Clinical trial results:
A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Presatovir (GS-5806) in Healthy Volunteers Infected with Respiratory Syncytial Virus (RSV-A Memphis 37b Strain)

Summary

EudraCT number	2012-002413-19
Trial protocol	GB
Global end of trial date	03 August 2013

Results information

Result version number	v1 (current)
This version publication date	20 February 2016
First version publication date	20 February 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-218-0103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01756482
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	Clinical Trial Mailbox, Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd , ClinicalTrialDisclosures@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	03 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2013
Global end of trial reached?	Yes
Global end of trial date	03 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the antiviral effect of presatovir (GS-5806) in healthy adults infected with RSV-A Memphis 37b (RSV). 4 quarantines were enrolled at a 1:1 ratio to receive presatovir 50 mg on Day 1 and 25 mg on Days 2-5, or placebo to match. 3 adaptive quarantines were enrolled at a 4:1 ratio to receive presatovir (either 50 mg on Day 1 followed by 25 mg on Days 2-3; a single 100 mg dose on Day 1; or 10 mg on Day 1 followed by 5 mg on Days 2-5) or placebo to match; the adaptive quarantines were exploratory in nature and were included in the safety population, but not in the efficacy analyses.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC approval were submitted by the investigator to the IEC 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	21 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 143
Worldwide total number of subjects	143
EEA total number of subjects	143

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	143
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a single study site in the United Kingdom. The first participant was screened on 21 November 2012. The last study visit occurred on 03 August 2013.

Pre-assignment

Screening details:

372 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:

Participants entered quarantine on Day -2 or -1, received presatovir for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.

Arm type	Experimental
Investigational medicinal product name	Presatovir
Investigational medicinal product code	
Other name	GS-5806
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Presatovir was administered as either: 50 mg on Day 1, followed by 25 mg on Days 2 to 5; 50 mg on Day 1, followed by 25 mg on Days 2 to 3; 100 mg on Day 1 (single dose); or 10 mg on Day 1, followed by 5 mg on Days 2-5.

Arm title	Placebo

Arm description:

Participants entered quarantine on Day -2 or -1, received presatovir placebo for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.

Arm type	Placebo
Investigational medicinal product name	Presatovir Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Presatovir placebo was administered for up to 5 days.

Number of subjects in period 1[1]	Presatovir	Placebo
Started	87	53
Completed	87	52
Not completed	0	1
Investigator's Discretion	-	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: 3 participants who were enrolled but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	Presatovir
Reporting group description:	
Participants entered quarantine on Day -2 or -1, received presatovir for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.	
Reporting group title	Placebo
Reporting group description:	
Participants entered quarantine on Day -2 or -1, received presatovir placebo for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.	

Reporting group values	Presatovir	Placebo	Total
Number of subjects	87	53	140
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	28.4	25.1	
standard deviation	± 6.88	± 3.7	-
Gender categorical Units: Subjects			
Female	22	13	35
Male	65	40	105
Race Units: Subjects			
Asian	5	1	6
Black or African American	5	4	9
White	74	46	120
Other	3	2	5
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	86	53	139

End points

End points reporting groups

Reporting group title	Presatovir

Reporting group description:

Participants entered quarantine on Day -2 or -1, received presatovir for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.

Reporting group title	Placebo

Reporting group description:

Participants entered quarantine on Day -2 or -1, received presatovir placebo for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.

Primary: AUC of Viral Load Post Initial Dose through Study Day 12 by qRT-PCR

End point title	AUC of Viral Load Post Initial Dose through Study Day 12 by qRT-PCR

End point description:

Adjusted means (displayed as arithmetic mean) are generated from ANCOVA model with baseline viral load as a covariate. Data for participants in the Full Analysis Set receiving complete course of presatovir 50 mg on Day 1 followed by 25 mg on Days 2 to 5, and who had documented RSV infection prior to initiation of study drug are presented.

AUC = viral load over time (area under the viral load versus time curve), measured in log10PFUe/mL × hour.
qRT-PCR = quantitative reverse transcriptase-polymerase chain reaction. PFUe/mL = plaque-forming unit equivalents per milliliter.

End point type	Primary

End point timeframe:

Baseline to Day 12

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: (log10 PFUe/mL)*hour				
arithmetic mean (standard error)	250.7 (± 31.36)	757.7 (± 64.28)		

Statistical analyses

Statistical analysis title	Difference in treatments

Statistical analysis description:

The p-value, difference in treatments, and 95% confidence intervals (CIs) were generated using a parametric ANCOVA with corresponding baseline viral load as a covariate in the model and tested at the 2-sided 0.05 level.

Comparison groups	Presatovir v Placebo

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	506.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	361.8
upper limit	652.1

Secondary: AUC of Viral Load Post Inoculation through Study Day 12 by qRT-PCR

End point title	AUC of Viral Load Post Inoculation through Study Day 12 by qRT-PCR

End point description:

Adjusted means (displayed as arithmetic mean) are generated from ANCOVA model with baseline viral load as a covariate. Data for participants in the Full Analysis Set receiving complete course of presatovir 50 mg on Day 1 followed by 25 mg on Days 2 to 5, and who had documented RSV infection prior to initiation of study drug are presented.

AUC = viral load over time (area under the viral load versus time curve), measured in log10PFUe/mL × hour.
qRT-PCR = quantitative reverse transcriptase-polymerase chain reaction. PFUe/mL = plaque-forming unit equivalents per milliliter.

End point type	Secondary

End point timeframe:

Baseline to Day 12

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: (log10 PFUe/mL)*hour				
arithmetic mean (standard error)	279.8 (± 40.64)	810.8 (± 71)		

Statistical analyses

Statistical analysis title	Difference in treatments

Statistical analysis description:

The difference in treatments and 95% CIs were generated using an ANCOVA model with corresponding baseline value as a covariate.

Comparison groups	Presatovir v Placebo

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	531
Confidence interval	
level	95 %
sides	2-sided
lower limit	365.3
upper limit	696.8

Secondary: Total Weight of Mucus Post Initial Dose through Last Dose of Study Drug

End point title	Total Weight of Mucus Post Initial Dose through Last Dose of Study Drug

End point description:

The adjusted means (displayed as arithmetic mean) and pooled standard errors (SE) were generated from an ANOVA model. Data for participants in the Full Analysis Set receiving complete course of presatovir 50 mg on Day 1 followed by 25 mg on Days 2 to 5, and who had documented RSV infection prior to initiation of study drug are presented.

End point type	Secondary

End point timeframe:

Baseline to Day 12

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: grams				
arithmetic mean (standard error)	6.9 (± 2.56)	15.1 (± 2.56)		

Statistical analyses

Statistical analysis title	Difference in treatments

Statistical analysis description:

The difference in treatments and 95% CIs were generated using an ANOVA model.

Comparison groups	Placebo v Presatovir
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	15.5

Secondary: AUC of Total Symptom Scores Change from Baseline Post Initial Dose of Study Drug through Study Day 12

End point title	AUC of Total Symptom Scores Change from Baseline Post Initial Dose of Study Drug through Study Day 12

End point description:

Adjusted means (displayed as arithmetic mean) are generated from ANCOVA model with corresponding baseline symptom score as a covariate. Data for participants in the Full Analysis Set receiving complete course of presatovir 50 mg on Day 1 followed by 25 mg on Days 2 to 5, and who had documented RSV infection prior to initiation of study drug are presented.

AUC = change in symptom score over time (area under the symptom score change versus time curve), measured in score × hour.

End point type	Secondary

End point timeframe:

Baseline to Day 12

End point values	Presatovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: score*hour				
arithmetic mean (standard error)	-20.2 (± 46.04)	204.9 (± 60.48)		

Statistical analyses

Statistical analysis title	Difference in treatments

Statistical analysis description:

The difference in treatments and 95% CIs were generated using an ANCOVA model with corresponding baseline value as a covariate.

Comparison groups	Presatovir v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	225.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	72.2
upper limit	378

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 12 plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: Participants were randomized and received at least 1 dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Presatovir

Reporting group description:

Participants entered quarantine on Day -2 or -1, received presatovir for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.

Reporting group title	Placebo

Reporting group description:

Participants entered quarantine on Day -2 or -1, received presatovir placebo for up to 5 days, were released from quarantine on Day 12, and had follow-up and end-of-study visits on Study Days 21 (± 3 days) and 26 (± 3 days), respectively.

Serious adverse events	Presatovir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 87 (0.00%)	0 / 53 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	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	34 / 87 (39.08%)	24 / 53 (45.28%)	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	8 / 87 (9.20%)	5 / 53 (9.43%)	
occurrences (all)	8	5	
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 87 (3.45%)	4 / 53 (7.55%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	20 / 87 (22.99%)	13 / 53 (24.53%)	
occurrences (all)	23	14	
Rhinorrhoea			
subjects affected / exposed	2 / 87 (2.30%)	7 / 53 (13.21%)	
occurrences (all)	2	7	
Nasal congestion			
subjects affected / exposed	4 / 87 (4.60%)	4 / 53 (7.55%)	
occurrences (all)	4	4	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	5 / 87 (5.75%)	4 / 53 (7.55%)	
occurrences (all)	5	4	
Rash			
subjects affected / exposed	1 / 87 (1.15%)	3 / 53 (5.66%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2012	Documented history of allergy to sulfa drugs was added to the exclusion criteria; electrocardiogram (ECG) monitoring at Tmax, defined as approximately 3 hours postdose, from the day of first dose through 5 days of dosing was included; development of bronchospasm, regardless of causality, was included as a protocol-specific stopping rule; the time points used for determination of the ECG stopping rule were clarified.
11 January 2013	Quarantine 5 was allowed an adaptive design, 2 additional quarantines with an adaptive dosing regimen based on data obtained from the prespecified dosing quarantines (1-4) were added.

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.

There were no limitations affecting the analysis or results.

Notes: