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

Summary

EudraCT number	2014-002475-29
Trial protocol	NL DE
Global end of trial date	17 April 2017

Results information

Result version number	v2 (current)
This version publication date	18 May 2019
First version publication date	12 April 2018
Version creation reason	• Correction of full data set Adding text to "Limitations and Caveats" section

Trial information

Trial identification

Sponsor protocol code	GS-US-218-1502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02254421
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 April 2017
Global end of trial reached?	Yes
Global end of trial date	17 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of presatovir on respiratory syncytial virus (RSV) viral load in autologous or allogeneic hematopoietic cell transplant (HCT) recipients with an acute RSV lower respiratory tract infection (LRTI).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Switzerland: 3
Worldwide total number of subjects	60
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	47
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Asia Pacific, Europe, and the United States. The first participant was screened on 31 January 2015. The last study visit occurred on 17 April 2017.

Pre-assignment

Screening details:

71 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Presatovir

Arm description:

Presatovir on Days 1, 5, 9, 13, and 17

Arm type	Experimental
Investigational medicinal product name	Presatovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use, Nasogastric use

Dosage and administration details:

Presatovir 200 mg (4 x 50 mg tablets) administered orally or via nasogastric tube

Arm title	Placebo

Arm description:

Placebo on Days 1, 5, 9, 13, and 17

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Placebo administered orally or via nasogastric tube

Number of subjects in period 1[1]	Presatovir	Placebo
Started	30	29
Completed	29	26
Not completed	1	3
Death	-	2
Withdrew consent	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant from the Presatovir group who was enrolled but not treated is not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	Presatovir
Reporting group description: Presatovir on Days 1, 5, 9, 13, and 17	
Reporting group title	Placebo
Reporting group description: Placebo on Days 1, 5, 9, 13, and 17	

Reporting group values	Presatovir	Placebo	Total
Number of subjects	30	29	59
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50.5	54.4	
standard deviation	± 16.27	± 12.59	-
Gender categorical Units: Subjects			
Female	9	6	15
Male	21	23	44
Race Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	4	3	7
Black or African American	1	2	3
White	23	18	41
Not Permitted	1	5	6
Ethnicity Units: Subjects			
Hispanic or Latino	5	6	11
Not Hispanic or Latino	23	18	41
Not Permitted	2	5	7
Stratification Factor: Supplemental O2 Requirement at Time of Randomization Units: Subjects			
Supplemental O2 Requirement ≤ 2 L/min	19	19	38
Supplemental O2 Requirement > 2 L/min	11	10	21
Stratification Factor: Treatment of Current RSV Infection with Ribavirin Units: Subjects			
Yes	12	11	23
No	18	18	36

End points

End points reporting groups	
Reporting group title	Presatovir
Reporting group description: Presatovir on Days 1, 5, 9, 13, and 17	
Reporting group title	Placebo
Reporting group description: Placebo on Days 1, 5, 9, 13, and 17	

Primary: Time-weighted Average Change in Nasal Respiratory Syncytial Viral (RSV) Load From Baseline to Day 9	
End point title	Time-weighted Average Change in Nasal Respiratory Syncytial Viral (RSV) Load From Baseline to Day 9
End point description: The time-weighted average change, often referred to as the DAVG, provides the average viral burden change from baseline. The mean values presented were calculated using the ANCOVA model and are adjusted for baseline value and stratification factors. The Full Analysis Set included all randomized participants who received at least 1 full dose of study drug and had an RSV viral load greater than or equal to the lower limit of quantification of the RT-qPCR assay in the Day 1 nasal sample, as determined by RT-qPCR at the central lab.	
End point type	Primary
End point timeframe: Baseline to Day 9	

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: log10 copies/mL				
arithmetic mean (standard error)	-1.00 (± 0.215)	-0.97 (± 0.218)		

Statistical analyses

Statistical analysis title	Statistical Analysis - Presatovir vs Placebo
Comparison groups	Placebo v Presatovir
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [1]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.57

Notes:

[1] - P-value was calculated from the ANCOVA model including baseline values and stratification factors.

Secondary: Number of Supplemental O2-Free Days Through Day 28

End point title	Number of Supplemental O2-Free Days Through Day 28

End point description:

The Full Analysis Set includes all randomized participants who received at least 1 full dose of study drug and had an RSV viral load greater than or equal to the lower limit of quantification of the RT-qPCR assay in the Day 1 nasal sample, as determined by RT-qPCR at the central lab.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: days				
median (inter-quartile range (Q1-Q3))	26 (10 to 28)	28 (9 to 28)		

Statistical analyses

Statistical analysis title	Statistical Analysis - Presatovir vs Placebo
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84 [2]
Method	Negative Binomial Model

Notes:

[2] - P-value was calculated from the negative binomial model with stratification factors as covariates.

Secondary: Percentage of Participants Developing Respiratory Failure Requiring Mechanical Ventilation Through Day 28

End point title	Percentage of Participants Developing Respiratory Failure Requiring Mechanical Ventilation Through Day 28

End point description:

The Full Analysis Set includes all randomized participants who received at least 1 full dose of study drug and had an RSV viral load greater than or equal to the lower limit of quantification of the RT-qPCR assay in the Day 1 nasal sample, as determined by RT-qPCR at the central lab.

End point type	Secondary

End point timeframe:
Up to Day 28

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: percentage of participants				
number (confidence interval 95%)	10.3 (2.2 to 27.4)	10.7 (2.3 to 28.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis - Presatovir vs Placebo
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - P-value was calculated from the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors.

Secondary: Percentage of All-Cause Mortality Among Participants Through Day 28

End point title	Percentage of All-Cause Mortality Among Participants Through Day 28

End point description:

The Full Analysis Set includes all randomized participants who received at least 1 full dose of study drug and had an RSV viral load greater than or equal to the lower limit of quantification of the RT-qPCR assay in the Day 1 nasal sample, as determined by RT-qPCR at the central lab.

End point type	Secondary

End point timeframe:
Up to Day 28

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 11.9)	7.1 (0.9 to 23.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis - Presatovir vs Placebo
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - P-value was calculated from the CMH test stratified by stratification factors.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Day 28	
Adverse event reporting additional description: Safety Analysis Set: participants who received at least 1 full dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Presatovir
Reporting group description: Presatovir on Days 1, 5, 9, 13, and 17	
Reporting group title	Placebo
Reporting group description: Placebo on Days 1, 5, 9, 13, and 17	

Serious adverse events	Presatovir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)	7 / 29 (24.14%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebral infarction			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	3 / 30 (10.00%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Presatovir	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 30 (63.33%)	17 / 29 (58.62%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 29 (10.34%)	
occurrences (all)	2	4	
Oedema peripheral			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Non-cardiac chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 30 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	3	
Epistaxis			
subjects affected / exposed	3 / 30 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 30 (10.00%)	1 / 29 (3.45%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Troponin T increased			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 30 (6.67%)	3 / 29 (10.34%)	
occurrences (all)	2	4	
Dizziness			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	3 / 29 (10.34%)	
occurrences (all)	1	3	
Thrombocytopenia			
subjects affected / exposed	1 / 30 (3.33%)	3 / 29 (10.34%)	
occurrences (all)	1	3	
Lymphopenia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Neutropenia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 30 (10.00%)	3 / 29 (10.34%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	3 / 30 (10.00%)	1 / 29 (3.45%)	
occurrences (all)	3	1	
Dry mouth			

subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Pruritus			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	3 / 30 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 29 (3.45%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2014	• An optional extended viral monitoring section was created and appropriate text was included throughout the protocol to describe the study procedures during this period. In addition, planned analyses of the optional extended viral monitoring data were added to applicable sections of the protocol. • The discontinuation criteria section was revised such that all Grade 3 or 4 adverse events (AEs) or serious adverse events (SAEs) must have been reviewed with the Gilead Sciences (Gilead) medical monitor to assess whether to continue study drug administration, to ensure that any Grade 3 or 4 AEs/SAEs that were associated with graft-versus-host disease (GVHD) or veno-occlusive disease were reviewed. • Updated study drug instructions to recommend that subjects avoid direct UV exposure for the duration of exposure to presatovir (ie, 8 days following study drug administration), as the potential risk of phototoxicity was unknown and presatovir should have been almost completely eliminated within 8 days. • The concomitant medications section was updated to address potential drug-drug interactions for presatovir and to clarify the need for safety monitoring consistent with the prescribing information for other agents when given concomitantly with presatovir, as presatovir affects transporters and has the potential to affect exposures of other drugs that depend on the same transporters. • Appendix 5 was updated to provide additional information regarding pregnancy precautions and contraceptive requirements. • The terminology of relevant endpoints was updated from daily averages to time-weighted averages as this term, along with time-weighted average change, is often used in literature. The definitions and calculations of the endpoints remained the same. • Inclusion Criterion 2 was updated to < 48 hours prior to screening for clarity. • Inclusion Criterion 7 was removed for consistency with Exclusion Criterion 3
22 September 2014	• Exclusion Criterion 2 (washout period for strong cytochrome P450 enzyme [CYP] inducers) was extended from 1 to 2 weeks to reflect a more conservative washout period. • Pregnancy testing was added at all dosing visits for females of childbearing potential for consistency with Appendix 5: Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirement. • Male contraceptive and sperm donation requirements were extended from 30 to 90 days after last dose of study drug for consistency with the investigator's brochure (IB). • Inclusion Criterion 6 (contraceptive requirements) was modified in alignment with changes made to contraceptive requirements in Appendix 5.
21 October 2014	• Removal of double-barrier method as contraceptive method to ensure all contraception is in accordance with the ICH M3 guidance that birth control methods need to be highly effective (ie, < 1% failure rate).

30 June 2015	● Reproductive toxicology data in the protocol background was updated to reflect the definitive rat and rabbit studies. ● Exclusion Criterion 8 was removed as the intent of the criterion is covered in Exclusion Criterion 13 ● Exclusion Criteria 16 and 17 (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] and total bilirubin [TBIL] requirements), discontinuation criteria, and safety labs were updated to include hepatic monitoring consistent with Canadian regulations. ● Study drug administration information updated to allow for nasogastric (NG) tube administration, and removal of the need for fasting or avoidance of direct UV exposure per new stability and phototoxicity data of GS-5806-02. ● Study drug discontinuation criteria updated to include extra hepatic monitoring and Hy's law in accordance with Canadian regulations. ● Secondary and exploratory endpoints and analyses updated ● Induced sputum removed as collection of this sample is not standard practice. ● Section 1.2.2 was updated for consistency with the IB. ● A new Inclusion Criterion 1 was added to clarify age ranges allowed in the study. ● Exclusion Criterion 2 (CYP restrictions) and Section 5.4: Prior and Concomitant Medications were updated to further exclude moderate CYP inducers, as DDI results indicated that moderate CYP inducers moderately decrease presatovir exposure. ● Exclusion Criterion 8 (other respiratory viruses) was updated to exclude coronaviruses due to severe clinical disease now known to be associated with Middle East respiratory syndrome. ●Exclusion Criterion 14 (allergy to sulfa drugs) was updated to clarify that the criterion applies to sulfa reactions that are of most concern. ● Hepatic monitoring and statistical texts were updated for clarity
30 November 2015	● Section 1.2.4.4: Ongoing Studies was added to provide consistency among protocols in the presatovir program. ● Inclusion Criteria 4 (documented RSV) and Section 6.11.1: Nasal Samples, Virology, and Antibody Titer were updated to clarify that spontaneous sputum is not allowed. ● Screening RSV testing was updated to allow for standard clinical practice procedures surrounding RSV diagnosis confirmation and in meeting study inclusion criteria. ● Electrocardiograms (ECGs), troponin testing, and collection of standard of care clinical data for central review were added. ● The prior and concomitant medications section was updated to attribute part of cyclosporine effect as a weak CYP3A inhibitor, to clarify that presatovir is not expected to alter PK of concomitant medications that are substrates of major CYP enzymes or drug transporters, and to note that the potential effect of strong- and moderate-CYP3A inhibitors on presatovir PK are under investigation. ● Vital signs and O2 saturation measurement were added to Visits 3 and 5, if not home visits, and study-specific assessments were added to all study visits for consistency. ● The O2 saturation measurement procedure was updated for consistency across the presatovir program and to allow subjects to remain on chronic O2 for standards in clinical care.
28 March 2016	● Screening procedures were modified such that subjects who were not tested for RSV as standard of care could consent to the study and be tested for RSV during the screening visit. ● Visit 3 was made optional if the subject was not hospitalized at the time of visit to reduce the visit burden during the first 9 days of the study. ● The number of sites was increased in order to accelerate enrollment. ● Sweden-specific requirements for obtaining consent via legal guardian were added to the inclusion criteria. ● Section 6.1.1: Visit 1: Screening Visit was updated to allow subjects who screen failed out of GS-US-218-0108 due to presence of LRTI to screen into GS-US-218-1502 and vice versa. ● Administrative clarifications were made to Section 8: Statistical Considerations.

Notes: