



## 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          | v1            |
| This version publication date  | 12 April 2018 |
| First version publication date | 12 April 2018 |

#### 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 |
|------------------------------|-----|

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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<br>1 <sup>[1]</sup> | Presatovir | Placebo |
|--------------------------------------------------|------------|---------|
|                                                  |            |         |
| Started                                          | 30         | 29      |
| Completed                                        | 29         | 26      |
| Not completed                                    | 1          | 3       |
| Death                                            | -          | 2       |
| Withdrew consent                                 | 1          | 1       |

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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:<br>Presatovir on Days 1, 5, 9, 13, and 17 |            |
| Reporting group title                                                  | Placebo    |
| Reporting group description:<br>Placebo on Days 1, 5, 9, 13, and 17    |            |

| Reporting group values             | Presatovir | Placebo | Total |
|------------------------------------|------------|---------|-------|
| Number of subjects                 | 30         | 29      | 59    |
| Age categorical<br>Units: Subjects |            |         |       |

|                                                                                                |                 |                 |    |
|------------------------------------------------------------------------------------------------|-----------------|-----------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                        | 50.5<br>± 16.27 | 54.4<br>± 12.59 | -  |
| Gender categorical<br>Units: Subjects                                                          |                 |                 |    |
| Female                                                                                         | 9               | 6               | 15 |
| Male                                                                                           | 21              | 23              | 44 |
| Race<br>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<br>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<br>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<br>Units: Subjects    |                 |                 |    |
| Yes                                                                                            | 12              | 11              | 23 |
| No                                                                                             | 18              | 18              | 36 |

|                                                                                                                        |         |         |   |
|------------------------------------------------------------------------------------------------------------------------|---------|---------|---|
| Nasal Viral Load                                                                                                       |         |         |   |
| Units: log10 copies/mL                                                                                                 |         |         |   |
| arithmetic mean                                                                                                        | 6.22    | 6.02    |   |
| standard deviation                                                                                                     | ± 1.365 | ± 1.574 | - |
| Oxygen Saturation                                                                                                      |         |         |   |
| Oxygen saturation is a measure of how much oxygen the blood is carrying as a percentage of the maximum it could carry. |         |         |   |
| Units: percent saturation                                                                                              |         |         |   |
| arithmetic mean                                                                                                        | 94      | 93      |   |
| standard deviation                                                                                                     | ± 3.8   | ± 5.1   | - |

## End points

### End points reporting groups

|                                                                        |            |
|------------------------------------------------------------------------|------------|
| Reporting group title                                                  | Presatovir |
| Reporting group description:<br>Presatovir on Days 1, 5, 9, 13, and 17 |            |
| Reporting group title                                                  | Placebo    |
| Reporting group description:<br>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:<br>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.<br><br>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:<br>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 ( $\pm$ 0.215) | -0.97 ( $\pm$ 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 <sup>[1]</sup>                        |
| 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 <sup>[3]</sup>                        |
| 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

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[4]</sup>                        |
| 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          |  |
| <b>Bacterial infection</b>                      |                 |                |  |
| 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          |  |
| <b>Clostridium difficile colitis</b>            |                 |                |  |
| 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          |  |
| <b>Febrile infection</b>                        |                 |                |  |
| 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          |  |
| <b>Influenza</b>                                |                 |                |  |
| 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          |  |
| <b>Sepsis</b>                                   |                 |                |  |
| 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 %

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

|                                                                                                              |                      |                      |  |
|--------------------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                  | 2 / 30 (6.67%)<br>2  | 3 / 29 (10.34%)<br>4 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                        | 1 / 30 (3.33%)<br>1  | 2 / 29 (6.90%)<br>2  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 30 (0.00%)<br>0  | 2 / 29 (6.90%)<br>2  |  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 30 (6.67%)<br>3  | 0 / 29 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 0 / 30 (0.00%)<br>0  | 3 / 29 (10.34%)<br>3 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                | 3 / 30 (10.00%)<br>3 | 0 / 29 (0.00%)<br>0  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 30 (3.33%)<br>1  | 2 / 29 (6.90%)<br>2  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 3 / 30 (10.00%)<br>3 | 1 / 29 (3.45%)<br>1  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 30 (6.67%)<br>2  | 1 / 29 (3.45%)<br>1  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 30 (6.67%)<br>2  | 0 / 29 (0.00%)<br>0  |  |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 30 (0.00%)<br>0  | 2 / 29 (6.90%)<br>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<br>occurrences (all) | 2 / 30 (6.67%)<br>2 | 1 / 29 (3.45%)<br>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      | <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• Appendix 5 was updated to provide additional information regarding pregnancy precautions and contraceptive requirements.</li><li>• 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.</li><li>• Inclusion Criterion 2 was updated to &lt; 48 hours prior to screening for clarity.</li><li>• Inclusion Criterion 7 was removed for consistency with Exclusion Criterion 3</li></ul> |
| 22 September 2014 | <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• 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).</li><li>• Inclusion Criterion 6 (contraceptive requirements) was modified in alignment with changes made to contraceptive requirements in Appendix 5.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 21 October 2014   | <ul style="list-style-type: none"><li>• 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, &lt; 1% failure rate).</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30 June 2015     | <ul style="list-style-type: none"> <li>• Reproductive toxicology data in the protocol background was updated to reflect the definitive rat and rabbit studies.</li> <li>• Exclusion Criterion 8 was removed as the intent of the criterion is covered in Exclusion Criterion 13</li> <li>• 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.</li> <li>• 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.</li> <li>• Study drug discontinuation criteria updated to include extra hepatic monitoring and Hy's law in accordance with Canadian regulations.</li> <li>• Secondary and exploratory endpoints and analyses updated</li> <li>• Induced sputum removed as collection of this sample is not standard practice.</li> <li>• Section 1.2.2 was updated for consistency with the IB.</li> <li>• A new Inclusion Criterion 1 was added to clarify age ranges allowed in the study.</li> <li>• 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.</li> <li>• 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.</li> <li>• Exclusion Criterion 14 (allergy to sulfa drugs) was updated to clarify that the criterion applies to sulfa reactions that are of most concern.</li> <li>• Hepatic monitoring and statistical texts were updated for clarity</li> </ul> |
| 30 November 2015 | <ul style="list-style-type: none"> <li>• Section 1.2.4.4: Ongoing Studies was added to provide consistency among protocols in the presatovir program.</li> <li>• 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.</li> <li>• Screening RSV testing was updated to allow for standard clinical practice procedures surrounding RSV diagnosis confirmation and in meeting study inclusion criteria.</li> <li>• Electrocardiograms (ECGs), troponin testing, and collection of standard of care clinical data for central review were added.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 28 March 2016    | <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• The number of sites was increased in order to accelerate enrollment.</li> <li>• Sweden-specific requirements for obtaining consent via legal guardian were added to the inclusion criteria.</li> <li>• 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.</li> <li>• Administrative clarifications were made to Section 8: Statistical Considerations.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported