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 Upper Respiratory Tract.

Summary

EudraCT number	2014-002474-36
Trial protocol	SE DE GB NL ES
Global end of trial date	14 July 2017

Results information

Result version number	v2 (current)
This version publication date	18 May 2019
First version publication date	26 July 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-218-0108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02254408
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	14 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2017
Global end of trial reached?	Yes
Global end of trial date	14 July 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 upper respiratory tract infection (URTI), the effect of presatovir on development of lower respiratory tract complication, being free of any supplemental oxygen progression to respiratory failure, and pharmacokinetics (PK), safety, and tolerability of presatovir.

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	23 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	United States: 116
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 18
Worldwide total number of subjects	189
EEA total number of subjects	23

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)	154
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in study centers North America, Europe, Australia, and Asia. The first participant was screened on 23 January 2015 and the last study visit occurred on 14 July 2017.

Pre-assignment

Screening details:

213 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	GS-5806
Pharmaceutical forms	Tablet
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Presatovir 200 mg (4 x 50 mg tablets) administered as a single dose, orally or via nasogastric (NG) tube on Days 1, 5, 9, 13, and 17

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 NG tube on Days 1, 5, 9, 13 and 17

Number of subjects in period 1[1]	Presatovir	Placebo
Started	95	90
Completed	88	83
Not completed	7	7
Adverse event, serious fatal	2	3
Consent withdrawn by subject	3	3
Adverse event, non-fatal	1	-
Investigator's Discretion	-	1
Lost to follow-up	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: 4 participants who were randomized but not treated were not included in the Baseline period.

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	95	90	185
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.1	51.4	
standard deviation	± 12.21	± 14.58	-
Gender categorical Units: Subjects			
Female	40	35	75
Male	55	55	110
Race Units: Subjects			
Asian	13	9	22
Black or African American	6	3	9
White	66	70	136
Other	2	0	2
Not Permitted	8	8	16
Ethnicity Units: Subjects			
Hispanic or Latino	8	6	14
Not Hispanic or Latino	81	75	156
Not Permitted	6	9	15
Nasal Viral Load			
Participants in the Safety Analysis Set with available data were analyzed.			
Units: Log10 copies/mL			
arithmetic mean	6.31	6.51	
standard deviation	± 1.899	± 1.437	-

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 Virus (RSV) Viral Load From Baseline (Day 1) to Day 9	
End point title	Time-Weighted Average Change in Nasal Respiratory Syncytial Virus (RSV) Viral Load From Baseline (Day 1) 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 factor.Participants in the Full Analysis Set (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) were analyzed.	
End point type	Primary
End point timeframe: Baseline; Day 9	

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	87		
Units: log10 copies/mL				
arithmetic mean (standard deviation)	-1.26 (± 0.964)	-0.91 (± 1.145)		

Statistical analyses

Statistical analysis title	Change in Nasal RSV Load - Presatovir v Placebo
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.02

Primary: Percentage of Participants Who Developed a Lower Respiratory Tract Complication

End point title	Percentage of Participants Who Developed a Lower Respiratory Tract Complication

End point description:

A Lower Respiratory Tract Complication (LRTC) was defined as one of the below as determined by the adjudication
committee :
• Primary RSV lower respiratory tract infection (LRTI)
• Secondary bacterial LRTI
• LRTI due to unusual pathogens
• Lower respiratory tract complication of unknown etiology
Participants in the Full Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to Day 28

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	87		
Units: percentage of participants				
number (confidence interval 95%)	11.2 (5.5 to 19.7)	19.5 (11.8 to 29.4)		

Statistical analyses

Statistical analysis title	LRTC - Presatovir v Placebo - 1
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.18

Statistical analysis title	LRTC - Presatovir v Placebo - 2
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Fisher exact

Secondary: Percentage of Participants Who Developed Respiratory Failure (of Any Cause) Requiring Mechanical Ventilation (Invasive or Noninvasive) or All-cause Mortality

End point title	Percentage of Participants Who Developed Respiratory Failure (of Any Cause) Requiring Mechanical Ventilation (Invasive or Noninvasive) or All-cause Mortality

End point description:

Participants were considered to have an event if either condition is met:
• Participant develops a respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) or
• Participant dies prior to or on Day 28

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	89	87		
Units: percentage of participants				
number (confidence interval 95%)	5.6 (1.8 to 12.6)	5.7 (1.9 to 12.9)		

Statistical analyses

Statistical analysis title	Respiratory Failure - Presatovir v Placebo - 1
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	3.63

Statistical analysis title	Respiratory Failure - Presatovir v Placebo - 2
Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 28 days	
Adverse event reporting additional description:	
Safety Analysis Set	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Presatovir
Reporting group description:	
Presatovir 200 mg (4 x 50 mg tablets) administered as a single dose, orally or via nasogastric (NG) tube on Days 1, 5, 9, 13 and 17	
Reporting group title	Placebo
Reporting group description:	
Placebo administered orally or via NG tube on Days 1, 5, 9, 13 and 17	

Serious adverse events	Presatovir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 95 (18.95%)	23 / 90 (25.56%)	
number of deaths (all causes)	2	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
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	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Somnolence			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 95 (4.21%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease in gastrointestinal tract			

subjects affected / exposed	2 / 95 (2.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (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 distress			
subjects affected / exposed	1 / 95 (1.05%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute lung injury			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia aspiration			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 95 (0.00%)	3 / 90 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 95 (3.16%)	6 / 90 (6.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	1 / 95 (1.05%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 95 (0.00%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 95 (1.05%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 95 (0.00%)	1 / 90 (1.11%)	
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	49 / 95 (51.58%)	47 / 90 (52.22%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 95 (5.26%)	7 / 90 (7.78%)	
occurrences (all)	7	7	
Dizziness			
subjects affected / exposed	7 / 95 (7.37%)	3 / 90 (3.33%)	
occurrences (all)	8	3	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 95 (3.16%)	5 / 90 (5.56%)	
occurrences (all)	6	5	
Febrile neutropenia			
subjects affected / exposed	2 / 95 (2.11%)	5 / 90 (5.56%)	
occurrences (all)	2	5	
Anaemia			
subjects affected / exposed	5 / 95 (5.26%)	1 / 90 (1.11%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 95 (10.53%)	9 / 90 (10.00%)	
occurrences (all)	11	10	
Asthenia			
subjects affected / exposed	3 / 95 (3.16%)	7 / 90 (7.78%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 95 (15.79%)	14 / 90 (15.56%)	
occurrences (all)	15	19	
Nausea			
subjects affected / exposed	13 / 95 (13.68%)	10 / 90 (11.11%)	
occurrences (all)	14	12	
Vomiting			
subjects affected / exposed	10 / 95 (10.53%)	12 / 90 (13.33%)	
occurrences (all)	12	15	

Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	9 / 95 (9.47%)	3 / 90 (3.33%)	
occurrences (all)	11	3	
Cough			
subjects affected / exposed	6 / 95 (6.32%)	4 / 90 (4.44%)	
occurrences (all)	6	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 95 (4.21%)	5 / 90 (5.56%)	
occurrences (all)	4	5	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 95 (3.16%)	5 / 90 (5.56%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 95 (7.37%)	6 / 90 (6.67%)	
occurrences (all)	8	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2014	•Incorporated EudraCT number •Updated all sections that include endpoints and endpoint analysis from "daily average" to "time-weighted average" •Changed "pneumonia" to "LRTI" in all references to definitions of LRTC •Added text to include Optional Extended Viral Monitoring •Added text to ensure subjects avoid direct UV exposure for 8 days after receiving IMP •Updated all references of "urine pregnancy test" to "urine or serum pregnancy test" •Updated all chest X-ray references of "within 2 days" to "< 48 hours" •Removed all references of vital signs needing to be obtained 5 – 10 minutes prior to IMP dosing •Updated "will" to "should" for study visit assessments being performed in order •Corrected spelling/grammatical errors and made formatting changes for consistency throughout the protocol •Updated section titles to reflect changes •Updated the Protocol Synopsis to ensure consistency with changes made to the main body of the protocol (changes to the Protocol Synopsis are not reflected herein)
22 September 2014	•Exclusion Criterion 2 washout period for strong cytochrome P450 enzyme (CYP) inducers extended from 1 to 2 weeks to reflect a more conservative washout period. •Addition of pregnancy testing at all dosing visits for females of childbearing potential for consistency with Appendix 5. •Extension of male contraceptive and sperm donation requirements from 30 to 90 days after last dose of study drug for consistency with the Investigator's Brochure (IB). •Inclusion Criterion 8 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	•Background Section 1.2.2 updated for consistency with the IB •Secondary and exploratory objectives and endpoints reprioritized and updated due to changes in design strategy •New Inclusion Criterion 1 added to clarify age ranges allowed in study •Inclusion Criterion 4 updated to clarify chronic respiratory conditions •Exclusion Criterion 2 and Section 5.4 updated to further exclude moderate CYP inducers •Exclusion Criterion 8 updated to exclude coronaviruses due to severe clinical disease now known to be associated with MERS •Exclusion Criterion 14 updated to clarify the criterion applies to sulfa reactions that are of most concern •MRI removed from SOC chest image collection •Hepatic monitoring and statistical texts updated for clarity •Protocol version and date were updated in all applicable sections, headers, and footers •Corrected spelling/grammatical/consistency errors throughout the protocol •Glossary of abbreviations was updated to reflect corresponding changes throughout the protocol •Corresponding changes made to the protocol body text were also made to the Protocol Synopsis and Study Procedures Table, where appropriate

20 November 2015	•Added ECGs, troponin testing, and collection of standard of care clinical data for central review •Prior and concomitant mediations section 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. •Added vital signs and oxygen saturation added to Visits 3 and 5, if not home visits, and study-specific assessments added to Visits 3 and 5, if not home visits, and post-randomization assessments for consistency with other study visits. •Interim analysis removed. Extending the duration for assessing these clinical endpoints that occur at lower frequencies may be useful for registrational trials
28 March 2016	•Increased the number of study centers participating to 80 and added Japan to the list of countries •Modified Screening procedures such that subjects who were not tested for RSV as standard of care may consent to the study and be tested for RSV during the Screening visit. •Modified primary endpoint to include development of lower respiratory tract complication (LRTC) co-primary endpoint, which was previously listed as a secondary endpoint •Included Japan specific definition of adult to the inclusion criteria •Included Sweden specific requirements for obtaining consent via legal guardian to the inclusion criteria •Modified Screening procedures to allow for RSV testing on subjects after consent •Updated text to allow subjects who screen fail out of GS-US-218-1502 due to absence of LRTI to screen into GS-US-218-0108 and vice versa •Included Japan specific instructions for obtaining nasal swab samples at Visit 1: Screening and Visit 2: Baseline •Updated Visit 3: Day 3 to an optional visit for subjects who are not participating in the PK subgroup •Updated Statistical Methods and Sample Size sections to reflect changes in primary and secondary endpoints •Updated Appendix 5 contraception language to include Japan specific requirements

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: