



Clinical trial results:

A 24-WEEK, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO AND ACTIVE CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 4 DOSES OF CHF 6001 DPI IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) ON A BACKGROUND THERAPY.

Summary

EudraCT number	2015-005548-32
Trial protocol	GB DE HU PL BG
Global end of trial date	09 January 2018

Results information

Result version number	v1 (current)
This version publication date	25 January 2019
First version publication date	25 January 2019

Trial information

Trial identification

Sponsor protocol code	CCD-06001AA1-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02986321
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., +39 0521 2791, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, 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	22 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2018
Global end of trial reached?	Yes
Global end of trial date	09 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to investigate the dose-response relationship of 4 doses of CHF 6001 dry powder inhaler (DPI) with respect to pre-dose forced expiratory volume in the 1st second (FEV1) after 12 weeks of treatment and to identify the optimal dose of CHF 6001 for further development in patients with moderate to severe COPD already treated with background therapy.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, and following all other requirements of local laws.

At all visits from screening onwards, concomitant medications and adverse events were recorded and physical examination of subjects was carried out. Vital signs were recorded pre-dose and pre-dose spirometry (including inspiratory capacity [IC], FEV1 and forced vital capacity [FVC]) was performed at screening, randomisation and all post-randomisation visits until the last treatment visit. Baseline Dyspnoea Index (BDI) was recorded at randomisation and Transition Dyspnoea Index (TDI) was recorded at all post-randomisation visits until the last treatment visit. COPD exacerbations were assessed at all post-randomisation visits.

Subjects were provided with salbutamol as rescue medication.

From screening, the electronic diary (eDiary) was completed by patients from home on a daily basis to record rescue medication use, compliance with background medication and study treatment, and COPD exacerbation-related outcomes (using the EXacerbations of Chronic pulmonary disease Tool - Patient Reported Outcome [EXACT-PRO]/Respiratory Symptoms [E-RS] questionnaire). Health related quality of life was assessed at all visits over the randomised treatment period using the St. George's Respiratory Questionnaire (SGRQ).

Blood collection for routine haematology and blood chemistry was performed at screening, randomisation, Week 12 and last treatment visits; thyroid functions were tested at screening. From screening, 12-lead electrocardiogram (ECG) parameters (heart rate [HR], Fridericia-corrected QT interval [QTcF], PR interval [PR] and QRS interval [QRS]) were recorded.

Background therapy:

Patients received formoterol fumarate 12 µg (one inhalation twice daily, total daily dose 24 µg) as background medication during the two-week run-in period, which was continued at the same dose throughout the study. Patients also received salbutamol as rescue medication (dose of 100 µg pressurized metered dose inhaler [pMDI] as needed [PRN], maximum of 8 puffs/day), to be used throughout the study.

Evidence for comparator:

Budesonide (ICS)

Actual start date of recruitment	15 December 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	Poland: 210
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Bulgaria: 126
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 87
Country: Number of subjects enrolled	Russian Federation: 263
Country: Number of subjects enrolled	Ukraine: 425
Worldwide total number of subjects	1130
EEA total number of subjects	442

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)	554
From 65 to 84 years	573
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Overall, 1593 patients were screened according to inclusion and exclusion criteria; of these, 1130 patients were randomised.

Pre-assignment

Screening details:

At screening, not more than 7 days after a pre-screening visit, inclusion/exclusion criteria were assessed. There were 463 screening failures (failure to meet randomisation criteria [418 patients], consent withdrawal [31 patients], other reasons [5 patients], AEs [4 patients], protocol deviations [3 patients], lost to follow-up [2 patients]).

Period 1

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

Blinding implementation details:

An Interactive Response Technology (IRT) system was used to generate the randomisation list.

Arms

Are arms mutually exclusive?	Yes
Arm title	CHF 6001 800 µg

Arm description:

Patients were randomised to receive CHF 6001 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period.

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

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®100 µg/actuation.

Double-blind double-dummy design: During study visits patients in the CHF 6001 800 µg group received two boxes, each with two NEXThaler®s with CHF 6001 100 µg/actuation and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 100 µg/actuation plus 2 inhalations of CHF 6001 100 µg/actuation plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).

Total daily dose: CHF 6001 800 µg.

Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).

Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

Arm title	CHF 6001 1600 µg
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Arm description:

Patients were randomised to receive CHF 6001 1600 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

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

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®400 µg/actuation.

Double-blind double-dummy design: During study visits patients in the CHF 6001 1600 µg group received two boxes, each with a NEXThaler® with CHF 6001 400 µg/actuation, a NEXThaler® with CHF 6001 matched Placebo and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other box to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 400 µg/actuation plus 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).

Total daily dose: CHF 6001 1600 µg.

Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).

Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

Arm title	CHF 6001 2400 µg
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Arm description:

Patients were randomised to receive CHF 6001 2400 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

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

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®300 µg/actuation.

Double-blind double-dummy design: During study visits patients in the CHF 6001 2400 µg group received two boxes, each with two NEXThaler®s with CHF 6001 300 µg/actuation and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 300 µg/actuation plus 2 inhalations of CHF 6001 300 µg/actuation plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).

Total daily dose: CHF 6001 2400 µg.

Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).

Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

Arm title	CHF 6001 3200 µg
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Arm description:

Patients were randomised to receive CHF 6001 3200 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

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

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®400 µg/actuation.

Double-blind double-dummy design: During study visits patients in the CHF 6001 3200 µg group received two boxes, each with two NEXThaler®s with CHF 6001 400 µg/actuation and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 400 µg/actuation plus 2 inhalations of CHF 6001 400 µg/actuation plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).

Total daily dose: CHF 6001 3200 µg.

Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).

Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

Arm title	Budesonide 800 µg
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Arm description:

Patients were randomised to receive Budesonide 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

Arm type	Active comparator
Investigational medicinal product name	Budesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Test product: Budesonide DPI Pulmicort® Turbohaler® 200 µg/actuation.

Double-blind double-dummy design: During study visits, patients in the Budesonide 800 µg group received two boxes, each with two NEXThaler®s with CHF 6001 matched Placebo and a Budesonide DPI (Pulmicort® Turbohaler®) 200 µg/actuation, one box to be used for morning administration and the other to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of Budesonide DPI 200 µg/actuation, all twice daily (BID).

Total daily dose: Budesonide 800 µg.

Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).

Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

Arm title	Placebo
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Arm description:

Patients were randomised to receive Placebo for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

Arm type	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:

Test product: Matched Placebo.

Double-blind double-dummy design: During study visits patients in the Placebo group received two boxes, each with two CHF 6001 DPI NEXThaler® matched Placebos and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).

Total daily dose: Not applicable.

Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).

Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

Number of subjects in period 1	CHF 6001 800 µg	CHF 6001 1600 µg	CHF 6001 2400 µg
Started	190	179	188
Completed	175	162	176
Not completed	15	17	12
Adverse event, serious fatal	1	1	1
Consent withdrawn by subject	7	10	5
No reason specified	2	1	1
Adverse event, non-fatal	3	2	3
Lost to follow-up	-	-	-
Lack of efficacy	2	1	2
Protocol deviation	-	2	-

Number of subjects in period 1	CHF 6001 3200 µg	Budesonide 800 µg	Placebo
Started	193	187	193
Completed	173	175	177
Not completed	20	12	16
Adverse event, serious fatal	2	-	-
Consent withdrawn by subject	5	4	7
No reason specified	4	1	3
Adverse event, non-fatal	6	2	5
Lost to follow-up	-	1	-
Lack of efficacy	3	4	1
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	CHF 6001 800 µg
Reporting group description:	
Patients were randomised to receive CHF 6001 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period.	
Reporting group title	CHF 6001 1600 µg
Reporting group description:	
Patients were randomised to receive CHF 6001 1600 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	CHF 6001 2400 µg
Reporting group description:	
Patients were randomised to receive CHF 6001 2400 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	CHF 6001 3200 µg
Reporting group description:	
Patients were randomised to receive CHF 6001 3200 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	Budesonide 800 µg
Reporting group description:	
Patients were randomised to receive Budesonide 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	Placebo
Reporting group description:	
Patients were randomised to receive Placebo for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	

Reporting group values	CHF 6001 800 µg	CHF 6001 1600 µg	CHF 6001 2400 µg
Number of subjects	190	179	188
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)	94	80	90
From 65-84 years	96	98	98
85 years and over	0	1	0

Gender categorical Units: Subjects			
Female	57	50	57
Male	133	129	131

Reporting group values	CHF 6001 3200 µg	Budesonide 800 µg	Placebo
Number of subjects	193	187	193
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)	104	91	95
From 65-84 years	89	95	97
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	58	55	60
Male	135	132	133

Reporting group values	Total		
Number of subjects	1130		
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)	554		
From 65-84 years	573		
85 years and over	3		
Gender categorical Units: Subjects			
Female	337		
Male	793		

End points

End points reporting groups

Reporting group title	CHF 6001 800 µg
Reporting group description: Patients were randomised to receive CHF 6001 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period.	
Reporting group title	CHF 6001 1600 µg
Reporting group description: Patients were randomised to receive CHF 6001 1600 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	CHF 6001 2400 µg
Reporting group description: Patients were randomised to receive CHF 6001 2400 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	CHF 6001 3200 µg
Reporting group description: Patients were randomised to receive CHF 6001 3200 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	Budesonide 800 µg
Reporting group description: Patients were randomised to receive Budesonide 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Reporting group title	Placebo
Reporting group description: Patients were randomised to receive Placebo for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period	
Subject analysis set title	CHF 6001 800 µg - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.	
Subject analysis set title	CHF 6001 1600 µg - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.	
Subject analysis set title	CHF 6001 2400 µg - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.	
Subject analysis set title	CHF 6001 3200 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

Subject analysis set title	Budesonide 800 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

Subject analysis set title	Placebo - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

Primary: Change from baseline in morning pre-dose FEV1 at Week 12

End point title	Change from baseline in morning pre-dose FEV1 at Week 12
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End point description:

Morning pre-dose forced expiratory volume in the first second (FEV1).

End point type	Primary
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End point timeframe:

Baseline (pre-dose at the randomisation visit, Week 0) to Week 12.

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177 ^[1]	166 ^[2]	178 ^[3]	178 ^[4]
Units: Litres				
least squares mean (confidence interval 95%)	-0.004 (-0.037 to 0.028)	0.011 (-0.022 to 0.044)	0.004 (-0.029 to 0.036)	-0.024 (-0.057 to 0.008)

Notes:

[1] - Number of patients in the ITT population = 190, number of patients with available data = 177

[2] - Number of patients in the ITT population = 179, number of patients with available data = 166

[3] - Number of patients in the ITT population = 188, number of patients with available data = 178

[4] - Number of patients in the ITT population = 193, number of patients with available data = 178

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178 ^[5]	176 ^[6]		
Units: Litres				
least squares mean (confidence interval 95%)	-0.002 (-0.035 to 0.030)	-0.006 (-0.039 to 0.026)		

Notes:

[5] - Number of patients in the ITT population = 187, number of patients with available data = 178

[6] - Number of patients in the ITT population = 193, number of patients with available data = 176

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB FEV1 at Week 12
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Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects

and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.932
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.048

Statistical analysis title	Adjusted mean difference in CFB FEV1 at Week 12
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Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.064

Statistical analysis title	Adjusted mean difference in CFB FEV1 at Week 12
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Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.673
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.056

Statistical analysis title	Adjusted mean difference in CFB FEV1 at Week 12
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Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.433
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.064
upper limit	0.027

Secondary: TDI score at Week 3

End point title	TDI score at Week 3
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End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

End point type	Secondary
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End point timeframe:

Week 3

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	181 ^[7]	172 ^[8]	183 ^[9]	185 ^[10]
Units: TDI focal scores				
least squares mean (confidence interval 95%)	0.84 (0.51 to 1.17)	0.74 (0.39 to 1.08)	0.65 (0.32 to 0.98)	0.58 (0.25 to 0.91)

Notes:

[7] - Number of patients in the ITT population = 190, number of patients with available data = 181

[8] - Number of patients in the ITT population = 179, number of patients with available data = 172

[9] - Number of patients in the ITT population = 188, number of patients with available data = 183

[10] - Number of patients in the ITT population = 193, number of patients with available data = 185

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181 ^[11]	187 ^[12]		
Units: TDI focal scores				
least squares mean (confidence interval 95%)	0.89 (0.56 to 1.22)	0.73 (0.40 to 1.06)		

Notes:

[11] - Number of patients in the ITT population = 187, number of patients with available data = 181

[12] - Number of patients in the ITT population = 193, number of patients with available data = 187

Statistical analyses

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.645
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.57

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are

presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.48

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.753
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.39

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.537
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.32

Secondary: TDI score at Week 6

End point title	TDI score at Week 6
End point description:	
The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.	
End point type	Secondary
End point timeframe:	
Week 6	

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	183 ^[13]	168 ^[14]	181 ^[15]	184 ^[16]
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.28 (0.96 to 1.61)	1.14 (0.79 to 1.48)	1.17 (0.83 to 1.50)	1.09 (0.75 to 1.42)

Notes:

[13] - Number of patients in the ITT population = 190, number of patients with available data = 183

[14] - Number of patients in the ITT population = 179, number of patients with available data = 168

[15] - Number of patients in the ITT population = 188, number of patients with available data = 181

[16] - Number of patients in the ITT population = 193, number of patients with available data = 184

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179 ^[17]	186 ^[18]		
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.44 (1.11 to 1.77)	1.15 (0.82 to 1.48)		

Notes:

[17] - Number of patients in the ITT population = 187, number of patients with available data = 179

[18] - Number of patients in the ITT population = 193, number of patients with available data = 186

Statistical analyses

Statistical analysis title	Adjusted mean difference in TDI focal scores
Statistical analysis description:	
The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.6

Statistical analysis title	Adjusted mean difference in TDI focal scores
Statistical analysis description:	
The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.957
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.46

Statistical analysis title	Adjusted mean difference in TDI focal score
Statistical analysis description:	
The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are	

presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.945
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.49

Statistical analysis title

Adjusted mean difference in TDI focal score

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.793
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.41

Secondary: TDI score at Week 12

End point title	TDI score at Week 12
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End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

End point type	Secondary
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End point timeframe:

Week 12

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	179 ^[19]	164 ^[20]	178 ^[21]	182 ^[22]
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.23 (0.88 to 1.57)	1.21 (0.84 to 1.57)	1.15 (0.80 to 1.50)	0.99 (0.64 to 1.34)

Notes:

[19] - Number of patients in the ITT population = 190, number of patients with available data = 179

[20] - Number of patients in the ITT population = 179, number of patients with available data = 164

[21] - Number of patients in the ITT population = 188, number of patients with available data = 178

[22] - Number of patients in the ITT population = 193, number of patients with available data = 182

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180 ^[23]	178 ^[24]		
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.03 (0.68 to 1.37)	1.21 (0.86 to 1.56)		

Notes:

[23] - Number of patients in the ITT population = 187, number of patients with available data = 180

[24] - Number of patients in the ITT population = 193, number of patients with available data = 178

Statistical analyses

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.948
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.51

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.988
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.5

Statistical analysis title

Adjusted mean difference in TDI focal score

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.44

Statistical analysis title

Adjusted mean difference in TDI focal score

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.387
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.28

Secondary: TDI score at Week 18

End point title	TDI score at Week 18
End point description:	
The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.	
End point type	Secondary
End point timeframe:	
Week 18	

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	178 ^[25]	164 ^[26]	178 ^[27]	172 ^[28]
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.09 (0.74 to 1.45)	1.14 (0.76 to 1.52)	1.07 (0.71 to 1.43)	1.11 (0.73 to 1.48)

Notes:

[25] - Number of patients in the ITT population = 190, number of patients with available data = 178

[26] - Number of patients in the ITT population = 179, number of patients with available data = 164

[27] - Number of patients in the ITT population = 188, number of patients with available data = 178

[28] - Number of patients in the ITT population = 193, number of patients with available data = 172

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	177 ^[29]	178 ^[30]		
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.19 (0.83 to 1.55)	0.96 (0.60 to 1.32)		

Notes:

[29] - Number of patients in the ITT population = 187, number of patients with available data = 177

[30] - Number of patients in the ITT population = 193, number of patients with available data = 178

Statistical analyses

Statistical analysis title	Adjusted mean difference in TDI focal scores
Statistical analysis description:	
The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.606
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.64

Statistical analysis title	Adjusted mean difference in TDI focal score
Statistical analysis description:	
The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.496
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.7

Statistical analysis title	Adjusted mean difference in TDI focal score
Statistical analysis description:	
The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are	

presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.678
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.62

Statistical analysis title

Adjusted mean difference in TDI focal score

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.66

Secondary: TDI score at Week 24

End point title	TDI score at Week 24
End point description:	
The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	175 ^[31]	159 ^[32]	175 ^[33]	172 ^[34]
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.54 (1.19 to 1.90)	1.28 (0.90 to 1.65)	1.49 (1.13 to 1.85)	1.44 (1.08 to 1.81)

Notes:

[31] - Number of patients in the ITT population = 190, number of patients with available data = 175

[32] - Number of patients in the ITT population = 179, number of patients with available data = 159

[33] - Number of patients in the ITT population = 188, number of patients with available data = 175

[34] - Number of patients in the ITT population = 193, number of patients with available data = 172

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	174 ^[35]	177 ^[36]		
Units: TDI focal scores				
least squares mean (confidence interval 95%)	1.49 (1.13 to 1.84)	1.46 (1.11 to 1.82)		

Notes:

[35] - Number of patients in the ITT population = 187, number of patients with available data = 174

[36] - Number of patients in the ITT population = 193, number of patients with available data = 177

Statistical analyses

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.58

Statistical analysis title	Adjusted mean difference in TDI focal scores
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Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.33

Statistical analysis title

Adjusted mean difference in TDI focal scores

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.53

Statistical analysis title

Adjusted mean difference in TDI focal scores

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.49

Secondary: TDI response

End point title	TDI response
End point description:	
TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24) . A TDI response is defined as TDI focal score ≥ 1 unit. TDI response was assessed at each post-randomisation visit. Patients with TDI focal score < 1 unit or with missing data at any visit were classed as non-responders.	
End point type	Secondary
End point timeframe:	
Week 3, Week 6, Week 12, Week 18, Week 24.	

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190 ^[37]	179 ^[38]	188 ^[39]	193 ^[40]
Units: Patients				
number (not applicable)				
Week 3	85	74	70	84
Week 6	94	83	83	94
Week 12	90	78	84	80
Week 18	83	81	81	80
Week 24	96	77	90	88

Notes:

[37] - ITT population

[38] - ITT population

[39] - ITT population

[40] - ITT population

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	187 ^[41]	193 ^[42]		
Units: Patients				
number (not applicable)				
Week 3	85	80		

Week 6	95	88		
Week 12	86	93		
Week 18	85	86		
Week 24	95	100		

Notes:

[41] - ITT population

[42] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 3 in SGRQ total score

End point title	Change from baseline to Week 3 in SGRQ total score
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End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

End point type	Secondary
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End point timeframe:

Baseline to Week 3.

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	184 ^[43]	173 ^[44]	185 ^[45]	186 ^[46]
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-1.49 (-3.08 to 0.10)	-2.90 (-4.53 to -1.26)	-2.37 (-3.95 to -0.79)	-2.87 (-4.44 to -1.30)

Notes:

[43] - Number of patients in the ITT population = 190, number of patients with available data = 184

[44] - Number of patients in the ITT population = 179, number of patients with available data = 173

[45] - Number of patients in the ITT population = 188, number of patients with available data = 185

[46] - Number of patients in the ITT population = 193, number of patients with available data = 186

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	183 ^[47]	189 ^[48]		
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-3.46 (-5.05 to -1.87)	-3.51 (-5.07 to -1.94)		

Notes:

[47] - Number of patients in the ITT population = 187, number of patients with available data = 183

[48] - Number of patients in the ITT population = 193, number of patients with available data = 189

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	4.25

Statistical analysis title

Adjusted mean difference in CFB, SGRQ total score

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.594
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	2.88

Statistical analysis title

Adjusted mean difference in CFB, SGRQ total score

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.314
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	3.37

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.572
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	2.86

Secondary: Change from baseline to Week 6 in SGRQ total score

End point title	Change from baseline to Week 6 in SGRQ total score
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End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

End point type	Secondary
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End point timeframe:

Baseline to Week 6

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	181 ^[49]	170 ^[50]	184 ^[51]	182 ^[52]
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-2.21 (-3.92 to -0.50)	-5.21 (-6.96 to -3.45)	-4.12 (-5.82 to -2.43)	-4.82 (-6.52 to -3.12)

Notes:

[49] - Number of patients in the ITT population = 190, number of patients with available data = 181

[50] - Number of patients in the ITT population = 179, number of patients with available data = 170

[51] - Number of patients in the ITT population = 188, number of patients with available data = 184

[52] - Number of patients in the ITT population = 193, number of patients with available data = 182

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182 ^[53]	184 ^[54]		
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-5.32 (-7.03 to -3.62)	-5.42 (-7.11 to -3.73)		

Notes:

[53] - Number of patients in the ITT population = 187, number of patients with available data = 182

[54] - Number of patients in the ITT population = 193, number of patients with available data = 184

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	3.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	5.61

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo

estimated by the model are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.865
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	2.65

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.289
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	3.69

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.624
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2.99

Secondary: Change from baseline to Week 12 in SGRQ total score

End point title	Change from baseline to Week 12 in SGRQ total score
End point description:	
The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	176 ^[55]	167 ^[56]	179 ^[57]	180 ^[58]
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-4.53 (-6.43 to -2.62)	-6.62 (-8.57 to -4.66)	-4.58 (-6.47 to -2.69)	-6.38 (-8.26 to -4.50)

Notes:

[55] - Number of patients in the ITT population = 190, number of patients with available data = 176

[56] - Number of patients in the ITT population = 179, number of patients with available data = 167

[57] - Number of patients in the ITT population = 188, number of patients with available data = 179

[58] - Number of patients in the ITT population = 193, number of patients with available data = 180

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180 ^[59]	179 ^[60]		
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-5.56 (-7.45 to -3.67)	-6.17 (-8.06 to -4.29)		

Notes:

[59] - Number of patients in the ITT population = 187, number of patients with available data = 180

[60] - Number of patients in the ITT population = 193, number of patients with available data = 179

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
Statistical analysis description:	
The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	4.33

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
Statistical analysis description:	
The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	2.27

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
Statistical analysis description:	
The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo	

estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	4.26

Statistical analysis title

Adjusted mean difference in CFB, SGRQ total score

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.879
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	2.46

Secondary: Change from baseline to Week 18 in SGRQ total score

End point title	Change from baseline to Week 18 in SGRQ total score
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End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

End point type	Secondary
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End point timeframe:

Baseline to Week 18

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	176 ^[61]	163 ^[62]	179 ^[63]	176 ^[64]
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-6.04 (-7.98 to -4.09)	-7.93 (-9.94 to -5.92)	-5.18 (-7.11 to -3.25)	-6.09 (-8.02 to -4.15)

Notes:

[61] - Number of patients in the ITT population = 190, number of patients with available data = 176

[62] - Number of patients in the ITT population = 179, number of patients with available data = 163

[63] - Number of patients in the ITT population = 188, number of patients with available data = 179

[64] - Number of patients in the ITT population = 193, number of patients with available data = 176

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176 ^[65]	178 ^[66]		
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-5.91 (-7.85 to -3.97)	-6.50 (-8.42 to -4.57)		

Notes:

[65] - Number of patients in the ITT population = 187, number of patients with available data = 176

[66] - Number of patients in the ITT population = 193, number of patients with available data = 178

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	3.2

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.22
upper limit	1.35

Statistical analysis title

Adjusted mean difference in CFB, SGRQ total score

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.344
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	4.05

Statistical analysis title

Adjusted mean difference in CFB, SGRQ total score

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	3.14

Secondary: Change from baseline to Week 24 in SGRQ total score

End point title	Change from baseline to Week 24 in SGRQ total score
End point description:	The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.
End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	172 ^[67]	162 ^[68]	175 ^[69]	173 ^[70]
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-5.54 (-7.64 to -3.43)	-8.06 (-10.24 to -5.89)	-5.95 (-8.04 to -3.86)	-6.96 (-9.06 to -4.87)

Notes:

[67] - Number of patients in the ITT population = 190, number of patients with available data = 172

[68] - Number of patients in the ITT population = 179, number of patients with available data = 162

[69] - Number of patients in the ITT population = 188, number of patients with available data = 175

[70] - Number of patients in the ITT population = 193, number of patients with available data = 173

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176 ^[71]	177 ^[72]		
Units: SGRQ total scores				
least squares mean (confidence interval 95%)	-7.11 (-9.20 to -5.02)	-7.48 (-9.57 to -5.40)		

Notes:

[71] - Number of patients in the ITT population = 187, number of patients with available data = 176

[72] - Number of patients in the ITT population = 193, number of patients with available data = 177

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
Statistical analysis description:	
The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.198
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	4.91

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
Statistical analysis description:	
The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.705
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.59
upper limit	2.43

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
Statistical analysis description:	
The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo	

estimated by the model are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	4.49

Statistical analysis title	Adjusted mean difference in CFB, SGRQ total score
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Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.43
upper limit	3.47

Secondary: SGRQ response

End point title	SGRQ response
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End point description:

SGRQ response is defined as a decrease from baseline in SGRQ total score ≥ 4 units. Baseline SGRQ total scores were recorded at the randomisation visit (Week 0), and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). Patients with decrease from baseline in SGRQ score ≥ 4 units at any visit were classed as responders. Patients with a decrease from baseline in SGRQ total score < 4 units or with missing data at any visit, were classed as non-responders.

End point type	Secondary
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End point timeframe:

Week 3, Week 6, Week 12, Week 18 and Week 24.

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190 ^[73]	179 ^[74]	188 ^[75]	193 ^[76]
Units: Patients				
number (not applicable)				
Week 3	83	71	81	74
Week 6	80	90	90	92
Week 12	93	96	87	97
Week 18	98	95	101	102
Week 24	91	98	94	90

Notes:

[73] - ITT population

[74] - ITT population

[75] - ITT population

[76] - ITT population

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	187 ^[77]	193 ^[78]		
Units: Patients				
number (not applicable)				
Week 3	92	88		
Week 6	93	95		
Week 12	95	90		
Week 18	92	97		
Week 24	93	92		

Notes:

[77] - ITT population

[78] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: CFB to the entire treatment period in average E-RS total score

End point title	CFB to the entire treatment period in average E-RS total score
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End point description:

The EXacerbations of Chronic pulmonary disease Tool (EXACT) collects patient-reported outcomes (PRO) data in order to capture frequency, severity and time course of COPD exacerbations. Digital platform technology was used for data collection in this study. Average EXACT-Respiratory Symptoms (E-RS) scores were recorded during the 2-week run-in period (baseline) and over the entire treatment period of 24 weeks. Change from baseline (CFB) over the entire treatment period was analysed. A decrease from baseline in average E-RS scores ≥ 2.0 is the minimal clinically important difference (MCID) for this instrument.

End point type	Secondary
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End point timeframe:

Baseline (run-in period) to 24 weeks treatment period.

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	187 ^[79]	176 ^[80]	186 ^[81]	187 ^[82]
Units: Average E-RS total scores				
least squares mean (confidence interval 95%)	-1.53 (-2.21 to -0.94)	-2.41 (-3.01 to -1.80)	-1.89 (-2.48 to -1.31)	-2.07 (-2.66 to -1.48)

Notes:

[79] - Number of patients in the ITT population = 190, number of patients with available data = 187

[80] - Number of patients in the ITT population = 179, number of patients with available data = 176

[81] - Number of patients in the ITT population = 188, number of patients with available data = 186

[82] - Number of patients in the ITT population = 193, number of patients with available data = 187

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	184 ^[83]	193 ^[84]		
Units: Average E-RS total scores				
least squares mean (confidence interval 95%)	-2.35 (-2.94 to -1.76)	-2.12 (-2.79 to -1.63)		

Notes:

[83] - Number of patients in the ITT population = 187, number of patients with available data = 184

[84] - Number of patients in the ITT population = 193, number of patients with available data = 193

Statistical analyses

Statistical analysis title	Adjusted mean difference in CFB, E-RS total score
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Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	1.5

Statistical analysis title	Adjusted mean difference in CFB, E-RS total score
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Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	0.64

Statistical analysis title

Adjusted mean difference in CFB, E-RS total score

Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	1.14

Statistical analysis title

Adjusted mean difference in CFB, E-RS total score

Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.97

Secondary: E-RS response

End point title	E-RS response
End point description:	
Average E-RS total scores were recorded during the run-in period (baseline) and for each inter-visit period over the treatment period of 24 weeks. The proportion of patients with a decrease from baseline in average E-RS total score ≥ 2.0 were classed as responders; patients with a decrease from baseline in average E-RS total score < 2.0 units or with missing data for any inter-visit period were classed as non-responders.	
End point type	Secondary
End point timeframe:	
Baseline (two-week run-in period) and inter-visit periods Week 1 to Week 3, Week 4 to Week 6, Week 7 to Week 12, Week 13 to Week 18 and Week 19 to Week 24.	

End point values	CHF 6001 800 μg - ITT	CHF 6001 1600 μg - ITT	CHF 6001 2400 μg - ITT	CHF 6001 3200 μg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190 ^[85]	179 ^[86]	188 ^[87]	193 ^[88]
Units: Patients				
number (not applicable)				
Week 1 to Week 3	58	65	54	58
Week 4 to Week 6	73	82	62	82
Week 7 to Week 12	78	86	72	87
Week 13 to Week 18	74	84	83	77
Week 19 to Week 24	79	94	80	82

Notes:

[85] - ITT population

[86] - ITT population

[87] - ITT population

[88] - ITT population

End point values	Budesonide 800 μg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	187 ^[89]	193 ^[90]		
Units: Patients				

number (not applicable)				
Week 1 to Week 3	60	62		
Week 4 to Week 6	76	73		
Week 7 to Week 12	89	81		
Week 13 to Week 18	90	93		
Week 19 to Week 24	86	89		

Notes:

[89] - ITT population

[90] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Moderate and severe COPD exacerbation rate over 24 weeks of treatment

End point title	Moderate and severe COPD exacerbation rate over 24 weeks of treatment
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End point description:

The rate of moderate or severe COPD exacerbations was evaluated over 24 weeks of treatment. Exacerbations were classified as moderate or severe as per European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) guideline definitions. A moderate exacerbation was defined as a sustained worsening of the patient's condition that required treatment with systemic (oral/IV/IM) corticosteroids and/or antibiotics. A severe exacerbation was defined as one that required hospitalisation or resulted in death. The recognition of potential COPD exacerbations was optimised by the daily reporting of worsened symptoms through the EXacerbations of Chronic pulmonary disease Tool - Patient Reported Outcome (EXACT-PRO) questionnaire.

End point type	Secondary
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End point timeframe:

Baseline to 24 weeks.

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190 ^[91]	179 ^[92]	188 ^[93]	193 ^[94]
Units: Adjusted exacerbation rate/patient/year				
number (confidence interval 95%)	0.563 (0.414 to 0.764)	0.585 (0.428 to 0.799)	0.593 (0.440 to 0.801)	0.487 (0.351 to 0.675)

Notes:

[91] - ITT population

[92] - ITT population

[93] - ITT population

[94] - ITT population

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	187 ^[95]	193 ^[96]		
Units: Adjusted exacerbation rate/patient/year				
number (confidence interval 95%)	0.415 (0.292 to 0.589)	0.681 (0.514 to 0.902)		

Notes:

[95] - ITT population

[96] - ITT population

Statistical analyses

Statistical analysis title	Adjusted exacerbation rate ratio
Statistical analysis description:	
The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.367
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.826
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.546
upper limit	1.251

Statistical analysis title	Adjusted exacerbation rate ratio
Statistical analysis description:	
The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.859
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.565
upper limit	1.307

Statistical analysis title	Adjusted exacerbation rate ratio
Statistical analysis description:	
The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.871
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.578
upper limit	1.313

Statistical analysis title	Adjusted exacerbation rate ratio
Statistical analysis description:	
The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.	
Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.715
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.465
upper limit	1.1

Secondary: Time to first moderate or severe COPD exacerbation	
End point title	Time to first moderate or severe COPD exacerbation
End point description:	
The number of patients at risk of a moderate or severe COPD exacerbation is presented.	
End point type	Secondary
End point timeframe:	
Baseline to 24 weeks	

End point values	CHF 6001 800 µg - ITT	CHF 6001 1600 µg - ITT	CHF 6001 2400 µg - ITT	CHF 6001 3200 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190 ^[97]	179 ^[98]	188 ^[99]	193 ^[100]
Units: Patients				
number (not applicable)	37	36	42	35

Notes:

[97] - ITT population

[98] - ITT population

[99] - ITT population

[100] - ITT population

End point values	Budesonide 800 µg - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	187 ^[101]	193 ^[102]		
Units: Patients				
number (not applicable)	32	49		

Notes:

[101] - ITT population

[102] - ITT population

Statistical analyses

Statistical analysis title	Hazard ratio - time to first exacerbation
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Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

Comparison groups	CHF 6001 800 µg - ITT v Placebo - ITT
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.731
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	1.12

Statistical analysis title	Hazard ratio - time to first exacerbation
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Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

Comparison groups	CHF 6001 1600 µg - ITT v Placebo - ITT
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Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.768
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.499
upper limit	1.181

Statistical analysis title	Hazard ratio - time to first exacerbation
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Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

Comparison groups	CHF 6001 2400 µg - ITT v Placebo - ITT
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.829
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.549
upper limit	1.252

Statistical analysis title	Hazard ratio - time to first exacerbation
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Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

Comparison groups	CHF 6001 3200 µg - ITT v Placebo - ITT
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.693
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.449
upper limit	1.07

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from the time of patient informed consent to study completion or discontinuation.

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) were defined as AEs starting on or after the first randomised study medication intake.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	CHF 6001 800 µg - Safety
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Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of study medication.

Reporting group title	CHF 6001 1600 µg - Safety
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Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	CHF 6001 2400 µg - Safety
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Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	CHF 6001 3200 µg - Safety
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Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	Budesonide 800 µg - Safety
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Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	Placebo - Safety
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Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Serious adverse events	CHF 6001 800 µg - Safety	CHF 6001 1600 µg - Safety	CHF 6001 2400 µg - Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 190 (5.79%)	13 / 179 (7.26%)	12 / 188 (6.38%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			

subjects affected / exposed	1 / 190 (0.53%)	0 / 179 (0.00%)	0 / 188 (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
Rectal cancer			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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
Meniscus injury			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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
Multiple fractures			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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
Radius fracture			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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

Angina unstable			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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
Atrial fibrillation			
subjects affected / exposed	1 / 190 (0.53%)	0 / 179 (0.00%)	0 / 188 (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
Cardiac arrest			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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
Myocardial infarction			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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			
Transient ischaemic attack			
subjects affected / exposed	1 / 190 (0.53%)	0 / 179 (0.00%)	0 / 188 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Eye disorders			
Cataract			
subjects affected / exposed	1 / 190 (0.53%)	0 / 179 (0.00%)	0 / 188 (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
Gastrointestinal disorders			
Duodenal stenosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 179 (0.00%)	0 / 188 (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
Inguinal hernia			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 190 (0.00%)	1 / 179 (0.56%)	0 / 188 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	6 / 190 (3.16%)	7 / 179 (3.91%)	7 / 188 (3.72%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			

Infectious pleural effusion			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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
Pneumonia			
subjects affected / exposed	1 / 190 (0.53%)	1 / 179 (0.56%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia escherichia			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 179 (0.00%)	0 / 188 (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	CHF 6001 3200 µg - Safety	Budesonide 800 µg - Safety	Placebo - Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 193 (3.63%)	10 / 187 (5.35%)	7 / 193 (3.63%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Rectal cancer			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Injury, poisoning and procedural complications			
Humerus fracture			

subjects affected / exposed	0 / 193 (0.00%)	1 / 187 (0.53%)	0 / 193 (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
Meniscus injury			
subjects affected / exposed	1 / 193 (0.52%)	0 / 187 (0.00%)	0 / 193 (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
Multiple fractures			
subjects affected / exposed	1 / 193 (0.52%)	0 / 187 (0.00%)	0 / 193 (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
Radius fracture			
subjects affected / exposed	0 / 193 (0.00%)	1 / 187 (0.53%)	0 / 193 (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
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Angina unstable			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Atrial fibrillation			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Coronary artery disease			
subjects affected / exposed	1 / 193 (0.52%)	0 / 187 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 193 (0.52%)	0 / 187 (0.00%)	0 / 193 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 193 (0.52%)	0 / 187 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Gastrointestinal disorders			
Duodenal stenosis			

subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Inguinal hernia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 187 (0.53%)	0 / 193 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 193 (1.04%)	5 / 187 (2.67%)	5 / 193 (2.59%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Infectious pleural effusion			
subjects affected / exposed	0 / 193 (0.00%)	1 / 187 (0.53%)	0 / 193 (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
Pneumonia			

subjects affected / exposed	0 / 193 (0.00%)	1 / 187 (0.53%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia escherichia			
subjects affected / exposed	0 / 193 (0.00%)	0 / 187 (0.00%)	0 / 193 (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
Urosepsis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 187 (0.00%)	0 / 193 (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

Frequency threshold for reporting non-serious adverse events: 3.5 %

Non-serious adverse events	CHF 6001 800 µg - Safety	CHF 6001 1600 µg - Safety	CHF 6001 2400 µg - Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 190 (45.26%)	90 / 179 (50.28%)	91 / 188 (48.40%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 190 (5.26%)	7 / 179 (3.91%)	7 / 188 (3.72%)
occurrences (all)	14	8	8
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	42 / 190 (22.11%)	41 / 179 (22.91%)	54 / 188 (28.72%)
occurrences (all)	68	58	66
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 190 (3.68%)	14 / 179 (7.82%)	11 / 188 (5.85%)
occurrences (all)	10	16	11

Non-serious adverse events	CHF 6001 3200 µg - Safety	Budesonide 800 µg - Safety	Placebo - Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 193 (43.01%)	89 / 187 (47.59%)	101 / 193 (52.33%)
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	11 / 193 (5.70%) 15	10 / 187 (5.35%) 12	8 / 193 (4.15%) 10
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	43 / 193 (22.28%) 60	39 / 187 (20.86%) 56	58 / 193 (30.05%) 75
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	12 / 193 (6.22%) 15	9 / 187 (4.81%) 10	13 / 193 (6.74%) 13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2016	There were three versions of the clinical study protocol. Version 1.0 was never used, and initial submissions were done with Version 2.0. Based on the Medicines and Healthcare products Regulatory Agency (MHRA) comments, there was one substantial protocol amendment, with the following main changes implemented further to the initial protocol version: - The thyroid function tests were added at the screening visit to confirm the exclusion of the uncontrolled thyroid disease as per exclusion criterion #16; - Monitoring of psychiatric adverse events was specified (including update of the physical examination section). The first Competent Authority approval of Version 3.0 was received on 27 October 2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported