministered with inhibitors of P-gp, BCRP, OATP 1B1, or OTAP1B3 without dose modification. The effect of co-administration with strong and moderate CYP3A inhibitors on presatovir PK is currently being investigated in a clinical drug-drug interaction study.

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

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

In addition to moderate and strong CYP450 inducers, subjects shall not have received any of the following prior medications:

- Any investigational medicinal product in the 28 days prior to screening
- Any investigational monoclonal antibody within 4 months or 5 half-lives of screening (whichever is longer)
- Any investigational RSV vaccine(s) at any time in the past

The following concomitant medications are also prohibited:

- Chronic use (> 28 days of use) of systemic immunosuppressive agents (ie, alkylating agents, calcineurin inhibitors, immunophilin-binding but not a calcineurin inhibitor, antimetabolites, polyclonal antibodies, monoclonal antibodies) during the 28 days prior to Screening, or use is anticipated during the 28 days after Screening
- Use of oral prednisone or other corticosteroid equivalent to:
  - — > 20 mg/day for > 14 days prior to screening is not permitted.
  - — > 20 mg/day for ≤ 14 days, including corticosteroids received during current hospitalization (ie, bolus doses), is permitted.
  - — ≤ 20 mg/day, regardless of duration, is permitted.

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 received and quantity of IMP bottles.
- Record the date, subject number, subject initials, the IMP bottle number dispensed.
- Record the date, quantity of used and unused IMP 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

All study procedures to be completed for each subject enrolled in the study will be performed as summarized in the Schedule of Assessments (Appendix 2) and described in the following text. 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. Screening Visit (Day −1)

Screening (Day −1) is a mandatory inpatient hospital visit.

Screening is defined as the day the subject signs their first consent form (RSV Testing Consent or Main Study Consent). In all cases, Screening must happen no later than Day 5 of the subject's symptoms.

Subjects will be screened prior to randomization to determine eligibility for participation in the study. There may be a 2-part consenting process for this study, depending on the subject's RSV status at the time of hospitalization.

If a subject's RSV status is unknown at the time of hospitalization, the subject will first sign the RSV Test Consent. These subjects will be tested for RSV. Influenza or other respiratory pathogen testing may also occur at this time. Subjects who test positive for RSV will be further consented to the treatment portion of the study via the Main Study Consent. These subjects must be randomized within 28 hours of signing the RSV Test Consent.

If a subject is known to be RSV positive at the time of Screening (based on standard of care test result) subjects only need to provide consent for the treatment portion of the study via the Main Study Consent. These subjects must be randomized within 72 hours of receiving RSV positive test results, and within 28 hours of signing the Main Study Consent.

No procedures may be performed prior to obtaining written informed consent. All screening labs and procedures will be performed locally and results will be reviewed by the investigator.

RSV Test Consent: Subjects with unknown RSV status at the time of Screening will be approached for informed consent for RSV testing. The following procedures will be performed and documented under this consent:

- Obtain written informed consent for RSV, influenza, and other respiratory pathogen testing
- Collect demographic information

- Perform RSV, influenza, and other respiratory pathogen testing, as needed, per local laboratory methods
- Record any SAEs that occur after consent, and any procedure-related AEs

Main Study Consent: RSV-positive subjects will be approached to consent for any remaining screening procedures and the treatment phase of the study.

- Obtain written informed consent for the treatment portion of the study
- Collect demographic information (if not previously collected)
- Complete remaining Screening procedures:
  - Vital signs including O2 saturation
  - Local hematology assessment (to include WBC with differential, Hgb, neutrophils, and platelets)
  - Local serum chemistry (to include BUN, creatinine, AST, ALT, and total bilirubin)
  - Urine pregnancy test in women unable to confirm menopause, hysterectomy and/or bilateral oophorectomy
- Review of all concomitant medications and adverse events
- Review inclusion and exclusion criteria

Should the following procedures be performed as part of standard of care and within 72 hours of Screening, these historic results may be used to support subject eligibility or baseline status:

- RSV-testing
- Influenza-testing
- Chest X-Ray/CT scan
- Hematology and serum chemistry blood tests (to include WBC with differential, Hgb, neutrophils, platelets, BUN, creatinine, AST, ALT, and total bilirubin)
- Arterial blood pH results (if obtained within 24 hours of Screening)
- Urine pregnancy test, as applicable
- Height and weight

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomized into the study. Under the following conditions, Screening and Baseline (Day 1) may occur on the same day:

- Qualitative RSV test results are available on the same day as testing, or positive RSV results are available from the current admission
- All other required lab results and procedures are available and satisfy the inclusion/exclusion criteria

From the time of consent through the first administration of IMP, record all SAEs, as well as any procedure-related AEs, and all concomitant medications in the subject source and in the electronic case report form (eCRF). See Section 7 Adverse Events and Toxicity Management for additional details.

6.1.2. Baseline Assessments (Day 1)

Baseline (Day 1) will occur within 28 hours of completion of the Screening (Day −1) visit. This visit is a mandatory inpatient hospital visit. The following procedures will be performed and documented on Day 1:

- Questionnaire assessment, prior to all other study procedures:
  - Clinical Frailty Score
  - FLU-PRO
  - EQ5D-5L
- Collection of medical history, including:
  - Evaluation of presence or absence of pleural effusion, if chest X-ray/CT scan was performed during the initial hospitalization
  - Arterial blood pH, if results are available from the initial hospitalization and within 24 hours of Screening
- Height and weight (may use height and weight from admission records)
- Collection of 1 nasal swab sample for viral load analysis at the central lab
- Collection of 1 nasal swab (opposite naris) for viral coinfection testing at the central lab
- Pre-dose blood sample collection for central laboratory analysis:
  - Hematology
  - Serum Chemistry

- Troponin analyzed locally
- Biomarker
- Serum antibody titer to RSV

- Pre-dose ECG
- Oxygen saturation on room air (pre-dose only)
- Vital signs collected 5 to 10 minutes pre-dose
- Randomization as per Section 6.2
- IMP administration

  Note: Subjects may be discharged 30 minutes after dosing, however, they are still required to complete all post-dose study procedures.

- Vital signs (heart rate and blood pressure only) collected 15 and 30 minutes post-dose
- Troponin sampling and PK sampling 2 hours ± 30 minutes post-dose
- ECG 2 hours ± 30 minutes post-dose
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)
- Assessment of AEs and concomitant medications 6.12.10

6.2. Randomization and Treatment Assessments

Randomization to presatovir or placebo will be based on a randomization schedule prepared by Gilead and/or designee before the start of the study. Eligible subjects will be centrally randomized at Baseline via Interactive Voice/Web Response System (IXRS). Prior to randomization, eligible subjects will be stratified by the following:

- No chronic airways or lung disease
- COPD
- Asthma
- Other chronic airways or lung disease

Within these strata, subjects will be randomized in a 1:1 ratio to receive blinded presatovir or placebo treatment.

Subjects will receive a single dose of 200 mg (four 50 mg tablets) of presatovir or matching placebo at Day 1. Eligible subjects will receive a single dose of 200 mg presatovir or placebo on Day 1. All IMP will be administered orally with water. Tablets are not to be crushed, chewed, split, or dissolved, and should always be handled with gloves. The entire dose must be taken within 1 hour. Subjects should not be discharged until 30 minutes after dosing. IMP is to be handled with gloves.

Day 1 (Baseline) through Day 7 will occur every 24 hours ± 4 hours. There will be no procedures performed on Days 4 and 6.

6.3. Days 2 and 3

These visits may be conducted in the hospital or clinic. Sites preapproved for home visits may also conduct these visits at the subject's home.

The following assessments will be performed and documented at these visits:

- FLU-PRO and EQ5D-5L questionnaire assessment, prior to all other study procedures
- Vital signs, including O_2 saturation
- Collection of nasal swab sample for analysis at the central lab
- PK draw (Day 3 only)
- Blood sample collection for central laboratory analysis (Day 3 only):
  - Hematology
  - Serum Chemistry
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

6.4. Day 5

The Day 5 visit may occur at the hospital or clinic. Sites preapproved for home visits may also conduct these visits at the subject's home. The following assessments will be performed:

- FLU-PRO and EQ5D-5L Questionnaire assessment, prior to all other study procedures.
- Vital Signs, including O_2 saturation
- Collection of 1 nasal swab sample for analysis at the central lab

- Blood sample collection
  - Hematology
  - Serum Chemistry
  - Biomarker
- PK draw
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

6.5. Day 7 and Day 14 (± 1 day)

The Day 7 and Day 14 (± 1day) visits may occur at the hospital or clinic. Sites preapproved for home visits may also conduct these visits at the subject's home. The following assessments will be performed:

- FLU-PRO and EQ5D-5L Questionnaire assessment, prior to all other study procedures
- Healthcare Utilization assessment
- Vital Signs, including O_2 saturation
- Collection of 1 nasal swab sample for analysis at the central lab
- Blood sample collection (Day 14 only)
  - Hematology
  - Serum Chemistry
  - Troponin analyzed locally
  - Serum antibody titer to RSV
- ECG (Day 14 only)
- Serum pregnancy test for females of child-bearing potential (Day 14 only)
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review

- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

6.6. Day 21 (± 1 day)

The Day 21 (± 1day) visit may occur at the hospital, clinic, or via telephone. The following assessments will be performed:

- Healthcare Utilization Assessment
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

6.7. Day 28 (+ 7 days)

This visit will occur no earlier than Day 28 and no later than Day 35. This visit may occur in the hospital, clinic, or via telephone. The following assessments will be performed and documented on Day 28:

- Healthcare Utilization Assessment
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

6.8. Assessments for Premature Discontinuation from Study

Every attempt should be made to keep subjects in the study and to perform the required study-related and procedures follow-up (see Sections 6.3 through 6.6). 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 for the Day 14 assessments (if not already done).

Reasons for premature discontinuation from the study include:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5

- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.9. Assessments for Unscheduled Visits

Subjects who are return to the clinic between scheduled study visits will have an unscheduled visit performed.

The following assessments will be performed and documented at these visits:

- FLU-PRO Questionnaire assessment, prior to all other study procedures
- EQ5D-5L
- Vital signs, including O_2 saturation
- Collection of nasal swab sample for analysis at the central lab.
- Assessment of AEs, concomitant medications, and Supplemental Oxygen Use Diary review
- If applicable, clinical data collection for standard of care cardiac-related tests performed during the study period (Section 6.12.10)

6.10. End of Study

End of study will occur when the subject has completed their Day 28 visit.

6.11. Post Study Care

RSV is a transient infectious disease. Presatovir will not be made available to subjects who have completed the study. Subjects will be able to pursue standard of care treatment after study completion.

6.12. Study Assessments

6.12.1. Nasal Swabs and Virology

6.12.1.1. Samples Collected

At Screening, unless documentation of a positive RSV test and a negative influenza test exists within the subject's current admission records, samples will be collected per local laboratory sampling procedures, and analyzed for RSV and influenza as per the local laboratory test methods. If the test results are available the same day as the samples are collected, a subject found positive for RSV and negative for flu may progress to Baseline (Day 1) for same day dosing of IMP, provided that all required lab results and procedures are available and satisfy the inclusion/exclusion criteria.

Nasal samples will be obtained at each of the following visits for RSV viral load analysis at the central laboratory: Baseline, and Days 2, 3, 5, 7, and 14. An additional sample will be collected from the opposite naris at Baseline for viral coinfection testing at the central laboratory.

All nasal swab samples for central laboratory analysis will be processed, placed in individual tubes, and stored/shipped to the central laboratory as per instructions outlined in the Laboratory Manual.

6.12.1.2. 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 patients according to the Virology Analysis Plan. Mutations 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.

6.12.2. FLU-PRO

The FLU-PRO will be administered after consent and prior to all other study procedures. The FLU-PRO is currently being validated for evaluation of symptoms in patients who are infected with influenza. There are no validated tools for evaluation of RSV symptoms, and there is significant overlap between RSV symptoms and influenza symptoms, this tool will be used to assess change in RSV symptoms in this study. This questionnaire will be completed at Baseline (Day 1), Days 2, 3, 5, 7, and 14. It should be completed before all other questionnaires and assessments requiring study personnel to interview or converse with patients (such as the CFS, EQ5D-5L, or Healthcare Utilization Assessment), and prior to all other study procedures.

Subjects should complete the FLU-PRO independently. However given the patient population, there may be circumstances in which a subject is unable to complete the FLU-PRO themself, for example, subjects who were transported to the hospital without their glasses or subjects who do not feel well enough to sit up. Under these circumstances delegated study staff (PI, Sub-Investigator, or Study Coordinator) may read the questions out loud and transcribe the subject's answer. Study staff member who transcribes the subject responses must include a comment on the FLU-PRO source that documents who read and transcribed the subject's response, and must include the signature and date of the transcriber.

Study staff members are not to complete the FLU-PRO for subjects who are not awake, are unconscious, or are otherwise unable to provide feedback to the questionnaire.

6.12.3. Clinical Frailty Score (CFS)

The CFS is a validated scale that has been demonstrated to predict mortality in elderly populations. The CFS is determined by the investigator through interview of the subject and review of the subject's medical history. The principal investigator or medically qualified sub-investigator (eg, medical doctor, doctor of osteopathy, or nurse practitioner) must assign a score to the subject, and record the score in the subject source and eCRF. The CFS will be evaluated at Baseline, after subjects complete the FLU-PRO.

6.12.4. Healthcare Utilization Assessment

Healthcare utilization patterns after the subject has been enrolled into this study will be evaluated at Days 7, 14, and 28 after subjects complete any written questionnaires. Healthcare utilization assessments will include the use of ICU, use of intermediate care facilities, or nursing homes; number of days on supplemental O_2 during the study; use of mechanical ventilation; and number of subsequent unplanned clinic visits, emergency room visits, urgent care visits, and rehospitalizations (for any respiratory illness).

These assessments will be determined on Days 7, 14 and 28 by interviewing the subject and by assessing information in the subject's medical records. Results will be documented in the subject source documents and eCRF. The information collected for assessments will be entered into the eCRF system. Source and eCRF for these assessments will be reviewed and verified by the site monitor. Other healthcare utilization assessments, such as length of stay in the hospital and death will be collected as part of adverse event safety assessments.

The Healthcare Utilization Assessment will be completed after subjects complete all other questionnaires (eg, FLU-PRO). Unplanned visits, for the purpose of this assessment, will be defined as any visit to a clinic due to the continuation or worsening of respiratory symptoms similar to those for which the hospital admission occurred.

6.12.5. EuroQoL 5-Dimensions Utility Measure (EQ5D-5L)

The EQ5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. It comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), with 5 levels of evaluation (no problems, slight problems, moderate problems, severe problems, and extreme problems). There is a 20cm vertical visual analog scale that is marked by the patients and is used as a quantitative measure of heath as judged by the individual participants.

This questionnaire will be completed after the FLU-PRO but prior to other study related procedures at Baseline and Days 2, 3, 5, 7, and 14. Subjects should complete the questionnaire based on the state of their health on the day of the visit.

Subjects should complete the EQ5D-5L independently. However given the patient population, there may be circumstances in which a subject is unable to complete the EQ5D-5L themself, for example, subjects who were transported to the hospital without their glasses or subjects who do not feel well enough to sit up. Under these circumstances, delegated study staff (PI, Sub-Investigator, or Study Coordinator) may read the questions out loud and transcribe the subject's answer. Study staff member who transcribes the subject responses must include a comment on the EQ5D-5L source that documents who read and transcribed the subject's response, and must include the signature and date of the transcriber.

Study staff members are not to complete the EQ5D-5L for subjects who are not awake, are unconscious, or are otherwise unable to provide feedback to the questionnaire.

6.12.6. Vital Signs

This assessment will include temperature, heart rate, respiratory rate, O_2 saturation, and blood pressure. The subject is required to sit quietly for approximately 2 minutes prior to obtaining VS. At Baseline all VS, including O_2 saturation, will be obtained 5-10 minutes prior to dosing IMP; only heart rate and blood pressure will be collected at 15 minutes and 30 minutes post-dose. Vital signs will be collected at Screening, Baseline (Day 1), and Days 2, 3, 5, 7, and 14.

6.12.7. Oxygen Saturation

Oxygen (O_2) saturation assessment will begin by first asking the subject to sit quietly for 1 minute. Oxygen saturation will be recorded while breathing room air. If the subject is prescribed supplemental O_2 for chronic use prior to this current illness (eg 2L/min via nasal cannula), then the prescribed amount should be noted in the source and eCRF and should also be used during the O_2 saturation assessment. Any additional supplemental O_2 being used (ie above room air or prescribed amount for chronic use prior to this current illness) should be removed for a period of 30 seconds prior to this assessment. The O_2 saturation will be documented in the source at regular intervals (approximately every 15 seconds) during the 2 minute testing period. O_2 saturation evaluation will be considered complete when the 2 minute period has elapsed, or when O_2 saturation drops to $\leq 87\%$, whichever occurs first. The lowest O_2 saturation recorded over the 2-minute interval will be captured in the eCRF. If the subject is unable to tolerate removal of supplemental O_2 for this assessment (eg subject dependent on high dose O_2 or on mechanical ventilation), a value of "< 87%" and the reason why should be recorded.

Oxygen saturation will be collected at Screening, Baseline (Day 1), and Days 2, 3, 5, 7, and 14.

6.12.8. Supplemental Oxygen Use Diary

All randomized subjects will complete the daily Supplemental Oxygen Use Diary. While the subjects are hospitalized, the study coordinator may complete the diary on behalf of the subject, or may assist the subject in daily completion of the diary. Study coordinators will provide training to subjects on proper diary completion, including how to complete the log, when to complete the log, and how to make corrections to the log. After discharge, subjects will continue to record their daily oxygen use on the log. The log will be returned to the site after the Day 28 study visit. Subjects may return the diary in person or via mail.

The Supplemental Oxygen Use Diary will record recent historical information regarding a subject's supplemental oxygen use. For those subjects who have a continuous, daily supplemental oxygen prescription related to a chronic condition, or who have used daily supplemental oxygen prior to their current RSV illness, the subject's pre-illness oxygen prescription will be recorded. A subject's pre-study oxygen use (Day −2 through Day −6) will also be recorded for up to 5 days prior to the subject signing consent. Pre-study oxygen use data will only be recorded for those days immediately prior to study entry if the subject was hospitalized during this time. Study coordinators will complete the historical sections of the Supplemental Oxygen Use Diary.

In addition to historical oxygen use, each day during study participation, the subject will record their highest flow rate or percentage of oxygen used during that 24 hour period (00:00 to 23:59 or 12:00am to 11:59pm). The delivery method of the highest oxygen use will be recorded into the diary using one of the following selections: Nasal Cannula; Tent; Ventimask; Non-rebreather Mask; High Flow Mask; CPAP; BiPAP; Intubation; Tracheostomy; or Other. Subjects who do not require supplemental oxygen will have 0 L/min recorded into the diary for each day they are without supplemental oxygen.

Subjects will continue to record daily supplemental oxygen use until completing their Day 28 (+ 7 days) study visit. Subjects will return the diary via post or in-person hospital visit. Data from the diary will be transcribed into EDC.

6.12.9. Electrocardiogram (ECG)

At Baseline, a pre-dose ECG will be performed on the institution equipment. A post-dose ECG will be performed 2 hours ± 30 minutes after dosing. A third ECG will also be collected on Day 14.

6.12.10. 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 follow-up, results these tests will be collected. Results will be collected form the following standard of care procedures:

- ECG tracings and report of any ECG performed
- All troponin results from testing completed at non-study facilities
- Cardiac enzyme testing (eg 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

6.12.11. Safety Labs

When available, the most recent laboratory values from the current hospitalization will be used for eligibility assessment. If an existing laboratory value is not available for eligibility assessment, the test will be performed using the local hospital laboratory. All testing of hematology and serum chemistry samples obtained after randomization will be performed at a central laboratory selected by GSI.

Testing of blood specimens will include WBC with differential, Hgb, platelets, BUN, creatinine, AST, ALT, and total bilirubin at Screening, and complete panels performed at Baseline (pre-dose), Days 3, 5, and 14.

Blood will also be drawn to monitor troponin levels at Baseline/Day 1 (pre-dose and 2 hours ± 30 minutes post-dose) and the Day 14 visit. At each of these time points, the sample will be sent to the local laboratory listed on the FDA Form 1572 for analysis using the laboratory-based troponin assay specific to the local site (eg, troponin-I or -T). Point-of-care "rapid" troponin tests are not acceptable for troponin testing.

Troponin test results that have been obtained as part of routine care may be used in place of the protocol-required troponin testing so long as the test has been completed at the protocol-specified time point (ie Baseline pre-dose) at the corresponding study visit. Troponin results should be reviewed before the subject leaves the clinical site in case a troponin value is positive and further medical care is advised. Results from the protocol-specified troponin testing will be entered into the EDC, along with any additional results from standard of care or serial troponin testing completed at the local laboratory.

Urine pregnancy tests will occur for all females of child-bearing potential at Screening, followed by a serum pregnancy test on Day 14.

6.12.12. Plasma PK

Blood will be drawn for PK at Baseline approximately 2 hours ± 30 minutes (T_{max}) after IMP administration. Additional PK samples will be drawn anytime on Days 3 and 5.

6.12.13. Biomarkers

Serum for biomarkers will be collected from all subjects at Baseline (pre-dose) and Day 5. Serum will be collected to measure antibody titers to RSV at Baseline (pre-dose) and Day 14.

Biomarkers of inflammation, procalcitonin, and host response (e.g. IP-10, CRP, etc.,) may be measured.

All swab samples will be retained for biomarker testing and/or additional viral analysis.

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 pharmaceutical 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. AEs 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 AE 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- 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.

7.1.3. 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 (e.g. clinical chemistry, hematology, etc.) 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 (e.g. electrocardiogram, x-rays, vital signs, etc.) 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 medically 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 Study Drugs and Procedures

The investigator or medically qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE 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 AE 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 AE has an etiology other than the study procedure.
- **Yes:** The AE 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 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

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 4 weeks after last administration of study IMP 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.

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 CRF/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 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 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.

All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline. The RAVE Safety Gateway (RSG or eSAE) will be used to capture SAE data for this study

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 SAE reporting form and submit within 24 hours to

  Gilead DSPH: Email: Safety_FC@gilead.com
  Fax: +1 (650) 522-5477.

- 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.

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

- 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 CRF/eCRF and the event description section of the SAE form.

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 investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. 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. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3.

Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, and pregnancy reports regardless of an associated AE. Also includes reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints.

A pregnancy report is used to report any pregnancy following maternal or paternal exposure to the medicinal product.

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 or 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.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Gilead DSPH Foster City contact information is as follows:

Email: Safety_FC@gilead.com
Fax: +1 (650) 522-5477

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 (e.g. 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 as follows:

Email: Safety_FC@gilead.com
Fax: +1 (650) 522-5477

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to 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 as follows:

Email: Safety_FC@gilead.com
Fax: +1 (650) 522-5477

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

7.6.2.2. 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 on the AE form.

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

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form (refer to Section 7.3). Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

Gilead DSPH Foster City contact information is as follows:

Email: Safety_FC@gilead.com
Fax: +1 (650) 522-5477

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is to evaluate the effects of presatovir on RSV viral load in RSV-positive adults hospitalized with acute respiratory infectious symptoms.

The secondary objectives of this study are to evaluate:

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

8.1.2. Primary Endpoint

The primary endpoint is the time-weighted average change in $\log_{10}$ viral load from Day 1 to Day 5. The time-weighted average change in $\log_{10}$ viral load from Day 1 to Day 5 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 in $\log_{10}$ viral load from Baseline 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 5. The time-weighted average change, often referred to as the DAVG, provides the average viral burden change from baseline.

8.1.3. Secondary Endpoints

The key secondary endpoints are:

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

8.1.4. Exploratory Endpoints

PPD

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analyses will be the evaluable analysis set, which will include those who have an RSV $\log_{10}$ viral load greater than the LLOQ of the RT-qPCR assay in the pre-dose Day 1 nasal swab sample, have a minimum of 3 nasal swabs (including baseline swab; swabs do not have to be consecutive) after enrollment, not including the screen swab, and have completed IMP administration.

The full analysis set (FAS) will also be used for specified efficacy analyses and is defined as all subjects who were randomized into the study and received at least a partial dose of study medication. Subjects will be included in the group according to actual treatment received.

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as all subjects who received a 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 PK data at the time points of interest.

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 (excluding Australia), and age.

Baseline data will include a summary of body weight, height, BMI, presence or absence of chronic airways disease, and type of chronic airways disease (None, COPD, asthma, or other).

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

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is time-weighted average change in $\log_{10}$ viral load from Day 1 to Day 5. 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 viral load, a parametric analysis of covariance (ANCOVA) model with corresponding baseline viral load and the stratification factor as covariates will be used, at a 2-sided 0.05 level. Adjusted means and 95% confidence intervals (CIs) will be presented.

8.5.2. Secondary Analyses

The evaluable 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.

Time-weighted average change in the FLU-PRO score from Baseline to Day 5 will be analyzed using an ANCOVA model with Baseline FLU-PRO and the stratification factor as covariates. Adjusted means and 95% CIs will be presented for this analysis. Duration of hospital stay following IMP administration will be analyzed using an ANCOVA model with treatment as a fixed effect and stratification factor as a covariate. Adjusted means and 95% CIs will be presented for this analysis. The rate of unplanned medical encounters related to respiratory illness after initial hospitalization discharge through Day 28 will be analyzed using a Negative binomial regression method with an offset parameter to account for follow-up time. Nonparametric methods such as a Wilcoxon rank sum tests may be implemented if statistical model assumptions are not met.

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}.

1) Time-weighted average change in the FLU-PRO score from Day 1 (pre-dose) to Day 5

2) Duration of hospital stay following IMP administration

3) Rate of unplanned medical encounters (clinic visits, emergency room visits, urgent care visits, and rehospitalizations) related to a respiratory illness after initial hospitalization discharge through Day 28

8.5.3. Exploratory Analyses

PPD

8.6. Safety Analysis

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 of subjects (n and percent) with events/abnormalities for categorical data and using descriptive statistics for continuous data.

8.6.1. 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.

8.6.2. Adverse Events

Clinical and laboratory AEs 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 AE will be defined as any AE that begins on or after the date of first dose of IMP through Day 28.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC, and PT) will be provided by treatment group:

8.6.3. 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 GSI 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.

8.6.4. Other Safety Evaluations

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

8.7. Pharmacokinetic Analysis

Concentrations of presatovir will be determined in plasma and using a validated bioanalytical assay. Individual subject presatovir concentration time data will be displayed using scheduled sampling times (Days 1, 3, and 5). Descriptive statistics (e.g. n, mean, standard deviation, % CV, median, and range) will be calculated for each sampling time. Plasma concentrations of presatovir over time will be plotted in semi-logarithmic and linear formats as mean ± standard deviation. Plasma concentration time data for each subject will be analyzed using standard non-compartmental methods. PK/PD (pharmacodynamics) relationships, including biomarker data, may be explored as appropriate.

8.8. Sample Size

Sample size calculations are based on results observed in subjects who received placebo in the GS-US-218-0103 study. The sample size calculation assumes the time-weighted average change in $\log_{10}$ viral load from Day 1 to Day 5 in the placebo group will be -2.9 $\log_{10}$ copies/ml with a corresponding standard deviation of 2.3 and that 85% of the subjects will be evaluable. Based on these assumptions, with 85 subjects per group there is approximately 80% power to detect a 1 $\log_{10}$ reduction in time-weighted average change in viral load 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.

8.9. Interim Analysis

Interim futility analyses of the primary endpoint, time-weighted average change in $\log_{10}$ viral load from Day 1 through Day 5, may be conducted after approximately 25% (n of ~50) and 50% (n of ~100) of the enrollment has been achieved. The results from these interim analyses will be reviewed by the DMC, who may recommend early termination for futility if the conditional power is < 20%. If the DMC recommends early termination for futility, Gilead personnel who are not involved with the study may perform an unblinded review of the interim data, and the decision may be made to stop the study and unblind treatment assignments. Further details of the interim analysis and assessment of futility will be described in the SAP, including the computation methods of conditional power such as those proposed by Lachin, 2005 {26904}.

8.10. Data Monitoring Committee

An independent DMC will monitor the safety and welfare of the study subjects as specified in the DMC charter. The DMC will meet at designated intervals to review accumulated data and may make recommendations regarding the study conduct. The DMC will also be responsible for reviewing the results of the interim analysis. Gilead retains final decision-making authority on all aspects of the study.

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.

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided in writing to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC 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 investigator brochure, this protocol, CRF/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, 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 AEs 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 eCRFs will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. 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 returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not 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 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, eCRF data, and study related regulatory documents to appropriately qualified personnel from GSI or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors (e.g. FDA, MHRA, EMA, etc.).

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 regulatory agency. 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. 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.

9.3.2. 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.

9.3.3. 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 Hospitalized Adults with Respiratory Syncytial Virus (RSV) Infection

GS-US-218-1227, Amendment 4, 17 November 2015

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

Seth Toback, MD
Name (Printed)

PPD
Signature

NOV 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

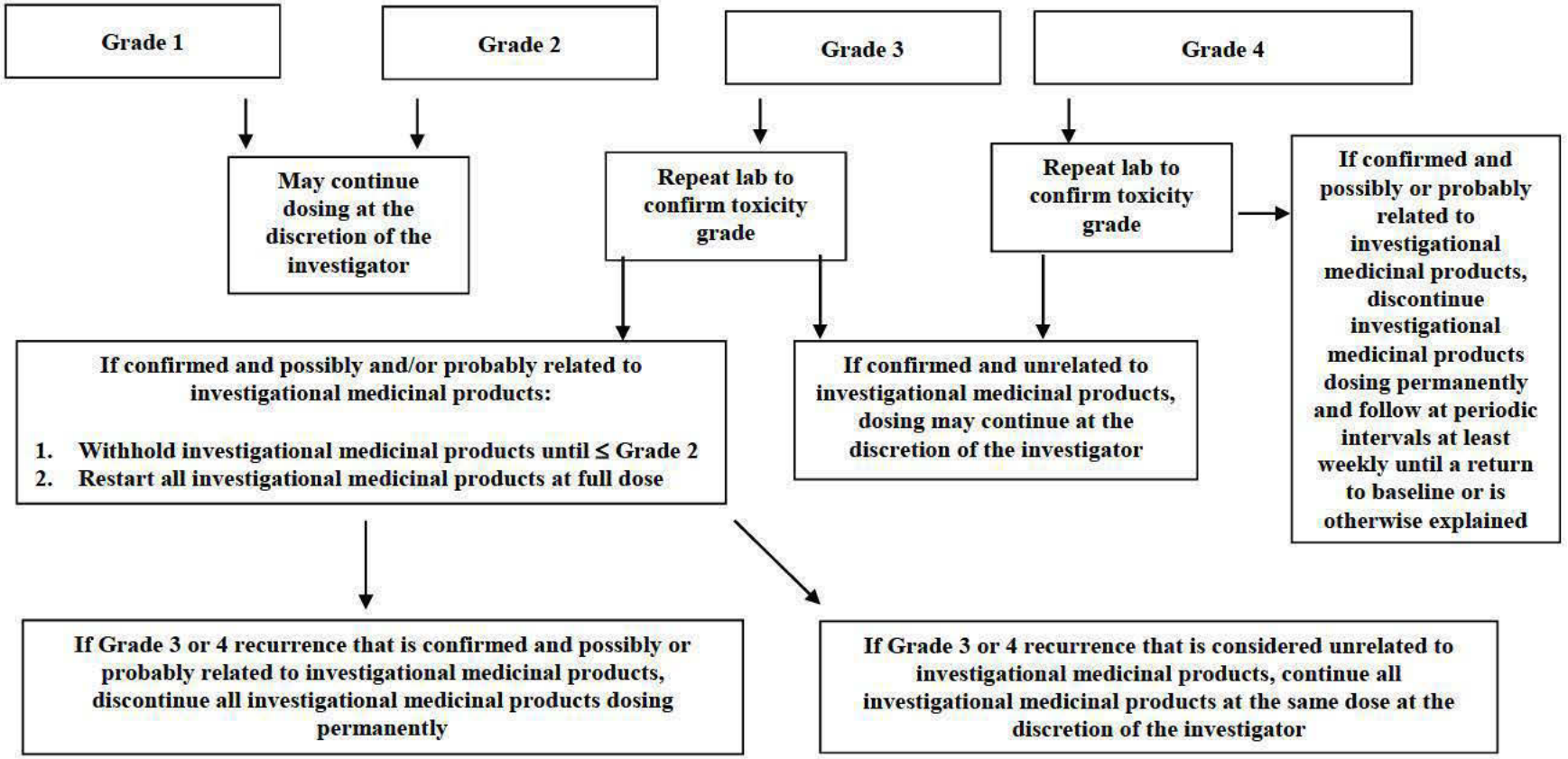
Appendix 2. Study Procedures Table

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

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

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

Appendix 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
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	— —	— —

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
Hyperbilirubinemia **Adult and Pediatric > 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	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
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)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

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

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

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

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences 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 pregnancy test will be performed at the screening visit to ensure pregnant women are not included 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 who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening/enrollment visit throughout the study period and for 90 days following the last dose of study drug. Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and 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; (2) two barrier methods where one method is the male condom; or (3) 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 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, documentation of the absence of sperm in the ejaculate post-vasectomy 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 pregnancy test at screening prior to receiving the first dose of study drug. A serum pregnancy test will be performed on Day 14. Lactating females must discontinue nursing before IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

<table>
<tr><th rowspan="2">Methods to Use by Themselves</th><th colspan="2">Combination Methods</th></tr>
<tr><th>Hormone Methods
(choose one and use with a barrier method)</th><th>Barrier Methods
(use both OR 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
OR
• 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 the subject. For a vasectomy, documentation of the absence of sperm in the ejaculate post-vasectomy 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 90 days or 14 weeks 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 7.6.2.1.