Clinical trial results:
A RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED, REPEATED DOSE, THREE-WAY CROSSOVER STUDY TO EVALUATE THE PHARMACODYNAMICS, PHARMACOKINETICS AND SAFETY OF TWO DOSES OF CHF 6001 DPI IN SUBJECTS WITH MODERATE, SEVERE COPD.

Summary

EudraCT number	2015-005550-35
Trial protocol	GB DE
Global end of trial date	28 December 2017

Results information

Result version number	v1 (current)
This version publication date	06 January 2019
First version publication date	06 January 2019

Trial information

Trial identification

Sponsor protocol code	CCD-06001AA1-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03004417
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., Chiesi Farmaceutici S.p.A., +39 0521 2791, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., Chiesi Farmaceutici S.p.A., +39 0521 2791, clinicaltrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2017
Global end of trial reached?	Yes
Global end of trial date	28 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study were:
- To evaluate the effect of CHF 6001 on biomarkers of inflammation in induced sputum and in blood, on pulmonary function and on symptoms benefits in comparison with placebo;
- To evaluate the safety and tolerability of CHF 6001;
- To assess the PK profile of CHF 6001 and its metabolites at steady state in patients with moderate, severe COPD.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practice (GCP) guidelines in force during study conduct and following all other requirements of local laws.
At all visits from screening onwards, concomitant medications and adverse events (AEs) were recorded. Height and weight were measured at screening and weight was measured at Day 1 and Day 32 of each treatment period. Physical examinations were performed at screening, on Day 1 and Day 32 of each treatment period and at the follow-up visit. Additional physical examinations could have been performed on Day 20 and Day 26 of each treatment period, as needed. Vital signs and 12-lead electrocardiograms (ECGs) were recorded at screening and pre-dose on Day 1 and Day 32 of each treatment period.
Patients were provided with salbutamol as rescue medication to use as needed throughout the study.
Patients were maintained on their regular medication (triple therapy) throughout the study.

Background therapy:

Patient's receiving daily maintenance with triple therapy (i.e. inhaled corticosteroid [ICS] plus long-acting beta-2 agonist [LABA] plus long-acting muscarinic anticholinergenic [LAMA]) at a stable dose and dosing regimen for at least 2 months prior to screening were enrolled in the study. Patients continued to receive this triple background medication throughout the study.

Evidence for comparator: -

Actual start date of recruitment	31 October 2016
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: 21
Country: Number of subjects enrolled	Germany: 40
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	24
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

140 patients were screened according to inclusion/exclusion criteria; 61 patients were randomised to 1 of 6 treatment sequences (Sequence CHF 6001 1600 µg [L]-CHF 6001 3200 µg [H]-placebo [P] [n=11], Sequence L-P-H [n=10], Sequence H-L-P [n=10], Sequence H-P-L [n=12], Sequence P-L-H [n=9], Sequence P-H-L [n=9]); 54 patients completed the study.

Pre-assignment

Screening details:

The study comprised a pre-screening visit, occurring no more than 1 week prior to a screening visit. At the screening visit, inclusion/exclusion criteria were assessed. There were 79 screening failures (78 patients did not meet inclusion/exclusion criteria and 1 patient was lost to follow-up).

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	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

At randomisation, patients were sequentially assigned to one of the six treatment sequences using a balanced block randomisation scheme and a pre-established randomisation list.
The randomisation list was provided to the labelling facility and to the analytical and biomarker laboratories, but was not available to patients, investigators, monitors or employees of the centre involved in the management of the study before unblinding of the data, unless in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence L-H-P

Arm description:

Patients were randomised to receive three different treatments (total daily doses of 1600 µg and 3200 µg of CHF 6001 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted 32 (+2) days and were separated by two washout periods of 28 to 42 days. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = matched placebo.

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

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained four inhalers (two inhalers for the morning administration and two inhalers for the evening administration). During each 32 (+2) day treatment period, the study medication was administered twice daily with patients taking two puffs from each "morning" inhaler and two puffs from each "evening" inhaler, adding up to eight puffs per day. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = placebo.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study

treatment kit for each period contained four inhalers (two inhalers for the morning administration and two inhalers for the evening administration). During each 32 (+2) day treatment period, the study medication was administered twice daily with patients taking two puffs from each "morning" inhaler and two puffs from each "evening" inhaler, adding up to eight puffs per day. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = placebo.

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Arm title	Sequence H-L-P

Arm description:

Patients were randomised to receive three different treatments (total daily doses of 1600 µg and 3200 µg of CHF 6001 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted 32 (+2) days and were separated by two washout periods of 28 to 42 days. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = matched placebo.

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Number of subjects in period 1	Sequence L-H-P	Sequence L-P-H	Sequence H-L-P
Started	11	10	10
Completed	10	9	9
Not completed	1	1	1
Adverse event, non-fatal	1	1	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Sequence H-P-L	Sequence P-L-H	Sequence P-H-L
Started	12	9	9
Completed	10	8	8
Not completed	2	1	1
Adverse event, non-fatal	1	1	1
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence L-H-P
Reporting group description:	
Patients were randomised to receive three different treatments (total daily doses of 1600 µg and 3200 µg of CHF 6001 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted 32 (+2) days and were separated by two washout periods of 28 to 42 days. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = matched placebo.	
Reporting group title	Sequence L-P-H
Reporting group description:	
Patients were randomised to receive three different treatments (total daily doses of 1600 µg and 3200 µg of CHF 6001 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted 32 (+2) days and were separated by two washout periods of 28 to 42 days. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = matched placebo.	
Reporting group title	Sequence H-L-P
Reporting group description:	
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Reporting group description:	
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Reporting group values	Sequence L-H-P	Sequence L-P-H	Sequence H-L-P
Number of subjects	11	10	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	3	5
From 65-84 years	8	7	5
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	3	4	3
Male	8	6	7

Reporting group values	Sequence H-P-L	Sequence P-L-H	Sequence P-H-L
Number of subjects	12	9	9
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	5	3
From 65-84 years	7	4	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	2	3
Male	9	7	6

Reporting group values	Total		
Number of subjects	61		
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)	24		
From 65-84 years	37		
85 years and over	0		
Gender categorical Units: Subjects			
Female	18		
Male	43		

End points

End points reporting groups

Reporting group title	Sequence L-H-P

Reporting group description:

Patients were randomised to receive three different treatments (total daily doses of 1600 µg and 3200 µg of CHF 6001 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted 32 (+2) days and were separated by two washout periods of 28 to 42 days. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = matched placebo.

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Reporting group title	Sequence P-L-H

Reporting group description:

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Reporting group title	Sequence P-H-L

Reporting group description:

Patients were randomised to receive three different treatments (total daily doses of 1600 µg and 3200 µg of CHF 6001 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted 32 (+2) days and were separated by two washout periods of 28 to 42 days. Treatment L = CHF 6001 1600 µg; Treatment H = CHF 6001 3200 µg; Treatment P = matched placebo.

Subject analysis set title	L: CHF 6001 1600 µg - PD
Subject analysis set type	Per protocol

Subject analysis set description:

Treatment L: CHF 6001 1600 µg; the population was defined as all patients from the Safety population with available evaluation in at least two treatment periods excluding patients without any pharmacodynamic (PD) measurement and with major protocol deviations affecting the PD evaluations.

Subject analysis set title	H: CHF 6001 3200 µg - PD
Subject analysis set type	Per protocol

Subject analysis set description:

Treatment H: CHF 6001 1600 µg; the population was defined as all patients from the Safety population with available evaluation in at least two treatment periods excluding patients without any pharmacodynamic (PD) measurement and with major protocol deviations affecting the PD evaluations.

Subject analysis set title	P: Placebo - PD
Subject analysis set type	Per protocol

Subject analysis set description:

Treatment P : placebo; the population was defined as all patients from the Safety population with available evaluation in at least two treatment periods excluding patients without any pharmacodynamic (PD) measurement and with major protocol deviations affecting the PD evaluations.

Subject analysis set title	L: CHF 6001 1600 µg - PK
Subject analysis set type	Per protocol

Subject analysis set description:

The PK population consisted of all patients from the Safety population excluding patients without any valid PK assessment and with major protocol deviations affecting the PK evaluations.

Subject analysis set title	H: CHF 6001 3200 µg - PK
Subject analysis set type	Per protocol

Subject analysis set description:

The PK population consisted of all patients from the Safety population excluding patients without any valid PK assessment and with major protocol deviations affecting the PK evaluations.

Primary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in TNF-α in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in TNF-α in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Primary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	39	44	47	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.488 (0.353 to 0.676)	0.658 (0.484 to 0.896)	1.012 (0.760 to 1.346)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

TNF-α level in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.482

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.314
upper limit	0.741

Notes:

[1] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

TNF-α level in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	H: CHF 6001 3200 µg - PD v P: Placebo - PD
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.049
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.651
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.424
upper limit	0.998

Notes:

[2] - Explorative

Secondary: Change from baseline to end to treatment (mean Day 20, 26 and 32 values) in absolute neutrophil count in induced sputum

End point title	Change from baseline to end to treatment (mean Day 20, 26 and 32 values) in absolute neutrophil count in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: 10^6/g				
geometric mean (confidence interval 95%)	1.095 (0.901 to 1.331)	0.943 (0.777 to 1.144)	0.912 (0.753 to 1.103)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Absolute neutrophil count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v L: CHF 6001 1600 µg - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.183
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.916
upper limit	1.575

Notes:

[3] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Absolute neutrophil count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.807
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.034

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.789
upper limit	1.354

Notes:

[4] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in absolute eosinophil count in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in absolute eosinophil count in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean of Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: 10^6/g				
geometric mean (confidence interval 95%)	0.829 (0.602 to 1.143)	0.875 (0.636 to 1.204)	1.016 (0.741 to 1.392)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Absolute eosinophil count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.371
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.817

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.522
upper limit	1.277

Notes:

[5] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Absolute eosinophil count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.508
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.862
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.552
upper limit	1.345

Notes:

[6] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in absolute macrophage count in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in absolute macrophage count in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: 10^6/g				
geometric mean (confidence interval 95%)	0.938 (0.774 to 1.135)	1.055 (0.874 to 1.275)	1.240 (1.029 to 1.495)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Absolute macrophage count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.04
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.756
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.579
upper limit	0.987

Notes:

[7] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Absolute macrophage count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.228
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.851

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.653
upper limit	1.108

Notes:

[8] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in absolute lymphocyte count in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in absolute lymphocyte count in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: 10^6/g				
geometric mean (confidence interval 95%)	1.378 (0.825 to 2.301)	1.450 (0.870 to 2.417)	2.026 (1.222 to 3.359)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Absolute lymphocyte count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data was log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.289
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.331
upper limit	1.395

Notes:

[9] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Absolute lymphocyte count in induced sputum, obtained on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.357
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.716
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.349
upper limit	1.466

Notes:

[10] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of neutrophils in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of neutrophils in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: percentage				
geometric mean (confidence interval 95%)	1.013 (0.979 to 1.049)	0.999 (0.965 to 1.035)	0.957 (0.925 to 0.991)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

percentage of neutrophils in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.023
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.008
upper limit	1.112

Notes:

[11] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

percentage of neutrophils in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.087
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.044

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.994
upper limit	1.097

Notes:

[12] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of eosinophils in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of eosinophils in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean of Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: percentage				
geometric mean (confidence interval 95%)	0.746 (0.584 to 0.952)	0.888 (0.696 to 1.134)	0.989 (0.779 to 1.257)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

percentage of eosinophils in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.103
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.754

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.536
upper limit	1.06

Notes:

[13] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

percentage of eosinophils in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.53
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.898
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.26

Notes:

[14] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of macrophages in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of macrophages in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: percentage				
geometric mean (confidence interval 95%)	1.001 (0.833 to 1.204)	1.226 (1.022 to 1.471)	1.414 (1.180 to 1.695)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

percentage of macrophages in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.009
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.708
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.547
upper limit	0.916

Notes:

[15] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

percentage of macrophages in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.27
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.867

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.671
upper limit	1.12

Notes:

[16] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of lymphocytes in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in percentage of lymphocytes in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean of Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	53	53	
Units: percentage				
geometric mean (confidence interval 95%)	1.011 (0.818 to 1.250)	0.990 (0.802 to 1.224)	1.190 (0.966 to 1.465)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

percentage of lymphocytes in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.279
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.632
upper limit	1.143

Notes:

[17] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

percentage of lymphocytes in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.221
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.832
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.619
upper limit	1.119

Notes:

[18] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in IL-6 in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in IL-6 in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	48	53	54	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.873 (0.754 to 1.011)	1.164 (1.015 to 1.335)	0.861 (0.754 to 0.984)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

IL-6 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.895
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.236

Notes:

[19] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

IL-6 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.351

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.116
upper limit	1.636

Notes:

[20] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in IL-8 in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in IL-8 in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily included the change from baseline in TNF-α in induced sputum as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	54	54	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.54 (0.46 to 0.63)	0.64 (0.55 to 0.75)	0.81 (0.70 to 0.94)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

IL-8 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.83

Notes:

[21] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

IL-8 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.035
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.98

Notes:

[22] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in MIP1β in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in MIP1β in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	31	38	34	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.510 (0.414 to 0.628)	0.508 (0.419 to 0.616)	0.813 (0.670 to 0.986)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

MIP1β in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.627
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.471
upper limit	0.834

Notes:

[23] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

MIP1β in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.625

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.478
upper limit	0.818

Notes:

[24] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in MCP-1 in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in MCP-1 in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	46	51	50	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.667 (0.576 to 0.772)	0.796 (0.693 to 0.914)	0.933 (0.814 to 1.070)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

MCP-1 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data werelog-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.715

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.588
upper limit	0.87

Notes:

[25] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

MCP-1 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.105
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.852
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.702
upper limit	1.035

Notes:

[26] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in leukotriene B4 in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in leukotriene B4 in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	53	54	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.697 (0.544 to 0.892)	0.593 (0.470 to 0.749)	1.058 (0.843 to 1.328)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Leukotriene B4 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.015
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.659
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.472
upper limit	0.919

Notes:

[27] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Leukotriene B4 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.561

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.405
upper limit	0.777

Notes:

[28] - Explorative

Secondary: Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in MMP9 in induced sputum

End point title	Change from baseline to end of treatment (mean Day 20, 26 and 32 values) in MMP9 in induced sputum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (mean Day 20, 26 and 32 values)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	53	54	
Units: ng/mL				
geometric mean (confidence interval 95%)	0.779 (0.647 to 0.938)	0.771 (0.641 to 0.928)	1.017 (0.848 to 1.220)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

MMP9 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.043
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.766

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.592
upper limit	0.992

Notes:

[29] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

MMP9 in induced sputum on Days 20, 26 and 32 was averaged for each subject when receiving each treatment. The averaged values were used in the analysis. Mean change from baseline was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.038
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.759
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.585
upper limit	0.985

Notes:

[30] - Explorative

Secondary: PK sputum concentration for CHF 6001 at steady state

End point title	PK sputum concentration for CHF 6001 at steady state

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Measured on Day 20, Day 26 or Day 32 at 2 hours post-dose.
Note: an aliquot of one of the sputum collections performed on Day 20, 26 or 32 was used for CHF 6001 determination.

End point values	L: CHF 6001 1600 µg - PK	H: CHF 6001 3200 µg - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	58		
Units: µg/mL				
arithmetic mean (standard deviation)	4.87 (± 6.18)	10.23 (± 12.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment (Day 32) in IL-6 in serum

End point title	Change from baseline to end of treatment (Day 32) in IL-6 in serum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily included the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Day 32)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	46	48	44	
Units: pg/mL				
geometric mean (confidence interval 95%)	1.444 (1.222 to 1.707)	1.484 (1.261 to 1.747)	1.281 (1.080 to 1.521)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.323
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.127

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.887
upper limit	1.432

Notes:

[31] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.224
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.912
upper limit	1.47

Notes:

[32] - Explorative

Secondary: Change from baseline to end of treatment (Day 32) in IL-8 in serum

End point title	Change from baseline to end of treatment (Day 32) in IL-8 in serum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Day 32)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	52	53	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.931 (0.855 to 1.014)	0.892 (0.818 to 0.972)	0.911 (0.837 to 0.992)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Non-normally distributed data was log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.726
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.906
upper limit	1.152

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Non-normally distributed data was log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.721
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.979
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.868
upper limit	1.103

Secondary: Change from baseline to end of treatment (Day 32) in TNF-α in vivo in serum

End point title	Change from baseline to end of treatment (Day 32) in TNF-α in vivo in serum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Day 32)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	55	53	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.935 (0.867 to 1.008)	0.935 (0.867 to 1.008)	0.888 (0.821 to 0.960)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.344
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.946
upper limit	1.171

Notes:

[33] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.354
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	1.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.944
upper limit	1.173

Notes:

[34] - Explorative

Secondary: Change from baseline to end of treatment (Day 32) in TNF-α ex vivo stimulated in plasma

End point title	Change from baseline to end of treatment (Day 32) in TNF-α ex vivo stimulated in plasma

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Day 32)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	57	55	
Units: pg/mL				
geometric mean (confidence interval 95%)	0.595 (0.439 to 0.806)	0.494 (0.366 to 0.665)	0.900 (0.662 to 1.224)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	L: CHF 6001 1600 µg - PD v P: Placebo - PD

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.057
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.661
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.431
upper limit	1.013

Notes:

[35] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	H: CHF 6001 3200 µg - PD v P: Placebo - PD
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.006
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.548
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.357
upper limit	0.841

Notes:

[36] - Explorative

Secondary: Change from baseline to end of treatment (Day 32) in SP-D in serum

End point title	Change from baseline to end of treatment (Day 32) in SP-D in serum

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Day 32)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	54	55	53	
Units: ng/mL				
geometric mean (confidence interval 95%)	0.79 (0.74 to 0.83)	0.81 (0.77 to 0.86)	0.98 (0.92 to 1.03)	

Statistical analyses

Statistical analysis title	CHF 6001 1600 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v L: CHF 6001 1600 µg - PD
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	0.87

Notes:

[37] - Explorative

Statistical analysis title	CHF 6001 3200 µg vs. placebo

Statistical analysis description:

Mean change from baseline to Day 32 was compared between treatments using an analysis of covariance (ANCOVA), including treatment, subject and period as fixed effects and baseline values as covariate. Data were log-transformed before analysis and results presented as ratio of geometric means.

Comparison groups	P: Placebo - PD v H: CHF 6001 3200 µg - PD
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	0.9

Notes:
[38] - Explorative

Secondary: Area under the plasma concentration-time curve for CHF 6001 from 0 to 12 hours post-dose at steady-state

End point title	Area under the plasma concentration-time curve for CHF 6001 from 0 to 12 hours post-dose at steady-state

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Measured at Day 32 (steady-state).
Blood samples were collected on Day 32 of each treatment period at 10 timepoints (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post-dose).

End point values	L: CHF 6001 1600 µg - PK	H: CHF 6001 3200 µg - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	58		
Units: h.pg/mL				
geometric mean (geometric coefficient of variation)	22116 (± 51.4)	40814 (± 53.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration of CHF 6001 at steady-state

End point title	Maximum plasma concentration of CHF 6001 at steady-state

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Measured on Day 32 (steady-state).
Blood samples were collected on Day 32 of each treatment period at 10 timepoints (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post-dose).

End point values	L: CHF 6001 1600 µg - PK	H: CHF 6001 3200 µg - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	58		
Units: pg/mL				
geometric mean (geometric coefficient of variation)	2439 (± 50.0)	4502 (± 50.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment (pre-dose Day 32) in FEV1

End point title	Change from baseline to end of treatment (pre-dose Day 32) in FEV1

End point description:

Note: all endpoints in this study were considered exploratory and none were defined as primary, secondary etc. In order to present results in the EudraCT system we have arbitrarily considered the change from baseline in TNF-α in induced sputum as the relevant endpoint to be labelled as the primary endpoint. All other endpoints were arbitrarily assigned as secondary endpoints.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (pre-dose Day 32)

End point values	L: CHF 6001 1600 µg - PD	H: CHF 6001 3200 µg - PD	P: Placebo - PD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	57	56	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.022 (-0.006 to 0.050)	-0.026 (-0.053 to 0.002)	0.009 (-0.018 to 0.037)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for AEs was from the signature of the informed consent form until the patient's participation in the study ended.

Adverse event reporting additional description:

All AEs starting on or after the time of first randomised study drug were classified as treatment-emergent adverse events (TEAEs) and were analysed in this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	L: CHF 6001 1600 µg

Reporting group description:

Treatment L = CHF 6001 1600 µg. The safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	H: CHF 6001 3200 µg

Reporting group description:

Treatment H = CHF 6001 3200 µg. The safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	P: Placebo

Reporting group description:

Treatment P = placebo. The safety population was defined as all randomised patients who received at least one dose of the study medication.

Serious adverse events	L: CHF 6001 1600 µg	H: CHF 6001 3200 µg	P: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 58 (3.45%)	2 / 59 (3.39%)	2 / 58 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood immunoglobulin A increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrospinal fistula			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 58 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 58 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 58 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 58 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis			

subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	L: CHF 6001 1600 µg	H: CHF 6001 3200 µg	P: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 58 (51.72%)	32 / 59 (54.24%)	24 / 58 (41.38%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 58 (1.72%)	7 / 59 (11.86%)	1 / 58 (1.72%)
occurrences (all)	1	7	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	0 / 58 (0.00%)
occurrences (all)	1	3	0
Chest pain			
subjects affected / exposed	2 / 58 (3.45%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Chest discomfort			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	2 / 58 (3.45%)
occurrences (all)	4	1	2
Diarrhoea			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences (all)	3	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	1	3	1
Oropharyngeal pain			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	0 / 58 (0.00%)
occurrences (all)	3	2	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 58 (1.72%)	2 / 59 (3.39%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Dyspnoea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 58 (6.90%)	1 / 59 (1.69%)	2 / 58 (3.45%)
occurrences (all)	4	1	2
Muscle spasms			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	2 / 58 (3.45%)
occurrences (all)	1	1	2
Osteoarthritis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 58 (8.62%)	6 / 59 (10.17%)	8 / 58 (13.79%)
occurrences (all)	5	6	8
Lower respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2016	Protocol v 2.0. was issued on 25 August 2016 to implement comments raised by the authority MHRA to monitor specifically psychiatric adverse events. It was submitted to both MHRA and EC on the 26th of August 2016 and approved by both on the 09th of September 2016. It was also submitted to both BfArM and EC on the 19th and the 21st of September 2016 respectively, and approved by BfArM on the 5th of October and by the EC on the 01st of December 2016.
29 September 2016	Protocol v 3.0 was issued on 29 Sep 2016 to implement a smoking diary to monitor the change in the patients smoking habits. It was submitted to both EC and BfArM on the 26 and 27 October 2016 respectively and approved by the EC the 1st December 2016 alongside the approval of the version 2.0 of the protocol, while BfArM considered it as non-substantial amendment. It was also submitted to both MHRA and EC on the 21st of October 2016 and approved by both, the 25th of November 2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported