



Clinical trial results:

A randomised, double-blind, double-dummy, placebo and active-controlled, three-way crossover study to evaluate the safety, tolerability and efficacy of 28-day inhaled CHF 6001 DPI (1200 microgrammes daily) in subjects with COPD.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-001005-25 |
| Trial protocol | GB |
| Global end of trial date | 25 October 2013 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 09 August 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setCorrection of Sponsor public contact and scientific contact. |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | CCD-1201-PR-0079 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01730404 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Chiesi Farmaceutici SpA |
| Sponsor organisation address | Via Palermo, 26/A, Parma, Italy, 43122 |
| Public contact | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.com |
| Scientific contact | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.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 | 25 October 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are:

- to evaluate the effect of CHF 6001 DPI on biological markers of inflammation in induced sputum and in the blood, and on pulmonary function.
- to evaluate the safety and tolerability of CHF 6001 DPI after 28 days of inhaled dosing.
- to assess the blood PK profile of CHF6001 and its metabolite at steady-state in GOLD stage 2-3 COPD patients.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements . Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 04 October 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: 55 |
| Worldwide total number of subjects | 55 |
| EEA total number of subjects | 55 |

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) | 43 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifty-five patients were actually randomised into the study; following the randomization 13 patients were withdrawn due to adverse events (AE), and 5 patients withdrew their consent for participation. All 55 patients were analysed as part of the Safety population. Fifty-three patients were analysed as part of the modified ITT population.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial by sequence (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sequence C--R--P |

Arm description:

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

3 inhalations of CHF 6001 400 µg administered using Aerolizer® DPI; giving a total dose of 1200 µg of CHF 6001

| | |
|--|-------------|
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 tablet Roflumilast 500 µg; giving a total dose of 500µg of Roflumilast

| | |
|--|---------------------|
| Investigational medicinal product name | CHF 6001 placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 Placebo DPI | |
| Investigational medicinal product name | Roflumilast placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast Placebo | |
| Arm title | Sequence P--C--R |

Arm description:

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 400 µg administered using Aerolizer® DPI; giving a total dose of 1200 µg of CHF 6001 | |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast 500 µg; giving a total dose of 500µg of Roflumilast | |
| Investigational medicinal product name | CHF 6001 placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 Placebo DPI | |

| | |
|--|---------------------|
| Investigational medicinal product name | Roflumilast placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast Placebo | |
| Arm title | Sequence R--P--C |

Arm description:

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|---|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast 500 µg; giving a total dose of 500µg of Roflumilast | |
| Investigational medicinal product name | Roflumilast placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast Placebo | |
| Investigational medicinal product name | CHF 6001 placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 Placebo DPI | |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 400 µg ; giving a total dose of 1200 µg of CHF 6001 | |
| Arm title | Sequence C--P--R |

Arm description:

- Test treatment (C):

3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

- Placebo (P):

3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

- Reference treatment (R):

3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 400 µg; giving a total dose of 1200 µg of CHF 6001 | |
| Investigational medicinal product name | CHF 6001 placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 Placebo DPI | |
| Investigational medicinal product name | Roflumilast placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast Placebo | |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast 500 µg; giving a total dose of 500µg of Roflumilast | |
| Arm title | Sequence P--R--C |

Arm description:

- Placebo (P):

3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

- Reference treatment (R):

3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

- Test treatment (C):

3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|---|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 Placebo DPI | |
| Investigational medicinal product name | Roflumilast placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast Placebo | |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast 500 µg; giving a total dose of 500µg of Roflumilast | |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 400 µg ; giving a total dose of 1200 µg of CHF 6001 | |
| Arm title | Sequence R--C--P |

Arm description:

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|---------------------|
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast 500 µg; giving a total dose of 500µg of Roflumilast | |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 400 µg ; giving a total dose of 1200 µg of CHF 6001 | |
| Investigational medicinal product name | CHF 6001 placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 3 inhalations of CHF 6001 Placebo DPI | |
| Investigational medicinal product name | Roflumilast placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 tablet Roflumilast Placebo | |

| Number of subjects in period 1 | Sequence C--R--P | Sequence P--C--R | Sequence R--P--C |
|---------------------------------------|------------------|------------------|------------------|
| Started | 10 | 10 | 8 |
| Completed | 6 | 7 | 4 |
| Not completed | 4 | 3 | 4 |
| Consent withdrawn by subject | 1 | 1 | - |
| Adverse event, non-fatal | 3 | 2 | 4 |

| Number of subjects in period 1 | Sequence C--P--R | Sequence P--R--C | Sequence R--C--P |
|---------------------------------------|------------------|------------------|------------------|
| Started | 9 | 8 | 10 |
| Completed | 9 | 5 | 6 |
| Not completed | 0 | 3 | 4 |
| Consent withdrawn by subject | - | 1 | 2 |
| Adverse event, non-fatal | - | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Sequence C--R--P |
|-----------------------|------------------|

Reporting group description:

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence P--C--R |
|-----------------------|------------------|

Reporting group description:

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence R--P--C |
|-----------------------|------------------|

Reporting group description:

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence C--P--R |
|-----------------------|------------------|

Reporting group description:

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence P--R--C |
|-----------------------|------------------|

Reporting group description:

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence R--C--P |
|-----------------------|------------------|

Reporting group description:

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| Reporting group values | Sequence C--R--P | Sequence P--C--R | Sequence R--P--C |
|--|------------------|------------------|------------------|
| Number of subjects | 10 | 10 | 8 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |

| | | | |
|-------------------|--|--|--|
| 85 years and over | | | |
|-------------------|--|--|--|

| | | | |
|---|----------------|----------------|----------------|
| Age continuous Units: years arithmetic mean standard deviation | 59.5 ± 7.25 | 61.7 ± 6.46 | 59.4 ± 5.71 |
| Gender categorical Units: Subjects | | | |
| Female | 5 | 4 | 5 |
| Male | 5 | 6 | 3 |

| Reporting group values | Sequence C--P--R | Sequence P--R--C | Sequence R--C--P |
|--|------------------|------------------|------------------|
| Number of subjects | 9 | 8 | 10 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | 55.2 ± 7.14 | 60.5 ± 5.32 | 59.3 ± 5.79 |
| Gender categorical Units: Subjects | | | |
| Female | 3 | 5 | 3 |
| Male | 6 | 3 | 7 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 55 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |

| | | | |
|---|----|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 25 | | |
| Male | 30 | | |

Subject analysis sets

| | |
|--|---|
| Subject analysis set title | Test treatment - Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomised subjects who will take at least one administration of study medication | |
| Subject analysis set title | Reference treatment - Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomised subjects who will take at least one administration of study medication | |
| Subject analysis set title | Placebo - Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomised subjects who will take at least one administration of study medication | |
| Subject analysis set title | Test treatment - mITT population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All randomised subjects who take at least one administration of study medication and with at least one post-baseline efficacy assessment | |
| Subject analysis set title | Reference treatment - mITT population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All randomised subjects who take at least one administration of study medication and with at least one post-baseline efficacy assessment. | |
| Subject analysis set title | Placebo - mITT population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All randomised subjects who take at least one administration of study medication and with at least one post-baseline efficacy assessment. | |
| Subject analysis set title | Test treatment - PK population |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All subjects from the safety population excluding subjects without any valid PK measurement and with major Protocol deviations affecting the PK evaluations | |

| Reporting group values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population |
|--|------------------------------------|---|-----------------------------|
| Number of subjects | 42 | 49 | 43 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) | | | |

| | | | |
|---|----|----|----|
| Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | ± | ± | ± |
| Gender categorical Units: Subjects | | | |
| Female | 16 | 21 | 16 |
| Male | 26 | 28 | 27 |

| Reporting group values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population |
|---|----------------------------------|---------------------------------------|---------------------------|
| Number of subjects | 42 | 47 | 43 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | ± | ± | ± |
| Gender categorical Units: Subjects | | | |
| Female | 16 | 19 | 16 |
| Male | 26 | 28 | 27 |

| Reporting group values | Test treatment - PK population | | |
|--|--------------------------------|--|--|
| Number of subjects | 40 | | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) | | | |

| | | | |
|---|-------|--|--|
| Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | \pm | | |
| Gender categorical Units: Subjects | | | |
| Female | 16 | | |
| Male | 24 | | |

End points

End points reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Sequence C--R--P |
|-----------------------|------------------|

Reporting group description:

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence P--C--R |
|-----------------------|------------------|

Reporting group description:

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001
- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence R--P--C |
|-----------------------|------------------|

Reporting group description:

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast
- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo
- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence C--P--R |
|-----------------------|------------------|

Reporting group description:

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence P--R--C |
|-----------------------|------------------|

Reporting group description:

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Sequence R--C--P |
|-----------------------|------------------|

Reporting group description:

- Reference treatment (R):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast 500 µg; giving a total dose of 500 µg of Roflumilast

- Test treatment (C):
3 inhalations of CHF 6001 400 µg + 1 tablet Roflumilast Placebo; giving a total dose of 1200 µg of CHF 6001

- Placebo (P):
3 inhalations of CHF 6001 Placebo DPI + 1 tablet Roflumilast Placebo

After a 15 ±2 days run-in Period, patients were randomised to receive CHF 6001 1200µg using Aerolizer® DPI (T), Roflumilast 500µg (Daxas®) (R) or matched Placebo daily in the morning for 28 days, according to the above sequence. Each treatment period was separated from the other by a wash-out Period of 4-5 weeks.

| | |
|----------------------------|------------------------------------|
| Subject analysis set title | Test treatment - Safety population |
|----------------------------|------------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All randomised subjects who will take at least one administration of study medication

| | |
|----------------------------|---|
| Subject analysis set title | Reference treatment - Safety population |
|----------------------------|---|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All randomised subjects who will take at least one administration of study medication

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Placebo - Safety population |
|----------------------------|-----------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All randomised subjects who will take at least one administration of study medication

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Test treatment - mITT population |
|----------------------------|----------------------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

All randomised subjects who take at least one administration of study medication and with at least one post-baseline efficacy assessment

| | |
|--|---------------------------------------|
| Subject analysis set title | Reference treatment - mITT population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All randomised subjects who take at least one administration of study medication and with at least one post-baseline efficacy assessment. | |
| Subject analysis set title | Placebo - mITT population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All randomised subjects who take at least one administration of study medication and with at least one post-baseline efficacy assessment. | |
| Subject analysis set title | Test treatment - PK population |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All subjects from the safety population excluding subjects without any valid PK measurement and with major Protocol deviations affecting the PK evaluations | |

Primary: Total cell count

| | |
|---|------------------|
| End point title | Total cell count |
| End point description: Data from Day 21, Day 24 and Day 28 were averaged and change from baseline was used in the analyses and reported here (see Table 14.2.1.4). This is an exploratory study therefore the objectives and the endpoints have not been identified as either primary or secondary. | |
| End point type | Primary |
| End point timeframe: Total cell count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: millions cells/g sputum | | | | |
| arithmetic mean (standard deviation) | 2.7301 (\pm 8.58667) | -0.6251 (\pm 17.58909) | 1.0149 (\pm 13.52405) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.6544 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.912 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.605 |
| upper limit | 1.376 |

Notes:

[1] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Placebo - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.0835 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.673 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4292 |
| upper limit | 1.0564 |

Notes:

[2] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.1875 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.355 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8571 |
| upper limit | 2.1422 |

Notes:

[3] - This is a "proof of concept" study: no statistical hypothesis is included

Secondary: Basophils

| | |
|------------------------|-----------|
| End point title | Basophils |
| End point description: | |
| End point type | |
| | Secondary |

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | -0.01 (± 0.028) | 0 (± 0.03) | 0 (± 0.023) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Basophils/Leukocytes

| | |
|-----------------|----------------------|
| End point title | Basophils/Leukocytes |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 | 43 | 39 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0 (± 0.29) | -0.1 (± 0.24) | 0 (± 0.27) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Eosinophils

| | |
|-----------------|-------------|
| End point title | Eosinophils |
|-----------------|-------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | 0.01 (± 0.104) | 0.02 (± 0.102) | 0.07 (± 0.173) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Eosinophis/Leukocytes

End point title Eosinophis/Leukocytes

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 | 43 | 39 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 1.39) | 0 (± 1.27) | 0.8 (± 2.06) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Erythrocytes

End point title Erythrocytes

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ¹² /L | | | | |
| arithmetic mean (standard deviation) | 0.015 (± 0.1844) | 0.005 (± 0.2089) | 0.022 (± 0.2293) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hematocrit

| | |
|-----------------|------------|
| End point title | Hematocrit |
|-----------------|------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | -0.001 (± 0.0177) | -0.003 (± 0.0183) | -0.001 (± 0.0201) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin

| | |
|-----------------|------------|
| End point title | Hemoglobin |
|-----------------|------------|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | -0.05 (± 0.567) | -0.15 (± 0.607) | -0.1 (± 0.669) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocytes

| | |
|--|------------|
| End point title | Leukocytes |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | 0.35 (± 1.673) | 0.39 (± 1.345) | 0.33 (± 1.517) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lymphocytes

| | |
|------------------------|-------------|
| End point title | Lymphocytes |
| End point description: | |

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | 0.18 (± 0.439) | 0.21 (± 0.457) | 0.12 (± 0.453) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lymphocytes/Leukocytes

| | |
|--|------------------------|
| End point title | Lymphocytes/Leukocytes |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 | 43 | 39 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 1.5 (± 5.18) | 1.3 (± 6.34) | 0.6 (± 6.44) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Monocytes

| | |
|------------------------|-----------|
| End point title | Monocytes |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | | | | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | -0.04 (± 0.183) | 0 (± 0.121) | -0.01 (± 0.176) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Monocytes/Leukocytes

| | |
|-----------------|----------------------|
| End point title | Monocytes/Leukocytes |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 | 43 | 39 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -0.8 (± 1.68) | -0.5 (± 1.46) | -0.6 (± 1.58) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophils

| | |
|-----------------|-------------|
| End point title | Neutrophils |
|-----------------|-------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | 0.18 (± 1.479) | 0.16 (± 1.237) | 0.15 (± 1.325) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophils/Leukocytes

End point title Neutrophils/Leukocytes

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 | 43 | 39 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -0.8 (± 5.58) | -0.6 (± 7.09) | -0.8 (± 6.69) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Platelets

End point title Platelets

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | 2.25 (± 19.847) | 13.44 (± 32.017) | -1.46 (± 23.999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine aminotransferase

| | |
|-----------------|--------------------------|
| End point title | Alanine aminotransferase |
|-----------------|--------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 40 | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | -1.19 (± 7.895) | -2.4 (± 6.13) | -0.94 (± 9.66) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Albumin

| | |
|-----------------|---------|
| End point title | Albumin |
|-----------------|---------|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: g/L | | | | |
| arithmetic mean (standard deviation) | -0.5 (± 2.192) | -0.17 (± 2.533) | -0.2 (± 2.131) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Alkaline phosphatase

| | |
|------------------------|----------------------|
| End point title | Alkaline phosphatase |
| End point description: | |

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 40 | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | -0.63 (± 9.352) | 1.7 (± 9.028) | 1.49 (± 7.882) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate aminotransferase

| | |
|-----------------|----------------------------|
| End point title | Aspartate aminotransferase |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 39 | 44 | 37 | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | 0.51 (± 8.583) | -1.2 (± 5.03) | 0.7 (± 6.479) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Bilirubin

| | |
|-----------------|-----------|
| End point title | Bilirubin |
|-----------------|-----------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 40 | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | -0.51 (± 3.948) | -0.48 (± 3.003) | 0.01 (± 3.078) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Calcium

| | |
|-----------------|---------|
| End point title | Calcium |
|-----------------|---------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 44 | 41 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -0.01 (± 0.1175) | 0.016 (± 0.0957) | -0.01 (± 0.0827) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Chloride

| | |
|-----------------|----------|
| End point title | Chloride |
|-----------------|----------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 37 | 44 | 36 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -0.14 (± 2.702) | -0.58 (± 2.281) | -0.23 (± 2.496) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Creatinine

| | |
|--|------------|
| End point title | Creatinine |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | -0.9 (± 6.183) | -0.18 (± 7.565) | -1.32 (± 6.274) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Gamma glutamyl transferase

| | |
|--|----------------------------|
| End point title | Gamma glutamyl transferase |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Routine hematology and chemistry were performed at screening and Day 28. | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 39 | 44 | 40 | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | -1.44 (± 8.542) | -0.76 (± 11.551) | -1.37 (± 12.08) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Glucose

| | |
|-----------------|---------|
| End point title | Glucose |
|-----------------|---------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 39 | 44 | 40 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | 0.187 (± 0.6213) | 0.167 (± 0.5524) | 0.212 (± 0.9286) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phosphate

| | |
|-----------------|-----------|
| End point title | Phosphate |
|-----------------|-----------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 40 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | 0.039 (± 0.1867) | 0.039 (± 0.1487) | 0.028 (± 0.1309) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Potassium

End point title Potassium

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 40 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -0.14 (\pm 0.3181) | -0.049 (\pm 0.523) | -0.124 (\pm 0.3382) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Protein

End point title Protein

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 40 | |
| Units: g/L | | | | |
| arithmetic mean (standard deviation) | -0.09 (\pm 3.775) | 0.27 (\pm 3.547) | 0.43 (\pm 3.083) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Sodium

End point title Sodium

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 45 | 41 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 2.1) | -0.3 (\pm 2.09) | -0.2 (\pm 2.06) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Urate

End point title Urate

End point description:

End point type Secondary

End point timeframe:

Routine hematology and chemistry were performed at screening and Day 28.

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 35 | 40 | 36 | |
| Units: μ mol/L | | | | |
| arithmetic mean (standard deviation) | -2.94 (\pm 31.936) | -12.15 (\pm 37.216) | -11.09 (\pm 31.245) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Neutrophils - absolute count

| | |
|-----------------|------------------------------|
| End point title | Neutrophils - absolute count |
|-----------------|------------------------------|

End point description:

Data from Day 21, Day 24 and Day 28 were averaged and change from baseline was used in the analyses and reported here (see Table 14.2.1.5)

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Neutrophil count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: millions neutrophils/g sputum | | | | |
| arithmetic mean (standard deviation) | 2.6588 (\pm 8.28804) | -0.647 (\pm 17.43528) | 0.8679 (\pm 13.13533) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.565 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.879 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5611 |
| upper limit | 1.3774 |

Notes:

[4] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|----------------------------|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.2238 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.358 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.823 |
| upper limit | 2.241 |

Notes:

[5] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.0815 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.647 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3958 |
| upper limit | 1.0587 |

Notes:

[6] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Neutrophils - differential count

| | |
|---|----------------------------------|
| End point title | Neutrophils - differential count |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and reported here (see Table 14.2.1.9 of CSR)) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Neutrophil count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0.4409 (\pm 14.89339) | -5.5694 (\pm 13.66577) | -1.0944 (\pm 16.06526) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.1779 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.953 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.888 |
| upper limit | 1.023 |

Notes:

[7] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | = 0.2549 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.957 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.885 |
| upper limit | 1.0339 |

Notes:

[8] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | = 0.9277 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.996 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9208 |
| upper limit | 1.0783 |

Notes:

[9] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Eosinophils - absolute count

| | |
|--|------------------------------|
| End point title | Eosinophils - absolute count |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and reported here (see Table 14.2.1.6 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Eosinophil count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|---------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: millions eosinophils /g sputum | | | | |
| arithmetic mean (standard deviation) | 0.0117 (± 1.19362) | -0.0099 (± 0.08537) | 0.0498 (± 0.30105) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1521 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.241 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0335 |
| upper limit | 1.7296 |

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| P-value | = 0.5608 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.536 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0626 |
| upper limit | 4.5957 |

Notes:

[10] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.4489 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.449 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0541 |
| upper limit | 3.7301 |

Notes:

[11] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Eosinophils - differential count

| | |
|---|----------------------------------|
| End point title | Eosinophils - differential count |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.10 of CSR) | |
| End point type | Other pre-specified |

End point timeframe:

Eosinophil count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -0.6263 (\pm 6.22173) | 0.5386 (\pm 2.328) | 1.3458 (\pm 4.51746) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| P-value | = 0.2485 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.238 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 2.8363 |

Notes:

[12] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| P-value | = 0.9687 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.949 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0639 |
| upper limit | 14.094 |

Notes:

[13] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| P-value | = 0.2957 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.251 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.018 |
| upper limit | 3.5089 |

Notes:

[14] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Macrophages - absolute count

| | |
|--|------------------------------|
| End point title | Macrophages - absolute count |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.7 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Macrophage count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: millions macrophages/g sputum | | | | |
| arithmetic mean (standard deviation) | 0.1048 (± 0.70455) | 0.0231 (± 0.77945) | 0.0961 (± 1.01861) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | = 0.9379 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.983 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6379 |
| upper limit | 1.5159 |

Notes:

[15] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[16] |
| P-value | = 0.3588 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.808 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5069 |
| upper limit | 1.2864 |

Notes:

[16] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[17] |
| P-value | = 0.4097 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.218 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7549 |
| upper limit | 1.9643 |

Notes:

[17] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Macrophages - differential count

| | |
|-----------------|----------------------------------|
| End point title | Macrophages - differential count |
|-----------------|----------------------------------|

End point description:

Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.11 of CSR)

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Macrophage count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0.4879 (\pm 14.69496) | 5.4444 (\pm 11.80631) | -0.7194 (\pm 14.45761) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[18] |
| P-value | = 0.9551 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6219 |
| upper limit | 1.6526 |

Notes:

[18] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[19] |
| P-value | = 0.3048 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.296 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7826 |
| upper limit | 2.1468 |

Notes:

[19] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[20] |
| P-value | = 0.3574 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.782 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4586 |
| upper limit | 1.3338 |

Notes:

[20] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Lymphocytes - absolute count

| | |
|--|------------------------------|
| End point title | Lymphocytes - absolute count |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table of 14.2.1.8 CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Lymphocyte count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: millions lymphocytes/g sputum | | | | |
| arithmetic mean (standard deviation) | -0.0017 (\pm 0.01046) | 0.001 (\pm 0.00567) | 0.0004 (\pm 0.00152) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| P-value | = 0.146 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 4.076 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 27.6916 |

Notes:

[21] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| P-value | = 0.2756 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 2.913 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4121 |
| upper limit | 20.5843 |

Notes:

[22] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| P-value | = 0.741 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.399 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1817 |
| upper limit | 10.7785 |

Notes:

[23] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Lymphocytes - differential count

| | |
|---|----------------------------------|
| End point title | Lymphocytes - differential count |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.12 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Lymphocyte count in sputum was performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -0.047 (± 0.21348) | 0.0046 (± 0.08674) | 0.0222 (± 0.09268) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[24] |
| P-value | = 0.1235 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 8.409 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5454 |
| upper limit | 129.647 |

Notes:

[24] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| P-value | = 0.3513 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 3.701 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2237 |
| upper limit | 61.2316 |

Notes:

[25] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF 6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[26] |
| P-value | = 0.571 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 2.272 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1244 |
| upper limit | 41.5049 |

Notes:

[26] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: IL-8 in sputum supernatant

| | |
|---|----------------------------|
| End point title | IL-8 in sputum supernatant |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.13 of CSR) | |
| End point type | Other pre-specified |

End point timeframe:

The level of IL-8 in sputum supernatant were performed on Day 1 (baseline values), Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 152.9594 (\pm 2546.18) | -923.286 (\pm 2862.978) | 462.8729 (\pm 3054.962) | |

Statistical analyses

| Statistical analysis title | CHF6001 vs placebo |
|---|--|
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| P-value | = 0.0039 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.718 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5792 |
| upper limit | 0.8908 |

Notes:

[27] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | Roflumilast vs placebo |
|---|---|
| Comparison groups | Placebo - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[28] |
| P-value | = 0.0014 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.671 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5333 |
| upper limit | 0.845 |

Notes:

[28] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[29] |
| P-value | = 0.602 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8228 |
| upper limit | 1.3915 |

Notes:

[29] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: IL-6 in sputum supernatant

| | |
|---|----------------------------|
| End point title | IL-6 in sputum supernatant |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.14 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| The level of IL-6 in sputum supernatant were performed on Day 1 (baseline values), Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 54.1723 (± 212.7271) | 17.2294 (± 137.5087) | -20.7899 (± 92.10865) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[30] |
| P-value | = 0.0801 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.373 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9604 |
| upper limit | 1.9617 |

Notes:

[30] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[31] |
| P-value | = 0.7928 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.952 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6502 |
| upper limit | 1.3932 |

Notes:

[31] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[32] |
| P-value | = 0.0724 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.442 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9652 |
| upper limit | 2.155 |

Notes:

[32] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Neutrophil elastase in sputum supernatant

| | |
|-----------------|---|
| End point title | Neutrophil elastase in sputum supernatant |
|-----------------|---|

End point description:

Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.15 of CSR)

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

The level of neutrophil elastase in sputum supernatant were performed on Day 1 (baseline values), Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | -215988 (\pm 1657361) | -575067 (\pm 1738260) | -473269 (\pm 1463202) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[33] |
| P-value | = 0.0773 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4706 |
| upper limit | 1.0418 |

Notes:

[33] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[34] |
| P-value | = 0.0034 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3623 |
| upper limit | 0.8049 |

Notes:

[34] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[35] |
| P-value | = 0.2322 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.297 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8408 |
| upper limit | 1.9997 |

Notes:

[35] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Myeloperoxidase in sputum supernatant

| | |
|---|---------------------------------------|
| End point title | Myeloperoxidase in sputum supernatant |
| End point description: | |
| Data from Day 21, Day 24 and Day 28 were averaged and change from baseline were used in the analyses and are reported here (see Table 14.2.1.16 of CSR) | |
| End point type | Other pre-specified |

End point timeframe:

The level of myeloperoxidase in sputum supernatant were performed on Day 1 (baseline values), Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | -4.2085 (\pm 1347.198) | -402.997 (\pm 1347.198) | -402.997 (\pm 1604.78) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Placebo - mITT population v Test treatment - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[36] |
| P-value | = 0.0368 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.676 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4693 |
| upper limit | 0.975 |

Notes:

[36] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[37] |
| P-value | = 0.0086 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.589 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3997 |
| upper limit | 0.8672 |

Notes:

[37] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[38] |
| P-value | = 0.5117 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.149 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7517 |
| upper limit | 1.7561 |

Notes:

[38] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in serum fibrinogen

| | |
|--|--|
| End point title | Change from baseline to Day 28 in serum fibrinogen |
| End point description: | |
| Data on change from baseline to Day 28 were used in the analyses and are reported here (see Table 14.2.2.4 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: ug/L | | | | |
| arithmetic mean (standard deviation) | 91.0237 (± 466.5769) | 98.4042 (± 572.3796) | 57.6753 (± 571.7863) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[39] |
| P-value | = 0.0646 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.889 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7846 |
| upper limit | 1.0073 |

Notes:

[39] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[40] |
| P-value | = 0.4629 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.956 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8456 |
| upper limit | 1.0801 |

Notes:

[40] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[41] |
| P-value | = 0.2416 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8233 |
| upper limit | 1.051 |

Notes:

[41] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in serum CRP

| | |
|--|---|
| End point title | Change from baseline to Day 28 in serum CRP |
| End point description: | |
| Data on change from baseline to Day 28 were used in the analyses and are reported here (see Table 14.2.2.1 of CSR) | |
| End point type | Other pre-specified |

End point timeframe:

At Day 28

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 0.391 (\pm 44.4402) | 15.331 (\pm 173.3361) | -72.364 (\pm 381.2791) | |

Statistical analyses

| Statistical analysis title | CHF6001 vs placebo |
|---|--|
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[42] |
| P-value | = 0.553 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.902 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6382 |
| upper limit | 1.2746 |

Notes:

[42] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | Roflumilast vs placebo |
|---|---|
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[43] |
| P-value | = 0.5279 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.898 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6389 |
| upper limit | 1.2612 |

Notes:

[43] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[44] |
| P-value | = 0.9774 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.005 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7182 |
| upper limit | 1.4057 |

Notes:

[44] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in blood IL-6

| | |
|--|--|
| End point title | Change from baseline to Day 28 in blood IL-6 |
| End point description: | |
| Data on change from baseline to Day 28 were used in the analyses and are reported here (see Table 14.2.2.2 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 0.3074 (± 1.32279) | 0.281 (± 1.79656) | -1.0879 (± 2.77641) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[45] |
| P-value | = 0.1517 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9549 |
| upper limit | 1.3375 |

Notes:

[45] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[46] |
| P-value | = 0.3013 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.091 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9229 |
| upper limit | 1.2908 |

Notes:

[46] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[47] |
| P-value | = 0.6741 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.035 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8783 |
| upper limit | 1.2208 |

Notes:

[47] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in blood IL-8

| | |
|--|--|
| End point title | Change from baseline to Day 28 in blood IL-8 |
| End point description: | |
| Data on change from baseline to Day 28 were used in the analyses and are reported here (see Table 14.2.2.3 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 0.0747 (\pm 4.90551) | -2.7426 (\pm 10.89529) | -3.8656 (\pm 7.08697) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[48] |
| P-value | = 0.0556 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.157 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9964 |
| upper limit | 1.3435 |

Notes:

[48] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[49] |
| P-value | = 0.8286 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.882 |
| upper limit | 1.1688 |

Notes:

[49] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[50] |
| P-value | = 0.0736 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.987 |
| upper limit | 1.3157 |

Notes:

[50] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline in pre-bronchodilator FEV1

| | |
|--|---|
| End point title | Change from baseline in pre-bronchodilator FEV1 |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.3.1. of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 9, Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.054 (\pm 0.2149) | 0.035 (\pm 0.1703) | -0.044 (\pm 0.2219) | |

Statistical analyses

| Statistical analysis title | CHF6001 vs placebo |
|---|--|
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[51] |
| P-value | = 0.6328 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0447 |
| upper limit | 0.073 |

Notes:

[51] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | Roflumilast vs placebo |
|---|---|
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[52] |
| P-value | = 0.0631 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.055 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0031 |
| upper limit | 0.1121 |

Notes:

[52] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | CHF6001 vs Roflumilast |
|-----------------------------------|--|
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[53] |
| P-value | = 0.1789 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0996 |
| upper limit | 0.0189 |

Notes:

[53] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline in post-bronchodilator FEV1

| | |
|---|--|
| End point title | Change from baseline in post-bronchodilator FEV1 |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (sse tab. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 9, Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.067 (± 0.2459) | 0.025 (± 0.1851) | -0.068 (± 0.2136) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[54] |
| P-value | = 0.8615 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.005 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0652 |
| upper limit | 0.0547 |

Notes:

[54] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[55] |
| P-value | = 0.6931 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.012 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0483 |
| upper limit | 0.0723 |

Notes:

[55] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[56] |
| P-value | = 0.5734 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.017 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.078 |
| upper limit | 0.0435 |

Notes:

[56] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline in pre-bronchodilator FVC

| | |
|--|--|
| End point title | Change from baseline in pre-bronchodilator FVC |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 is reported here (see tab. 14.2.3.2 of CSR). | |
| End point type | Other pre-specified |

End point timeframe:

At Day 1, Day 9, Day 21, Day 24 and Day 28.

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: Liter | | | | |
| arithmetic mean (standard deviation) | -0.079 (\pm 0.2833) | 0.06 (\pm 0.3552) | -0.109 (\pm 0.3519) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[57] |
| P-value | = 0.2267 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.058 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0371 |
| upper limit | 0.154 |

Notes:

[57] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[58] |
| P-value | = 0.0292 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.105 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0109 |
| upper limit | 0.1994 |

Notes:

[58] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[59] |
| P-value | = 0.3315 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.047 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1421 |
| upper limit | 0.0486 |

Notes:

[59] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline in post-bronchodilator FVC

| | |
|--|---|
| End point title | Change from baseline in post-bronchodilator FVC |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 is reported here (tab. 14.2.3.2 of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 9, Day 21, Day 24 and Day 28. | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.135 (± 0.3188) | 0.007 (± 0.347) | -0.128 (± 0.2882) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[60] |
| P-value | = 0.6355 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.023 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0743 |
| upper limit | 0.121 |

Notes:

[60] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[61] |
| P-value | = 0.4213 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0578 |
| upper limit | 0.1368 |

Notes:

[61] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[62] |
| P-value | = 0.7455 |
| Method | ANCOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.016 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.115 |
| upper limit | 0.0827 |

Notes:

[62] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in VC

| | |
|---|--------------------------------------|
| End point title | Change from baseline to Day 28 in VC |
| End point description: | |
| Only data on change from baseline to Day 28 are reported here (see tab. 14.2.4..1 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 1 and Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 0.0013 (\pm 0.50406) | 0.0612 (\pm 0.29528) | 0.0853 (\pm 0.34144) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[63] |
| P-value | = 0.3709 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.984 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9494 |
| upper limit | 1.0198 |

Notes:

[63] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[64] |
| P-value | = 0.243 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.021 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9857 |
| upper limit | 1.0575 |

Notes:

[64] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[65] |
| P-value | = 0.0311 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.964 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9321 |
| upper limit | 0.9965 |

Notes:

[65] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in IC

| | |
|---|--------------------------------------|
| End point title | Change from baseline to Day 28 in IC |
| End point description: | |
| Only data on change from baseline to Day 28 are reported here (see tab 14.2.4.2). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 0.0354 (± 0.43351) | 0.0312 (± 0.37439) | 0.0017 (± 0.40019) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[66] |
| P-value | = 0.5088 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.982 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9314 |
| upper limit | 1.0362 |

Notes:

[66] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[67] |
| P-value | = 0.5606 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.985 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9341 |
| upper limit | 1.038 |

Notes:

[67] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[68] |
| P-value | = 0.9306 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.998 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9469 |
| upper limit | 1.0512 |

Notes:

[68] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in RV

| | |
|--|--------------------------------------|
| End point title | Change from baseline to Day 28 in RV |
| End point description: | |
| Only data on change from baseline to Day 28 are reported here (see tab. 14.2.4.3 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.0587 (± 1.08645) | 0.016 (± 0.58512) | 0.0097 (± 0.63798) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[69] |
| P-value | = 0.6873 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.011 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9583 |
| upper limit | 1.0664 |

Notes:

[69] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|----------------------------|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[70] |
| P-value | = 0.1946 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.965 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9152 |
| upper limit | 1.0186 |

Notes:

[70] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[71] |
| P-value | = 0.0796 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.047 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9944 |
| upper limit | 1.1024 |

Notes:

[71] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in FRC

| | |
|--|---------------------------------------|
| End point title | Change from baseline to Day 28 in FRC |
| End point description: | |
| Data on change from baseline to Day 28 are reported here (see table 14.2.4.4 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.0726 (± | 0.0607 (± | 0.0867 (± | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[72] |
| P-value | = 0.9914 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9635 |
| upper limit | 1.0383 |

Notes:

[72] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[73] |
| P-value | = 0.9262 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.998 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.962 |
| upper limit | 1.036 |

Notes:

[73] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[74] |
| P-value | = 0.9154 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.002 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9664 |
| upper limit | 1.0387 |

Notes:

[74] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change form baseline to Day 28 in TLC

| | |
|--|---------------------------------------|
| End point title | Change form baseline to Day 28 in TLC |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.4.5. of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.0564 (± 0.79366) | 0.0723 (± 0.53586) | 0.0956 (± 0.62812) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[75] |
| P-value | = 0.696 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.995 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9706 |
| upper limit | 1.0202 |

Notes:

[75] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3702 ^[76] |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.989 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9648 |
| upper limit | 1.0136 |

Notes:

[76] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHf6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[77] |
| P-value | = 0.6072 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.006 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9823 |
| upper limit | 1.0309 |

Notes:

[77] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in RV/TLC

| | |
|---|--|
| End point title | Change from baseline to Day 28 in RV/TLC |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.4.6 of CSR). | |
| End point type | Other pre-specified |

End point timeframe:

At Day 28

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 8.01) | -0.2 (± 4.38) | -0.4 (± 5.37) | |

Statistical analyses

| Statistical analysis title | CHF6001 vs placebo |
|---|--|
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[78] |
| P-value | = 0.3623 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.018 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9797 |
| upper limit | 1.057 |

Notes:

[78] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | Roflumilast vs placebo |
|---|---|
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[79] |
| P-value | = 0.2407 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.978 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9416 |
| upper limit | 1.0155 |

Notes:

[79] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[80] |
| P-value | = 0.311 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.041 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.0037 |
| upper limit | 1.0789 |

Notes:

[80] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in ITV

| | |
|--|---------------------------------------|
| End point title | Change from baseline to Day 28 in ITV |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.4.7. of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | -0.0267 (± 0.91372) | -0.0112 (± 0.48576) | 0.0822 (± 0.57956) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[81] |
| P-value | = 0.7135 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.994 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9604 |
| upper limit | 1.0282 |

Notes:

[81] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[82] |
| P-value | = 0.5332 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9572 |
| upper limit | 1.0231 |

Notes:

[82] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[83] |
| P-value | = 0.8037 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9713 |
| upper limit | 1.0381 |

Notes:

[83] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in sGAW

| | |
|--|--|
| End point title | Change from baseline to Day 28 in sGAW |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.4.8. of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: kPa/s | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 0.2071) | 0.0302 (\pm 0.1805) | 0.0086 (\pm 0.27717) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[84] |
| P-value | = 0.4104 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.952 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.845 |
| upper limit | 1.0721 |

Notes:

[84] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | roflumilast vs placebo |
| Comparison groups | Placebo - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[85] |
| P-value | = 0.2505 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.071 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9518 |
| upper limit | 1.2046 |

Notes:

[85] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[86] |
| P-value | = 0.0445 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.889 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7925 |
| upper limit | 0.997 |

Notes:

[86] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Change from baseline to Day 28 in GAW

| | |
|--|---------------------------------------|
| End point title | Change from baseline to Day 28 in GAW |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.4.9. of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: kPa*s/liters | | | | |
| arithmetic mean (standard deviation) | -0.0003 (± 0.17315) | -0.0388 (± 0.16972) | -0.0051 (± 0.08507) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[87] |
| P-value | = 0.3202 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.947 |
| upper limit | 1.1782 |

Notes:

[87] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[88] |
| P-value | = 0.3705 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.952 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.855 |
| upper limit | 1.061 |

Notes:

[88] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[89] |
| P-value | = 0.0531 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.109 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9986 |
| upper limit | 1.2318 |

Notes:

[89] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: TDI scores on Day 28

| | |
|--|----------------------|
| End point title | TDI scores on Day 28 |
| End point description: | |
| Only data on change from Day 1 (baseline) to Day 28 are reported here (See tab. 14.2.5.1. of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: integer | | | | |
| arithmetic mean (standard deviation) | 0.2 (± 0.7) | 0.2 (± 0.57) | 0 (± 0.42) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF6001 vs placebo |
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[90] |
| P-value | = 0.3202 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.947 |
| upper limit | 1.1782 |

Notes:

[90] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|----------------------------|---|
| Statistical analysis title | Roflumilast vs placebo |
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[91] |
| P-value | = 0.3705 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 0.952 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.855 |
| upper limit | 1.061 |

Notes:

[91] - This is a "proof of concept" study: no statistical hypothesis is included

| | |
|---|--|
| Statistical analysis title | CHF6001 vs Roflumilast |
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[92] |
| P-value | = 0.0531 |
| Method | ANCOVA |
| Parameter estimate | geometric LSM |
| Point estimate | 1.109 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9986 |
| upper limit | 1.2318 |

Notes:

[92] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: Rescue drug use over the 28-day period

| | |
|--|--|
| End point title | Rescue drug use over the 28-day period |
| End point description: | |
| Rescue drug use was expressed as mean number of puffs/day of salbutamol rescue medication. Data on table 14.2.6. of CSR are reported here. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Throughout the 28-day period | |

| End point values | Test treatment - mITT population | Reference treatment - mITT population | Placebo - mITT population | |
|--------------------------------------|----------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 47 | 43 | |
| Units: puffs/day | | | | |
| arithmetic mean (standard deviation) | 1.71 (± 2.244) | 2.11 (± 2.667) | 1.99 (± 2.583) | |

Statistical analyses

| Statistical analysis title | CHF6001 vs placebo |
|---|--|
| Comparison groups | Test treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[93] |
| P-value | = 0.1185 |
| Method | ANOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.521 |
| upper limit | 0.06 |

Notes:

[93] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | Roflumilast vs placebo |
|---|---|
| Comparison groups | Reference treatment - mITT population v Placebo - mITT population |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[94] |
| P-value | = 0.9173 |
| Method | ANOVA |
| Parameter estimate | least square mean |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.269 |
| upper limit | 0.299 |

Notes:

[94] - This is a "proof of concept" study: no statistical hypothesis is included

| Statistical analysis title | CHF6001 vs Roflumilast |
|-----------------------------------|--|
| Comparison groups | Test treatment - mITT population v Reference treatment - mITT population |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[95] |
| P-value | = 0.0904 |
| Method | ANOVA |
| Parameter estimate | least square mean |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.04 |

Notes:

[95] - This is a "proof of concept" study: no statistical hypothesis is included

Other pre-specified: FEV1 on Day 1

| | |
|---|---------------------|
| End point title | FEV1 on Day 1 |
| End point description: | |
| FEV1, to assess potential occurrence of paradoxical bronchospasm on Day 1 (2-hour spirometry measurement). Absolute change values are reported here (see table 14.3.9 of CSR) | |
| End point type | Other pre-specified |
| End point timeframe: | |
| On Day 1 (2-hour spirometry measurement) | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 0.254 (± 0.1532) | 0.246 (± 0.1853) | 0.233 (± 0.158) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Heart rate

| | |
|---|---------------------|
| End point title | Heart rate |
| End point description: | |
| Vital signs (HR and BP) were assessed after 5 min in supine position at pre-dose, 30 minutes, and 1, 2, 3, 6, 8 and 10 hours post-dose. | |
| Only data on Day 28, 10 hours post-dose are reported here (See tab. 14.3.6.1.1 of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 1 and Day 28 | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 73.9 (\pm 12.89) | 76.6 (\pm 11.5) | 74 (\pm 11.36) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Systolic blood pressure

| | |
|---|-------------------------|
| End point title | Systolic blood pressure |
| End point description: Vital signs (HR and BP) were assessed after 5 min in supine position at pre-dose, 30 minutes, and 1, 2, 3, 6, 8 and 10 hours post-dose. Only data from 10 hours post-dose measurement at Day 28 are reported here (sse table 14.3.6.2.1 of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: On Day 1 and Day 28 | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 128.6 (\pm 18.99) | 129.3 (\pm 16.73) | 134.9 (\pm 16.47) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Diastolic blood pressure

| | |
|---|--------------------------|
| End point title | Diastolic blood pressure |
| End point description: Vital signs (HR and BP) were assessed after 5 min in supine position at pre-dose, 30 minutes, and 1, 2, 3, 6, 8 and 10 hours post-dose. | |

Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.6.3.1 of CSR).

| | |
|----------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| On Day 1 and Day 28 | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 73.6 (± 12.37) | 72.1 (± 11.04) | 74.6 (± 10.95) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Body weight

| | |
|--|---------------------|
| End point title | Body weight |
| End point description: | |
| Only data at Day 28 are reported here (see table 14.3.8 of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| On Day 1 and Day 28 | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | 74.62 (± 16.446) | 74.7 (± 15.971) | 76.19 (± 16.868) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12-lead ECG HR

| | |
|-----------------|----------------|
| End point title | 12-lead ECG HR |
|-----------------|----------------|

End point description:

Triplicate serial 12-lead ECG was performed after 10 min in supine position at: pre-dose, 30 min, 1, 2, 3, 6, 8 and 10 hrs post-dose on Day 1 and Day 28.

Single 12-lead ECG was performed at screening while triplicate 12-lead ECG was performed after 10 min in supine position at pre-dose on Day 9, 21, 24 of each Period.

Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.7.1.1 of CSR).

| | |
|--|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 1, Day 9, Day 21, Day 24 and Day 28 | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 74.4 (\pm 12.22) | 76 (\pm 11.5) | 74.8 (\pm 11.22) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12-lead ECG PR

| | |
|---|---------------------|
| End point title | 12-lead ECG PR |
| End point description: | |
| Triplicate serial 12-lead ECG was performed after 10 min in supine position at: pre-dose, 30 min, 1, 2, 3, 6, 8 and 10 hrs post-dose on Day 1 and Day 28. | |
| Single 12-lead ECG was performed at screening while triplicate 12-lead ECG was performed after 10 min in supine position at pre-dose on Day 9, 21, 24 of each Period. | |
| Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.7.2.1 of CSR). | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 1, Day 9, Day 21, Day 24 and Day 28 | |

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 155.9 (\pm | 153.3 (\pm | 157.9 (\pm | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12-lead ECG QRS

| | |
|-----------------|-----------------|
| End point title | 12-lead ECG QRS |
|-----------------|-----------------|

End point description:

Triplicate serial 12-lead ECG was performed after 10 min in supine position at: pre-dose, 30 min, 1, 2, 3, 6, 8 and 10 hrs post-dose on Day 1 and Day 28.

Single 12-lead ECG was performed at screening while triplicate 12-lead ECG was performed after 10 min in supine position at pre-dose on Day 9, 21, 24 of each Period.

Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.7.3.1 of CSR).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 1, Day 9, Day 21, Day 24 and Day 28

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|------------------------------------|---|-----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 91.1 (± 10.4) | 92.4 (± 9.96) | 91.4 (± 9.81) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12-lead ECG QT

| | |
|-----------------|----------------|
| End point title | 12-lead ECG QT |
|-----------------|----------------|

End point description:

Triplicate serial 12-lead ECG was performed after 10 min in supine position at: pre-dose, 30 min, 1, 2, 3, 6, 8 and 10 hrs post-dose on Day 1 and Day 28.

Single 12-lead ECG was performed at screening while triplicate 12-lead ECG was performed after 10 min in supine position at pre-dose on Day 9, 21, 24 of each Period.

Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.7.4.1 of CSR).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 1, Day 9, Day 21, Day 24 and Day 28

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 387.1 (± 25.61) | 383.4 (± 25.29) | 385.7 (± 26.75) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12-lead ECG QTcB

| | |
|-----------------|------------------|
| End point title | 12-lead ECG QTcB |
|-----------------|------------------|

End point description:

Triplicate serial 12-lead ECG was performed after 10 min in supine position at: pre-dose, 30 min, 1, 2, 3, 6, 8 and 10 hrs post-dose on Day 1 and Day 28.

Single 12-lead ECG was performed at screening while triplicate 12-lead ECG was performed after 10 min in supine position at pre-dose on Day 9, 21, 24 of each Period.

Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.7.5.1 of CSR).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 1, Day 9, Day 21, Day 24 and Day 28

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 427.5 (± 18.06) | 428.7 (± 15.91) | 427.4 (± 18.25) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12-lead ECG QTcF

| | |
|-----------------|------------------|
| End point title | 12-lead ECG QTcF |
|-----------------|------------------|

End point description:

Triplicate serial 12-lead ECG was performed after 10 min in supine position at: pre-dose, 30 min, 1, 2, 3, 6, 8 and 10 hrs post-dose on Day 1 and Day 28.

Single 12-lead ECG was performed at screening while triplicate 12-lead ECG was performed after 10 min in supine position at pre-dose on Day 9, 21, 24 of each Period.

Only data from 10 hours post-dose measurement at Day 28 are reported here (see table 14.3.7.6.1 of CSR).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 1, Day 9, Day 21, Day 24 and Day 28

| End point values | Test treatment - Safety population | Reference treatment - Safety population | Placebo - Safety population | |
|--------------------------------------|--|--|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 49 | 43 | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 413.3 (± 14.05) | 412.8 (± 14.24) | 412.8 (± 15.65) | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-t_{ss} of CHF6001

| | |
|-----------------|---------------------------------|
| End point title | AUC0-t _{ss} of CHF6001 |
|-----------------|---------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|---|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: pg*h/ml | | | | |
| geometric mean (geometric coefficient of variation) | 16954 (± 42.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-t,ss of CHF5956

| | |
|-----------------|----------------------|
| End point title | AUC0-t,ss of CHF5956 |
|-----------------|----------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: pg*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1097 (\pm 78.9) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-t,ss of CHF6095

| | |
|-----------------|----------------------|
| End point title | AUC0-t,ss of CHF6095 |
|-----------------|----------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: pg*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 322 (\pm 61.3) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-24h,ss of CHF6001

| | |
|-----------------|------------------------|
| End point title | AUC0-24h,ss of CHF6001 |
|-----------------|------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: pg*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 17344 (\pm 39.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-24h,ss of CHF5956

| | |
|-----------------|------------------------|
| End point title | AUC0-24h,ss of CHF5956 |
|-----------------|------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 34 | | | |
| Units: pg*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1193 (\pm 63.2) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-24h,ss of CHF6095

| | |
|---|------------------------|
| End point title | AUC0-24h,ss of CHF6095 |
| End point description: PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |
| End point timeframe: At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: pg*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 374 (\pm 49) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cmin,ss of CHF6001

| | |
|---|---------------------|
| End point title | Cmin,ss of CHF6001 |
| End point description: PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|---|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 486 (\pm 48.4) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: C_{max,ss} of CHF6001

| | |
|-----------------|--------------------------------|
| End point title | C _{max,ss} of CHF6001 |
|-----------------|--------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|---|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1204 (\pm 35.4) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: C_{max,ss} of CHF5956

| | |
|-----------------|--------------------------------|
| End point title | C _{max,ss} of CHF5956 |
|-----------------|--------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 130 (\pm 60.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: C_{max,ss} of CHF6095

| | |
|---|--------------------------------|
| End point title | C _{max,ss} of CHF6095 |
| End point description: | |
| PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 49.4 (\pm 45.4) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: C_{av,ss} of CHF6001

| | |
|-----------------|-------------------------------|
| End point title | C _{av,ss} of CHF6001 |
|-----------------|-------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|---|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 723 (\pm 39.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cav,ss of CHF5956

| | |
|-----------------|-------------------|
| End point title | Cav,ss of CHF5956 |
|-----------------|-------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|---|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 34 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 49.7 (\pm 63.2) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cav,ss of CHF6095

| | |
|-----------------|-------------------|
| End point title | Cav,ss of CHF6095 |
|-----------------|-------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|---|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 15.6 (± 49) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tmax,ss for CHF6001

| | |
|-----------------|---------------------|
| End point title | Tmax,ss for CHF6001 |
|-----------------|---------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|-------------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 1.78 (0.98 to 6.03) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tmax,ss for CHF5956

| | |
|-----------------|---------------------|
| End point title | Tmax,ss for CHF5956 |
|-----------------|---------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|-------------------------------|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 3 (0 to 8.02) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tmax,ss for CHF6095

| | |
|-----------------|---------------------|
| End point title | Tmax,ss for CHF6095 |
|-----------------|---------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|-------------------------------|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 2.98 (0 to 6.03) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T_{min,ss} for CHF6001

| | |
|-----------------|---------------------------------|
| End point title | T _{min,ss} for CHF6001 |
|-----------------|---------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|-------------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 24 (9.75 to 24.2) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T_{min,ss} for CHF5956

| | |
|-----------------|---------------------------------|
| End point title | T _{min,ss} for CHF5956 |
|-----------------|---------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|-------------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 24 (8 to 24.2) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T_{min,ss} of CHF6095

| | |
|-----------------|--------------------------------|
| End point title | T _{min,ss} of CHF6095 |
|-----------------|--------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|-------------------------------|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 24 (5.98 to 24.2) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T_{1/2,ss} for CHF6001

| | |
|-----------------|---------------------------------|
| End point title | T _{1/2,ss} for CHF6001 |
|-----------------|---------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | 27.5 (\pm 43.9) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T1/2,ss for CHF5956

| | |
|---|---------------------|
| End point title | T1/2,ss for CHF5956 |
| End point description: PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |
| End point timeframe: At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | 11 (\pm 77.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T1/2,ss for CHF6095

| | |
|---|---------------------|
| End point title | T1/2,ss for CHF6095 |
| End point description: PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |
| End point timeframe: At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 17 | | | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | 13.7 (\pm 128) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CL/F, ss for CHF6001

| | |
|---|----------------------|
| End point title | CL/F, ss for CHF6001 |
| End point description: PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |
| End point timeframe: At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: mL/min | | | | |
| geometric mean (geometric coefficient of variation) | 1153 (\pm 39.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CL/F, ss for CHF5956

| | |
|---|----------------------|
| End point title | CL/F, ss for CHF5956 |
| End point description: PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 34 | | | |
| Units: mL/min | | | | |
| geometric mean (geometric coefficient of variation) | 16758 (\pm 63.2) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CI/F, ss for CHF6095

| | |
|-----------------|----------------------|
| End point title | CI/F, ss for CHF6095 |
|-----------------|----------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: mL/min | | | | |
| geometric mean (geometric coefficient of variation) | 53466 (\pm 49) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vz/F,ss for CHF6001

| | |
|-----------------|---------------------|
| End point title | Vz/F,ss for CHF6001 |
|-----------------|---------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period.

| | |
|----------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: liters | | | | |
| geometric mean (geometric coefficient of variation) | 2636 (\pm 69.8) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vz/F_{ss} for CHF5956

| | |
|---|--------------------------------|
| End point title | Vz/F _{ss} for CHF5956 |
| End point description: | |
| PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose (on Day 29) of each study Period. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At Day 28 | |

| | | | | |
|---|-----------------------------------|--|--|--|
| End point values | Test treatment - PK population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: liters | | | | |
| geometric mean (geometric coefficient of variation) | 15537 (\pm 97.7) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vz/F_{ss} for CHF6095

| | |
|-----------------|--------------------------------|
| End point title | Vz/F _{ss} for CHF6095 |
|-----------------|--------------------------------|

End point description:

PK blood collection will be performed on Day 28 at pre-dose and at 15, 30, min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs postdose
(on Day 29) of each study Period.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Day 28

| End point values | Test treatment - PK population | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 17 | | | |
| Units: liters | | | | |
| geometric mean (geometric coefficient of variation) | 53865 (\pm 123) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study (from run-in to follow-up)

Adverse event reporting additional description:

It was the responsibility of the Investigator to collect all AEs (both serious and non-serious), derived by spontaneous, unsolicited reports of patients, by observation and by routine open questioning

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Period of treatment with roflumilast - Safety population |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Period of treatment with placebo - Safety population |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Period of treatment with CHF6001 - Safety population |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--------------------------------|
| Reporting group title | Followp up - Safety population |
|-----------------------|--------------------------------|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Period of wash out - Safety population |
|-----------------------|--|

Reporting group description: -

| Serious adverse events | Period of treatment with roflumilast - Safety population | Period of treatment with placebo - Safety population | Period of treatment with CHF6001 - Safety population |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gallbladder empyema | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Followup up - Safety population | Period of wash out - Safety population | |
|---|---------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gallbladder empyema | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| 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: 1 %

| Non-serious adverse events | Period of treatment with roflumilast - Safety population | Period of treatment with placebo - Safety population | Period of treatment with CHF6001 - Safety population |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 49 (75.51%) | 30 / 43 (69.77%) | 32 / 42 (76.19%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 3 / 43 (6.98%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Exercise tolerance decreased | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Feeling hot | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Thirst subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 2 | 1 / 42 (2.38%) 1 |
| Vessel puncture site haematoma subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 0 | 0 / 42 (0.00%) 0 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 6 / 43 (13.95%) 7 | 1 / 42 (2.38%) 1 |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 4 / 43 (9.30%) 4 | 3 / 42 (7.14%) 3 |
| Dyspnoea subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 5 | 3 / 43 (6.98%) 3 | 4 / 42 (9.52%) 6 |
| Haemoptysis subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 1 / 42 (2.38%) 1 |
| Wheezing | | | |

| | | | |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 43 (4.65%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sputum increased | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 1 | 1 |
| Dry throat | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Sputum discoloured | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 1 | 1 |
| Psychiatric disorders | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Anxiety subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Depressed mood subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Panic attack subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Terminal insomnia subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Investigations Blood cholesterol increased subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Sputum abnormal subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Muscle strain subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Procedural site reaction subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Arthropod sting | | | |

| | | | |
|-----------------------------|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 2 |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Periorbital haematoma | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Post procedural swelling | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural vomiting | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 49 (34.69%) | 6 / 43 (13.95%) | 12 / 42 (28.57%) |
| occurrences (all) | 19 | 9 | 15 |
| Migrane | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 2 | 0 | 1 |
| Dizziness | | | |

| | | | |
|-----------------------------|------------------|----------------|-----------------|
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 1 | 0 | 1 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Cerumen impaction | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 49 (20.41%) | 2 / 43 (4.65%) | 5 / 42 (11.90%) |
| occurrences (all) | 10 | 2 | 8 |
| Toothache | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 43 (0.00%) | 2 / 42 (4.76%) |
| occurrences (all) | 2 | 0 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 43 (0.00%) | 2 / 42 (4.76%) |
| occurrences (all) | 2 | 0 | 2 |
| Nausea | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 3 | 0 | 1 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Constipation | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 43 (4.65%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rush | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Dermal cyst subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Skin discolouration subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 3 | 1 / 43 (2.33%) 1 | 1 / 42 (2.38%) 1 |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 2 / 42 (4.76%) 2 |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 2 / 42 (4.76%) 2 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 1 / 42 (2.38%) 1 |
| Arthritis subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Coccydynia subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Muscle spasms | | | |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 2 / 43 (4.65%) | 4 / 42 (9.52%) |
| occurrences (all) | 4 | 2 | 4 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 1 / 43 (2.33%) | 2 / 42 (4.76%) |
| occurrences (all) | 2 | 1 | 2 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 43 (2.33%) | 0 / 42 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 2 / 42 (4.76%) |
| occurrences (all) | 1 | 0 | 2 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 1 | 0 | 1 |
| Gallbladder empyema | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 0 / 42 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingival abscess | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 43 (0.00%) | 1 / 42 (2.38%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Gingival infection subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Skin infection subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Tooth abscess subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 42 (0.00%) 0 |
| Tooth infection subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Viral infection subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 42 (0.00%) 0 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 2 / 43 (4.65%) 2 | 0 / 42 (0.00%) 0 |

| Non-serious adverse events | Followup up - Safety population | Period of wash out - Safety population | |
|--|---------------------------------|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 9 / 46 (19.57%) | 32 / 48 (66.67%) | |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| General disorders and administration site conditions Catheter site haematoma | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Exercise tolerance decreased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thirst | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vessel puncture site haematoma | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 7 / 48 (14.58%) | |
| occurrences (all) | 0 | 7 | |
| Chronic obstructive pulmonary disease | | | |

| | | |
|------------------------------|----------------|-----------------|
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 48 (10.42%) |
| occurrences (all) | 1 | 5 |
| Dyspnoea | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 4 / 48 (8.33%) |
| occurrences (all) | 1 | 4 |
| Haemoptysis | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) |
| occurrences (all) | 1 | 0 |
| Wheezing | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 1 |
| Dysphonia | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Nasal congestion | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oropharyngeal pain | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 3 |
| Productive cough | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 1 |
| Sputum increased | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Dry throat | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Epistaxis | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Respiratory tract congestion | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 1 |
| Rhinorrhoea | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Synus congestion subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Sputum discoloured subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Depressed mood subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Panic attack subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Terminal insomnia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Investigations Blood cholesterol increased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Sputum abnormal subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Contusion | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural site reaction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Foreign body | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Periorbital haematoma | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Post procedural swelling | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Procedural vomiting | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Palpitations | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 4 / 48 (8.33%) | |
| occurrences (all) | 0 | 4 | |
| Migrane | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear and labyrinth disorders | | | |
| Cerumen impaction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 48 (4.17%) | |
| occurrences (all) | 0 | 2 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |

| | | |
|----------------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Abdominal discomfort | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Abdominal pain | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 2 |
| Constipation | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 48 (6.25%) |
| occurrences (all) | 1 | 3 |
| Dyspepsia | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Frequent bowel movements | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Abdominal distension | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 1 |
| Abdominal pain lower | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 1 |
| Abdominal pain upper | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Food poisoning | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Lip dry | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Peritonitis | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Rush | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 48 (4.17%) | |
| occurrences (all) | 1 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal pain | | | |

| | | | |
|-----------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Coccydynia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 48 (4.17%) | |
| occurrences (all) | 1 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 48 (6.25%) | |
| occurrences (all) | 0 | 3 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 48 (4.17%) | |
| occurrences (all) | 0 | 2 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|----------------|----------------|--|
| Gallbladder empyema | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gingival abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gingival infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 16 July 2012 | <p>Substantial Amendment 01 was written following a request from the Medicines and Healthcare products Regulatory Agency (MHRA) to modify the exclusion criteria such that patients with known contraindications or hypersensitivity to roflumilast, tiotropium bromide, or salbutamol, and patients with moderate or severe hepatic impairment, would not be considered eligible for the study. The MHRA also requested that rationale to justify both the selected dose of CHF 6001 and duration of its use in this study be added.</p> <p>Requests made by the IEC to amend the Information Sheet and Informed Consent Form (II of the protocol) were also addressed in this amendment, as follows:</p> <p>1. Information Sheet</p> <ul style="list-style-type: none">• the language and terminology used were simplified;• prohibited medications were included;• information on the National Health Service Patient Advice and Liaison Service was added;• it was included that patients should not donate blood during participation;• it was included that participants should be advised to use 2 forms of contraception during the course of the study and for 3 months later. <p>2. Informed Consent Form</p> <ul style="list-style-type: none">• the term 'patients' was amended to read 'patients' or 'participants'. <p>This amendment also added the evaluation of the systemic exposure to metabolite CHF 5956 to the pharmacokinetic assessments in this study. Preclinical studies and preliminary data from the human metabolic profiling of CHF 6001 suggest that its main metabolites are CHF 5956 and CHF 6095, though the investigation of systemic exposure to CHF 6001 metabolites had been focussed only on CHF 5956 which had appeared to be the most abundant compound. More recent preliminary toxicokinetic data had shown detectable concentrations of metabolite CHF 6095 in plasma samples from the rat and dog. Consequently, CHF 6095 was considered of interest and its evaluation was thus added to this protocol.</p> |

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.

No limitations or caveats are reported in this study

Notes: