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	v1
This version publication date	12 July 2016
First version publication date	09 August 2015

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	Oriana Esposito, Chiesi Farmaceutici S.p.A., 39 05211689204, o.esposito@chiesi.com
Scientific contact	Oriana Esposito, Chiesi Farmaceutici S.p.A., 39 05211689204, o.esposito@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	59.5	61.7	59.4
standard deviation	± 7.25	± 6.46	± 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	55.2	60.5	59.3
standard deviation	± 7.14	± 5.32	± 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 Male	25 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	±		
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 (± 8.58667)	-0.6251 (± 17.58909)	1.0149 (± 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: Akaline phosphatase

End point title	Akaline 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 amintransferase

End point title	Aspartate amintransferase

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 (± 0.3181)	-0.049 (± 0.523)	-0.124 (± 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 (± 3.775)	0.27 (± 3.547)	0.43 (± 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 (± 2.1)	-0.3 (± 2.09)	-0.2 (± 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: µmol/L				
arithmetic mean (standard deviation)	-2.94 (± 31.936)	-12.15 (± 37.216)	-11.09 (± 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 (± 8.28804)	-0.647 (± 17.43528)	0.8679 (± 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 (± 14.89339)	-5.5694 (± 13.66577)	-1.0944 (± 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 (± 6.22173)	0.5386 (± 2.328)	1.3458 (± 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 (± 14.69496)	5.4444 (± 11.80631)	-0.7194 (± 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 (± 0.01046)	0.001 (± 0.00567)	0.0004 (± 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 (± 2546.18)	-923.286 (± 2862.978)	462.8729 (± 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 (± 1657361)	-575067 (± 1738260)	-473269 (± 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 (± 1347.198)	-402.997 (± 1347.198)	-402.997 (± 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 (± 44.4402)	15.331 (± 173.3361)	-72.364 (± 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 (± 4.90551)	-2.7426 (± 10.89529)	-3.8656 (± 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 (± 0.2149)	0.035 (± 0.1703)	-0.044 (± 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 (± 0.2833)	0.06 (± 0.3552)	-0.109 (± 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 (± 0.50406)	0.0612 (± 0.29528)	0.0853 (± 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 (±	

0.99242)	0.48505)	0.60328)

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 (± 0.2071)	0.0302 (± 0.1805)	0.0086 (± 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 form baseline to Day 28 in GAW	
End point title	Change form 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 resue 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 (sse 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 (± 12.89)	76.6 (± 11.5)	74 (± 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 (± 18.99)	129.3 (± 16.73)	134.9 (± 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 (± 12.22)	76 (± 11.5)	74.8 (± 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 (±	153.3 (±	157.9 (±	

19.89)	19.46)	24.65)

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 (± 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 (± 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 (± 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 (± 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 (± 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 (± 48.4)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cmax,ss of CHF6001

End point title	Cmax,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 (± 35.4)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cmax,ss of CHF5956

End point title	Cmax,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 (± 60.1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cmax,ss of CHF6095

End point title	Cmax,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 (± 45.4)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cav,ss of CHF6001

End point title	Cav,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 (± 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 (± 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: Tmin,ss for CHF6001

End point title	Tmin,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: Tmin,ss for CHF5956

End point title	Tmin,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: Tmin,ss of CHF6095

End point title	Tmin,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: T1/2,ss for CHF6001

End point title	T1/2,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 (± 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 (± 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 (± 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 (± 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 (± 63.2)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Cl/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 (± 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 (± 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 (± 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 (± 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 CHF6001 - Safety population
Reporting group description: -	
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 wash out - Safety population
Reporting group description: -	
Reporting group title	Followp up - Safety population
Reporting group description: -	

Serious adverse events	Period of treatment with CHF6001 - Safety population	Period of treatment with roflumilast - Safety population	Period of treatment with placebo - Safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 49 (0.00%)	0 / 43 (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 / 42 (0.00%)	0 / 49 (0.00%)	0 / 43 (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 / 42 (0.00%)	0 / 49 (0.00%)	0 / 43 (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	Period of wash out - Safety population	Followp up - Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Peritonitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gallbladder empyema			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 CHF6001 - Safety population	Period of treatment with roflumilast - Safety population	Period of treatment with placebo - Safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 42 (76.19%)	37 / 49 (75.51%)	30 / 43 (69.77%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 42 (0.00%)	1 / 49 (2.04%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 42 (0.00%)	1 / 49 (2.04%)	3 / 43 (6.98%)
occurrences (all)	0	1	3
Chest discomfort			
subjects affected / exposed	0 / 42 (0.00%)	1 / 49 (2.04%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Exercise tolerance decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 49 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Feeling hot			

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gallbladder empyema			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Gingival abscess			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Gingival infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Tooth abscess			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Tooth infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (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	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. 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: 1. Information Sheet • 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. 2. Informed Consent Form • the term 'patients' was amended to read 'patients' or 'participants'. 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.

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: