Clinical trial results:
A multicenter, randomised, double blind, placebo-controlled, incomplete block, 3-way cross-over study to evaluate the efficacy and safety of 4 doses of glycopyrronium bromide DPI in moderate to severe patients with chronic obstructive pulmonary disease (COPD)

Summary

EudraCT number	2015-000558-40
Trial protocol	DE HU CZ RO
Global end of trial date	06 February 2017

Results information

Result version number	v1 (current)
This version publication date	31 January 2018
First version publication date	31 January 2018

Trial information

Trial identification

Sponsor protocol code	CCD-06302AA1-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02680197
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., ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2017
Global end of trial reached?	Yes
Global end of trial date	06 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to identify the optimal dose of CHF 5259 glycopyrronium bromide (GB) to be further developed for the treatment of patients with COPD.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. There was no anticipated benefit for patients receiving placebo. However, patients were closely monitored and the risks for patients were minimised by measures such as training of patients in the early recognition of COPD exacerbations and on appropriate early actions to be taken, including contacting the investigator if their condition was worsening, and discontinuation in case of disease worsening. Moreover, patients received placebo only for a maximum of one out the three treatment periods and had access to rescue medication as needed throughout the study.

Background therapy:

If the patient was receiving treatment with inhaled corticosteroid (ICS) in combination with a bronchodilator (long-acting β2 agonist [LABA] or long-acting muscarinic agonist [LAMA]) at the time of informed consent signature, the combination was discontinued at screening and an equipotent daily dose of Flixotide® Accuhaler® DPI 250 µg/actuation was prescribed according to the Global Initiative for asthma pocket guide for health professionals. This background treatment was maintained for the entire run-in period and the remainder of the study.

Evidence for comparator: -

Actual start date of recruitment	29 February 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	Romania: 31
Country: Number of subjects enrolled	Czech Republic: 88
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Hungary: 64
Worldwide total number of subjects	202
EEA total number of subjects	202

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	118
From 65 to 84 years	84
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 202 patients were randomised into one of the ten treatment sequences (Sequence A-C-D [n=20], Sequence E-D-B [n=20], Sequence C-B-E [n=20], Sequence D-E-C [n=20], Sequence B-C-A [n=20], Sequence B-A-D [n=20], Sequence A-D-E [n=20], Sequence D-B-C [n=21], Sequence E-A-B [n=20], Sequence C-E-A [n=21]) and 178 patients completed the study.

Pre-assignment

Screening details:

This study comprised a pre-screening visit, occurring no more than seven days prior to a screening visit. A total of 262 patients were screened, 202 (77.1%) were randomised and 60 (22.9%) failed screening due to inclusion/exclusion criteria (51 patients), consent withdrawal (3 patients), adverse events (2 patients) and other reasons (4 patients)

Period 1

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

Blinding implementation details:

At randomisation, patients in each centre were centrally assigned to one of the ten treatment sequences by the interactive response technology system using a list-based randomisation algorithm. The randomisation list was provided to the labelling facility but was not available to patients, investigators, monitors or employees of the centre involved in the management of the study before unblinding of the data, unless in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A-C-D

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment D = CHF 5259 DPI 100 µg.

Arm type	Experimental - experimental - experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

Arm title	Sequence E-D-B

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259

DPI 25 µg.

Arm type	Placebo - experimental - experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

Arm title	Sequence C-B-E

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment E = Placebo.

Arm type	Experimental - experimental - placebo
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

Arm title	Sequence D-E-C

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo; Treatment C = CHF 5259 DPI 50 µg.

Arm type	Experimental - placebo - experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

Arm title	Sequence B-C-A

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment A = CHF 5259 DPI 12.5 µg.

Arm type	Experimental - experimental - experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily).

Arm title	Sequence B-A-D

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg;

Arm type	Experimental - experimental - experimental

Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

Arm title	Sequence A-D-E

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo.

Arm type	Experimental - experimental - placebo
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

Arm title	Sequence D-B-C

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg.

Arm type	Experimental - experimental - experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

Arm title	Sequence E-A-B

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg; Treatment B = CHF 5259 DPI 25 µg.

Arm type	Placebo - experimental - experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily).

Arm title	Sequence C-E-A

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg.

Arm type	Experimental - placebo - experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	CHF 5259
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

Number of subjects in period 1	Sequence A-C-D	Sequence E-D-B	Sequence C-B-E
Started	20	20	20
Completed	17	15	16
Not completed	3	5	4
Consent withdrawn by subject	1	2	2
Adverse event, non-fatal	2	3	2
Other (family problems)	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Sequence D-E-C	Sequence B-C-A	Sequence B-A-D
Started	20	20	20
Completed	20	17	18
Not completed	0	3	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	2	2
Other (family problems)	-	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Sequence A-D-E	Sequence D-B-C	Sequence E-A-B
Started	20	21	20
Completed	17	20	17
Not completed	3	1	3
Consent withdrawn by subject	1	-	2
Adverse event, non-fatal	2	1	-
Other (family problems)	-	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Sequence C-E-A
Started	21
Completed	21
Not completed	0

Consent withdrawn by subject	-
Adverse event, non-fatal	-
Other (family problems)	-
Lost to follow-up	-

Reporting groups	
Reporting group title	Sequence A-C-D
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment D = CHF 5259 DPI 100 µg.	
Reporting group title	Sequence E-D-B
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg.	
Reporting group title	Sequence C-B-E
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment E = Placebo.	
Reporting group title	Sequence D-E-C
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo; Treatment C = CHF 5259 DPI 50 µg.	
Reporting group title	Sequence B-C-A
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment A = CHF 5259 DPI 12.5 µg.	
Reporting group title	Sequence B-A-D
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg;	
Reporting group title	Sequence A-D-E
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo.	
Reporting group title	Sequence D-B-C
Reporting group description:	
Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg.	
Reporting group title	Sequence E-A-B

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg; Treatment B = CHF 5259 DPI 25 µg.

Reporting group title	Sequence C-E-A

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg.

Reporting group values	Sequence A-C-D	Sequence E-D-B	Sequence C-B-E
Number of subjects	20	20	20
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)	8	12	14
From 65-84 years	12	8	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.3	60.4	62
standard deviation	± 7.5	± 7	± 6.6
Gender categorical Units: Subjects			
Female	8	7	6
Male	12	13	14

Reporting group values	Sequence D-E-C	Sequence B-C-A	Sequence B-A-D
Number of subjects	20	20	20
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)	12	12	10
From 65-84 years	8	8	10
85 years and over	0	0	0

Age continuous			
Units: years			
arithmetic mean	59.5	64	64.7
standard deviation	± 9.3	± 8.8	± 7.8
Gender categorical			
Units: Subjects			
Female	10	9	8
Male	10	11	12

Reporting group values	Sequence A-D-E	Sequence D-B-C	Sequence E-A-B
Number of subjects	20	21	20
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)	14	12	12
From 65-84 years	6	9	8
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	61.5	62.9	63.3
standard deviation	± 6.3	± 6.5	± 7.9
Gender categorical			
Units: Subjects			
Female	6	10	9
Male	14	11	11

Reporting group values	Sequence C-E-A	Total	
Number of subjects	21	202	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	118	
From 65-84 years	9	84	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	64		
standard deviation	± 6.5	-	

Gender categorical Units: Subjects			
Female	6	79	
Male	15	123	

End points

End points reporting groups

Reporting group title	Sequence A-C-D

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment D = CHF 5259 DPI 100 µg.

Reporting group title	Sequence E-D-B

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg.

Reporting group title	Sequence C-B-E

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment E = Placebo.

Reporting group title	Sequence D-E-C

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo; Treatment C = CHF 5259 DPI 50 µg.

Reporting group title	Sequence B-C-A

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment A = CHF 5259 DPI 12.5 µg.

Reporting group title	Sequence B-A-D

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg;

Reporting group title	Sequence A-D-E

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo.

Reporting group title	Sequence D-B-C

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg.

Reporting group title	Sequence E-A-B

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg; Treatment B = CHF 5259 DPI 25 µg.

Reporting group title	Sequence C-E-A

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg.

Subject analysis set title	A) CHF 5259 DPI 12.5 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Treatment A = CHF 5259 DPI 12.5 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

Subject analysis set title	B) CHF 5259 DPI 25 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Treatment B = CHF 5259 DPI 25 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

Subject analysis set title	C) CHF 5259 DPI 50 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Treatment C = CHF 5259 DPI 50 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

Subject analysis set title	D) CHF 5259 DPI 100 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Treatment D = CHF 5259 DPI 100 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

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

Subject analysis set description:

Treatment E = Placebo; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

Primary: FEV1 AUC0-12h on Day 28

End point title	FEV1 AUC0-12h on Day 28

End point description:

Forced expiratory volume in the 1st second (FEV1) area under the curve between 0 and 12 hours (AUC0-12h) normalised by time was calculated based on the actual times using the linear trapezoidal rule. Results for FVC were comparable to those observed with FEV1

End point type	Primary

End point timeframe:

FEV1, assessed in each treatment period at 15 min, 30 min, 45 min and 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 11.5 h and 12 h post-morning dose, was used to calculate FEV1 area under the curve between 0-12 h (AUC0-12h) on Day 28.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	104[1]	106[2]	112[3]	108[4]
Units: litre(s)				
least squares mean (confidence interval 95%)	1.505 (1.483 to 1.528)	1.517 (1.495 to 1.539)	1.535 (1.513 to 1.556)	1.579 (1.557 to 1.601)

Notes:

[1] - ITT population, available for change from baseline (complete ITT population n=113)

[2] - ITT population, available for change from baseline (complete ITT population n=110)

[3] - ITT population, available for change from baseline (complete ITT population n=117)

[4] - ITT population, available for change from baseline (complete ITT population n=112)

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	103[5]			
Units: litre(s)				
least squares mean (confidence interval 95%)	1.392 (1.369 to 1.414)			

Notes:

[5] - ITT population, available for change from baseline (complete ITT population n=108)

Statistical analyses

Statistical analysis title	CHF 5259 DPI 12.5 µg vs. placebo

Statistical analysis description:

The value N=207, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.154

Statistical analysis title	CHF 5259 DPI 25 µg vs. placebo

Statistical analysis description:

The value N=209, shown below, is generated automatically and is due to innate error of the EudraCT

database system

Comparison groups	B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.166

Statistical analysis title	CHF 5259 DPI 50 µg vs. placebo

Statistical analysis description:

The value N=215, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.104
upper limit	0.183

Statistical analysis title	CHF 5259 DPI 100 µg vs. placebo

Statistical analysis description:

The value N=211, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.187

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.147
upper limit	0.228

Secondary: Change from baseline in morning pre-dose FEV1 on Day 28

End point title	Change from baseline in morning pre-dose FEV1 on Day 28

End point description:

Morning pre-dose FEV1 was defined as the mean of 45 min and 10 min pre-dose measurements. Baseline was defined as the mean of 45 min and 10 min pre-dose measurements on Day 1.

End point type	Secondary

End point timeframe:

The change from baseline in morning pre-dose FEV1 was analysed on Day 28.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111[6]	109[7]	115[8]	109[9]
Units: litre(s)				
least squares mean (confidence interval 95%)	0.084 (0.059 to 0.109)	0.072 (0.047 to 0.097)	0.097 (0.073 to 0.122)	0.136 (0.111 to 0.162)

Notes:

[6] - ITT population, available for change from baseline

[7] - ITT population, available for change from baseline

[8] - ITT population, available for change from baseline

[9] - ITT population, available for change from baseline

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	107[10]			
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.023 (-0.048 to 0.003)			

Notes:

[10] - ITT population, available for change from baseline

Statistical analyses

Statistical analysis title	CHF 5259 DPI 12.5 µg vs. placebo

Statistical analysis description:

The value N=218, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.142

Statistical analysis title	CHF 5259 DPI 25 µg vs. placebo
Statistical analysis description:	
The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system	
Comparison groups	B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.131

Statistical analysis title	CHF 5259 DPI 50 µg vs. placebo
Statistical analysis description:	
The value N=222, shown below, is generated automatically and is due to innate error of the EudraCT database system	
Comparison groups	C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.084
upper limit	0.155

Statistical analysis title	CHF 5259 DPI 100 µg vs. placebo

Statistical analysis description:

The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.123
upper limit	0.195

Secondary: Change from baseline in trough FEV1 at 12 h on Day 28

End point title	Change from baseline in trough FEV1 at 12 h on Day 28

End point description:

Trough FEV1 was defined as the mean of 11.5 h and 12 h post-dose measurements. Baseline was defined as the mean of 45 min and 10 min pre-dose measurements on Day 1.

End point type	Secondary

End point timeframe:

The change from baseline in trough FEV1 at 12 h was analysed on Day 28.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	104[11]	106[12]	112[13]	108[14]
Units: litre(s)				
least squares mean (confidence interval 95%)	0.052 (0.024 to 0.08)	0.07 (0.042 to 0.097)	0.092 (0.066 to 0.119)	0.132 (0.105 to 0.159)

Notes:

[11] - ITT population, available for change from baseline

[12] - ITT population, available for change from baseline

[13] - ITT population, available for change from baseline

[14] - ITT population, available for change from baseline

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	103[15]			
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.025 (-0.053 to 0.003)			

Notes:

[15] - ITT population, available for change from baseline

Statistical analyses

Statistical analysis title	CHF 5259 DPI 12.5 µg vs. placebo

Statistical analysis description:

The value N=207, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.116

Statistical analysis title	CHF 5259 DPI 25 µg vs. placebo

Statistical analysis description:

The value N=209, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.094

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.134

Statistical analysis title	CHF 5259 DPI 50 µg vs. placebo

Statistical analysis description:

The value N=215, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.156

Statistical analysis title	CHF 5259 DPI 100 µg vs. placebo

Statistical analysis description:

The value N=211, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117
upper limit	0.196

Secondary: Change from baseline in peak0-4h FEV1 on Day 28

End point title	Change from baseline in peak0-4h FEV1 on Day 28

End point description:

Peak0-4h FEV1 was defined as the maximum FEV1 value from 15 min to 4 h post-dose. Baseline was defined as the mean of 45 min and 10 min pre-dose measurements on Day 1.

End point type	Secondary

End point timeframe:

The change from baseline in peak0-4h FEV1 was analysed on Day 28.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111[16]	109[17]	115[18]	109[19]
Units: litre(s)				
least squares mean (confidence interval 95%)	0.24 (0.214 to 0.265)	0.25 (0.225 to 0.276)	0.269 (0.244 to 0.294)	0.31 (0.284 to 0.336)

Notes:

[16] - ITT population, available for change from baseline

[17] - ITT population, available for change from baseline

[18] - ITT population, available for change from baseline

[19] - ITT population, available for change from baseline

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	107[20]			
Units: litre(s)				
least squares mean (confidence interval 95%)	0.105 (0.079 to 0.131)			

Notes:

[20] - ITT population, available for change from baseline

Statistical analyses

Statistical analysis title	CHF 5259 DPI 12.5 µg vs. placebo

Statistical analysis description:

The value N=218, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.172

Statistical analysis title	CHF 5259 DPI 25 µg vs. placebo
Statistical analysis description:	
The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system	
Comparison groups	B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.145
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.183

Statistical analysis title	CHF 5259 DPI 50 µg vs. placebo
Statistical analysis description:	
The value N=222, shown below, is generated automatically and is due to innate error of the EudraCT database system	
Comparison groups	C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.127
upper limit	0.2

Statistical analysis title	CHF 5259 DPI 100 µg vs. placebo
Statistical analysis description:	
The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system	
Comparison groups	D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.204
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.167
upper limit	0.242

Secondary: TDI focal score on Day 28

End point title	TDI focal score on Day 28

End point description:

Dyspnoea at baseline was assessed with the Baseline Dyspnoea Index (BDI) , which covers three domains: functional impairment, magnitude of task and magnitude of effort with the values added for a combined focal score. The BDI scores ranged from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12). The changes from baseline were measured by the Transition Dyspnoea Index (TDI) score which ranged from -3 (major deterioration) to +3 (major improvement) for each domain, with the TDI focal score consisting of the sum of each domain (-9 to +9).

End point type	Secondary

End point timeframe:

TDI was assessed in the morning of Day 28 of each treatment period or in case of ET visit. (BDI was assessed in the morning of Day 1 of each treatment period.)

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	113[21]	110[22]	117[23]	111[24]
Units: unit(s)				
arithmetic mean (confidence interval 95%)	1.372 (0.878 to 1.865)	1.718 (1.264 to 2.173)	1.462 (1.000 to 1.923)	2.036 (1.559 to 2.513)

Notes:

[21] - ITT population, available for change from baseline

[22] - ITT population, available for change from baseline

[23] - ITT population, available for change from baseline

[24] - ITT population, available for change from baseline

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	108[25]			
Units: unit(s)				
arithmetic mean (confidence interval 95%)	0.750 (0.266 to 1.234)			

Notes:

[25] - ITT population, available for change from baseline

Statistical analyses

No statistical analyses for this end point

Secondary: TDI focal score responders on Day 28

End point title	TDI focal score responders on Day 28

End point description:

Responders were patients with a TDI focal score ≥1 on Day 28. Real non-responders were patients with a TDI focal score <1 on Day 28. Non-responders due to missing values were patients with a missing TDI focal score on Day 28.

End point type	Secondary

End point timeframe:

TDI focal score responders were analysed on Day 28.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	113[26]	110[27]	117[28]	112[29]
Units: patients				
Responders	59	67	65	71
Real non-responders	54	43	52	40
Non-responders due to missing values	0	0	0	1

Notes:

[26] - ITT population

[27] - ITT population

[28] - ITT population

[29] - ITT population

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	108[30]			
Units: patients				
Responders	48			
Real non-responders	60			
Non-responders due to missing values	0			

Notes:

[30] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients using rescue medication

End point title	Number of patients using rescue medication

End point description:

End point type	Secondary

End point timeframe:

Number of patients who used rescue medication at least once during the treatment period.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	113[31]	110[32]	117[33]	112[34]
Units: patients	81	80	87	77

Notes:

[31] - ITT population

[32] - ITT population

[33] - ITT population

[34] - ITT population

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	108[35]			
Units: patients	89			

Notes:

[35] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Days with rescue medication administration during the treatment period (%)

End point title	Days with rescue medication administration during the treatment period (%)

End point description:

The percentage of days with intake of rescue medication was calculated as: (number of days with rescue medication intake / number of days with available data) * 100.

End point type	Secondary

End point timeframe:

Treatment period.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	107[36]	104[37]	113[38]	110[39]
Units: days (%)				
arithmetic mean (confidence interval 95%)	46.332 (38.517 to 54.147)	48.844 (41.158 to 56.530)	49.006 (41.679 to 56.334)	36.572 (29.446 to 43.697)

Notes:

[36] - ITT population, available for change from baseline

[37] - ITT population, available for change from baseline

[38] - ITT population, available for change from baseline

[39] - ITT population, available for change from baseline

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	103[40]			
Units: days (%)				
arithmetic mean (confidence interval 95%)	59.452 (51.847 to 67.058)			

Notes:

[40] - ITT population, available for change from baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Average use of rescue medication during the treatment period (puffs/day)

End point title	Average use of rescue medication during the treatment period (puffs/day)

End point description:

The average use of rescue medication was calculated as total number of puffs / number of days with available data.

End point type	Secondary

End point timeframe:

Treatment period.

End point values	A) CHF 5259 DPI 12.5 µg - ITT	B) CHF 5259 DPI 25 µg - ITT	C) CHF 5259 DPI 50 µg - ITT	D) CHF 5259 DPI 100 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	107[41]	104[42]	113[43]	110[44]
Units: puffs/day				
arithmetic mean (confidence interval 95%)	1.358 (1.018 to 1.698)	1.331 (1.003 to 1.659)	1.130 (0.868 to 1.392)	1.085 (0.753 to 1.416)

Notes:

[41] - ITT population, available for change from baseline

[42] - ITT population, available for change from baseline

[43] - ITT population, available for change from baseline

[44] - ITT population, available for change from baseline

End point values	E) Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	103[45]			
Units: puffs/day				
arithmetic mean (confidence interval 95%)	1.831 (1.448 to 2.214)			

Notes:

[45] - ITT population, available for change from baseline

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for AEs was from the signature of the informed consent form until the patient's participation in the study ended (follow-up call included).

Adverse event reporting additional description:

All AEs starting on or after the time of first study treatment intake and before the last visit in Treatment Period 3 or the early termination visit (as applicable) were classified as treatment emergent AEs (TEAEs). TEAEs were assigned to the last study medication received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	A) CHF 5259 DPI 12.5 µg - Safety

Reporting group description:

Treatment A = CHF 5259 DPI 12.5 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	B) CHF 5259 DPI 25 µg - Safety

Reporting group description:

Treatment B = CHF 5259 DPI 25 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	C) CHF 5259 DPI 50 µg - Safety

Reporting group description:

Treatment C = CHF 5259 DPI 50 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	D) CHF 5259 DPI 100 µg - Safety

Reporting group description:

Treatment D = CHF 5259 DPI 100 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

Reporting group title	E) Placebo - Safety

Reporting group description:

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

Serious adverse events	A) CHF 5259 DPI 12.5 µg - Safety	B) CHF 5259 DPI 25 µg - Safety	C) CHF 5259 DPI 50 µg - Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 116 (0.86%)	1 / 111 (0.90%)	0 / 119 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer extensive stage			

subjects affected / exposed	1 / 116 (0.86%)	0 / 111 (0.00%)	0 / 119 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Limb traumatic amputation			
subjects affected / exposed	0 / 116 (0.00%)	0 / 111 (0.00%)	0 / 119 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 116 (0.00%)	0 / 111 (0.00%)	0 / 119 (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
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	0 / 116 (0.00%)	1 / 111 (0.90%)	0 / 119 (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

Serious adverse events	D) CHF 5259 DPI 100 µg - Safety	E) Placebo - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 112 (1.79%)	2 / 115 (1.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer extensive stage			
subjects affected / exposed	0 / 112 (0.00%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Limb traumatic amputation			

subjects affected / exposed	0 / 112 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 112 (1.79%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	0 / 112 (0.00%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	A) CHF 5259 DPI 12.5 µg - Safety	B) CHF 5259 DPI 25 µg - Safety	C) CHF 5259 DPI 50 µg - Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 116 (14.66%)	18 / 111 (16.22%)	13 / 119 (10.92%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 116 (3.45%)	1 / 111 (0.90%)	1 / 119 (0.84%)
occurrences (all)	4	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 116 (4.31%)	7 / 111 (6.31%)	3 / 119 (2.52%)
occurrences (all)	5	7	3

Non-serious adverse events	D) CHF 5259 DPI 100 µg - Safety	E) Placebo - Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 112 (13.39%)	16 / 115 (13.91%)	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 112 (0.89%)	3 / 115 (2.61%)	
occurrences (all)	1	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 112 (0.89%)	1 / 115 (0.87%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported