Clinical trial results:
A phase II, multicentre, randomised, double-blind, double-dummy, active-controlled, 3-way cross-over study to evaluate the efficacy of CHF 5993 administered via Dry Powder Inhaler (DPI) versus CHF 5993 via pressurized Metered Dose Inhaler (pMDI) and CHF 1535 pMDI in patients with chronic obstructive pulmonary disease

Summary

EudraCT number	2017-004405-41
Trial protocol	DE HU CZ BG PL IT
Global end of trial date	06 March 2019

Results information

Result version number	v1 (current)
This version publication date	20 March 2020
First version publication date	20 March 2020

Trial information

Trial identification

Sponsor protocol code	CLI-05993BA1-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03590379
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 Trials Transparency, Chiesi Farmaceutici S.p.A., +39 05212791, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trials Transparency, Chiesi Farmaceutici S.p.A., +39 05212791, clinicaltrials_info@chiesi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2019
Global end of trial reached?	Yes
Global end of trial date	06 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:
•To demonstrate the non-inferiority between CHF 5993 DPI and CHF 5993 pMDI in terms of forced expiratory volume in the 1st second (FEV1) area under the curve between 0 and 12 hours (AUC0-12h) normalised by time on Day 28;
•To demonstrate the non-inferiority between CHF 5993 DPI and CHF 5993 pMDI in terms of trough FEV1 at 24 hours on Day 28.*

*Minor changes to the wording of these objectives for clarification purposes, which did not alter the meaning, were made in this results posting compared to the protocol.

Protection of trial subjects:

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

At all visits from screening to the end of the treatment period, concomitant medications and adverse events (AEs) were recorded and physical examination of patients was carried out (concomitant medications and AEs were additionally recorded at the follow-up call). Vital signs (pre-dose) and 12-lead electrocardiograms (ECGs) (pre-dose at screening, pre- and post-dose at all visits during the treatment period) were recorded. Spirometry was performed (pre- and post-bronchodilator FEV1 and forced vital capacity [FVC] at screening and pre-dose and serial post-dose spirometry [FEV1 and FVC] at randomisation and all post-randomisation visits during the treatment period).

Patients completed the diary card at home daily from screening until the end of the treatment period. The St. George's Respiratory Questionnaire (SGRQ) was completed at randomisation and at all post-randomisation visits during the treatment period.

Blood collection for routine haematology and blood chemistry was performed at screening and again at the end of the treatment period. Heart rate, Fridericia-corrected QT interval, PR interval and QRS interval were evaluated on 12-lead ECGs.

Patients were provided with salbutamol as rescue medication.

Background therapy: -

Evidence for comparator:

CHF 5993 DPI (beclometasone dipropionate [BDP]/formoterol fumarate [FF]/glycopyrronium bromide [GB] 100/6/12.5 µg/inhalation) was compared to CHF 5993 pMDI (BDP/FF/GB 100/6/12.5 µg/actuation) and to CHF 1535 pMDI (BDP/FF 100/6 µg/actuation).

CHF 5993 pMDI was chosen as reference treatment as it contains the same active ingredients and is currently authorised as a maintenance treatment in adult patients with COPD who are not adequately treated by combinations of either an inhaled corticosteroid (ICS) and a long-acting β2 agonist (LABA) or a LABA and a long-acting muscarinic antagonist (LAMA). The aim of the study was to demonstrate non-inferiority of CHF 5993 DPI to CHF 5993 pMDI in accordance with the Orally Inhaled Products guideline.

Superiority of the triple therapy CHF 5993 pMDI (ICS/LABA/LAMA) to double therapy with CHF 1535 pMDI (ICS/LABA) was tested to demonstrate assay sensitivity. CHF 1535 pMDI was chosen as reference treatment as it is currently marketed for the treatment of patients with COPD who have significant symptoms despite long-acting bronchodilator therapy.

Actual start date of recruitment	15 June 2018
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: 123
Country: Number of subjects enrolled	Bulgaria: 72
Country: Number of subjects enrolled	Czech Republic: 34
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Hungary: 105
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	366
EEA total number of subjects	366

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)	175
From 65 to 84 years	191
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 449 patients were screened; 366 patients were randomised to one of six treatment sequences (Sequence ABC [n=63], Sequence CAB [n=60], Sequence BCA [n=60], Sequence ACB [n=62], Sequence BAC [n=60], Sequence CBA [n=61] [note: A=CHF 5993 DPI, B=CHF 5993 pMDI, C=CHF 1535 pMDI]); 342 patients completed the study.

Pre-assignment

Screening details:

At screening, no more than 7 days after a pre-screening visit, inclusion/exclusion criteria were assessed. A total of 83 patients failed screening due to: inclusion/exclusion criteria (66 patients), consent withdrawal (7 patients), other reasons (5 patients), adverse events (3 patients), death (1 patient) and lost to follow-up (1 patient).

Period 1

Period 1 title	Period 1 (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 were assigned to one of six treatment sequences using a balanced block randomisation scheme and a pre-established randomisation list.

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 ABC

Arm description:

Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment A=CHF 5993 DPI; Treatment B=CHF 5993 pMDI; Treatment C=CHF 1535 pMDI.

Arm type	Experimental
Investigational medicinal product name	CHF 5993 DPI
Investigational medicinal product code	CHF 5993 DPI
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Study treatment kits for each period contained two DPI inhalers and two pMDI inhalers. Within the same period, patients receiving CHF 5993 DPI active were administered CHF 5993 pMDI placebo. Similarly, patients receiving CHF 5993 pMDI or CHF 1535 pMDI were administered CHF 5993 DPI placebo. Thus, each day during the treatment periods patients administered 2 inhalations from the first DPI and 2 puffs from the first pMDI in the morning, then 2 inhalations from the second DPI and 2 puffs from the second pMDI in the evening. Treatment A=CHF 5993 DPI (2 inhalations of CHF 5993 DPI and 2 puffs of CHF 5993 pMDI placebo twice daily [total daily dose: BDP/FF/GB 400/24/50 µg]); Treatment B=CHF 5993 pMDI (2 puffs of CHF 5993 pMDI and 2 inhalations of CHF 5993 DPI placebo twice daily [total daily dose: BDP/FF/GB 400/24/50 µg]); Treatment C=CHF 1535 pMDI (2 puffs of CHF 1535 pMDI and 2 inhalations of CHF 5993 DPI placebo twice daily [total daily dose: BDP/FF 400/24 µg]).

Investigational medicinal product name	CHF 5993 pMDI
Investigational medicinal product code	CHF 5993 pMDI
Other name	
Pharmaceutical forms	Inhalation solution

Routes of administration	Inhalation use

Dosage and administration details:

Study treatment kits for each period contained two DPI inhalers and two pMDI inhalers. Within the same period, patients receiving CHF 5993 DPI active were administered CHF 5993 pMDI placebo. Similarly, patients receiving CHF 5993 pMDI or CHF 1535 pMDI were administered CHF 5993 DPI placebo. Thus, each day during the treatment periods patients administered 2 inhalations from the first DPI and 2 puffs from the first pMDI in the morning, then 2 inhalations from the second DPI and 2 puffs from the second pMDI in the evening. Treatment A=CHF 5993 DPI (2 inhalations of CHF 5993 DPI and 2 puffs of CHF 5993 pMDI placebo twice daily [total daily dose: BDP/FF/GB 400/24/50 µg]); Treatment B=CHF 5993 pMDI (2 puffs of CHF 5993 pMDI and 2 inhalations of CHF 5993 DPI placebo twice daily [total daily dose: BDP/FF/GB 400/24/50 µg]); Treatment C=CHF 1535 pMDI (2 puffs of CHF 1535 pMDI and 2 inhalations of CHF 5993 DPI placebo twice daily [total daily dose: BDP/FF 400/24 µg]).

Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	CHF 1535 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Study treatment kits for each period contained two DPI inhalers and two pMDI inhalers. Within the same period, patients receiving CHF 5993 DPI active were administered CHF 5993 pMDI placebo. Similarly, patients receiving CHF 5993 pMDI or CHF 1535 pMDI were administered CHF 5993 DPI placebo. Thus, each day during the treatment periods patients administered 2 inhalations from the first DPI and 2 puffs from the first pMDI in the morning, then 2 inhalations from the second DPI and 2 puffs from the second pMDI in the evening. Treatment A=CHF 5993 DPI (2 inhalations of CHF 5993 DPI and 2 puffs of CHF 5993 pMDI placebo twice daily [total daily dose: BDP/FF/GB 400/24/50 µg]); Treatment B=CHF 5993 pMDI (2 puffs of CHF 5993 pMDI and 2 inhalations of CHF 5993 DPI placebo twice daily [total daily dose: BDP/FF/GB 400/24/50 µg]); Treatment C=CHF 1535 pMDI (2 puffs of CHF 1535 pMDI and 2 inhalations of CHF 5993 DPI placebo twice daily [total daily dose: BDP/FF 400/24 µg]).

Arm title	Sequence CAB

Arm description:

Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment C=CHF 1535 pMDI; Treatment A=CHF 5993 DPI; Treatment B=CHF 5993 pMDI.

Arm type	Experimental
Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	CHF 1535 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 DPI
Investigational medicinal product code	CHF 5993 DPI
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 pMDI
Investigational medicinal product code	CHF 5993 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Arm title	Sequence BCA

Arm description:

Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment B=CHF 5993 pMDI; Treatment C=CHF 1535 pMDI; Treatment A=CHF 5993 DPI.

Arm type	Experimental
Investigational medicinal product name	CHF 5993 pMDI
Investigational medicinal product code	CHF 5993 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	CHF 1535 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 DPI
Investigational medicinal product code	CHF 5993 DPI
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Arm title	Sequence ACB

Arm description:

Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment A=CHF 5993 DPI; Treatment C=CHF 1535 pMDI; Treatment B=CHF 5993 pMDI.

Arm type	Experimental
Investigational medicinal product name	CHF 5993 DPI
Investigational medicinal product code	CHF 5993 DPI
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	CHF 1535 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 pMDI
Investigational medicinal product code	CHF 5993 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Arm title	Sequence BAC

Arm description:

Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment B=CHF 5993 pMDI; Treatment A=CHF 5993 DPI; Treatment C=CHF 1535 pMDI.

Arm type	Experimental
Investigational medicinal product name	CHF 5993 pMDI
Investigational medicinal product code	CHF 5993 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 DPI
Investigational medicinal product code	CHF 5993 DPI
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	CHF 1535 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Arm title	Sequence CBA

Arm description:

Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment C=CHF 1535 pMDI; Treatment B=CHF 5993 pMDI; Treatment A=CHF 5993 DPI.

Arm type	Experimental
Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	CHF 1535 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 pMDI
Investigational medicinal product code	CHF 5993 pMDI
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

See Sequence ABC.

Investigational medicinal product name	CHF 5993 DPI
Investigational medicinal product code	CHF 5993 DPI
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
See Sequence ABC.

Number of subjects in period 1	Sequence ABC	Sequence CAB	Sequence BCA
Started	63	60	60
Completed	60	54	56
Not completed	3	6	4
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	1	2	2
Other: pre-planned intervention	-	-	1
Adverse event, non-fatal	2	1	1
Other: patient couldn't attend a planned visit	-	-	-
Other: investigator decision (compliance concerns)	-	1	-
Lost to follow-up	-	-	-
Other: non-compliance	-	1	-

Number of subjects in period 1	Sequence ACB	Sequence BAC	Sequence CBA
Started	62	60	61
Completed	60	57	55
Not completed	2	3	6
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	1	5
Other: pre-planned intervention	-	-	-
Adverse event, non-fatal	1	1	1
Other: patient couldn't attend a planned visit	-	1	-
Other: investigator decision (compliance concerns)	-	-	-
Lost to follow-up	1	-	-
Other: non-compliance	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence ABC
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment A=CHF 5993 DPI; Treatment B=CHF 5993 pMDI; Treatment C=CHF 1535 pMDI.	
Reporting group title	Sequence CAB
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment C=CHF 1535 pMDI; Treatment A=CHF 5993 DPI; Treatment B=CHF 5993 pMDI.	
Reporting group title	Sequence BCA
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment B=CHF 5993 pMDI; Treatment C=CHF 1535 pMDI; Treatment A=CHF 5993 DPI.	
Reporting group title	Sequence ACB
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment A=CHF 5993 DPI; Treatment C=CHF 1535 pMDI; Treatment B=CHF 5993 pMDI.	
Reporting group title	Sequence BAC
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment B=CHF 5993 pMDI; Treatment A=CHF 5993 DPI; Treatment C=CHF 1535 pMDI.	
Reporting group title	Sequence CBA
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment C=CHF 1535 pMDI; Treatment B=CHF 5993 pMDI; Treatment A=CHF 5993 DPI.	

Reporting group values	Sequence ABC	Sequence CAB	Sequence BCA
Number of subjects	63	60	60
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)	28	28	27
From 65-84 years	35	32	33
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.9	65.2	65.4
standard deviation	± 6.6	± 6.7	± 7.4

Gender categorical Units: Subjects			
Female	26	22	25
Male	37	38	35

Reporting group values	Sequence ACB	Sequence BAC	Sequence CBA
Number of subjects	62	60	61
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)	35	26	31
From 65-84 years	27	34	30
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.1	64.6	64.5
standard deviation	± 6.9	± 6.8	± 7.1
Gender categorical Units: Subjects			
Female	30	25	23
Male	32	35	38

Reporting group values	Total		
Number of subjects	366		
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)	175		
From 65-84 years	191		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	151		
Male	215		

End points

End points reporting groups

Reporting group title	Sequence ABC
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment A=CHF 5993 DPI; Treatment B=CHF 5993 pMDI; Treatment C=CHF 1535 pMDI.	
Reporting group title	Sequence CAB
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment C=CHF 1535 pMDI; Treatment A=CHF 5993 DPI; Treatment B=CHF 5993 pMDI.	
Reporting group title	Sequence BCA
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment B=CHF 5993 pMDI; Treatment C=CHF 1535 pMDI; Treatment A=CHF 5993 DPI.	
Reporting group title	Sequence ACB
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment A=CHF 5993 DPI; Treatment C=CHF 1535 pMDI; Treatment B=CHF 5993 pMDI.	
Reporting group title	Sequence BAC
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment B=CHF 5993 pMDI; Treatment A=CHF 5993 DPI; Treatment C=CHF 1535 pMDI.	
Reporting group title	Sequence CBA
Reporting group description:	
Patients were randomised to receive three different treatments during three treatment periods. Treatment periods each lasted 4 weeks (+/- 2 days) and were separated by 2-week wash-out periods. Treatment C=CHF 1535 pMDI; Treatment B=CHF 5993 pMDI; Treatment A=CHF 5993 DPI.	
Subject analysis set title	A) CHF 5993 DPI - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Treatment A=CHF 5993 DPI; the Intention-to-treat (ITT) set was defined as all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after baseline.	
Subject analysis set title	A) CHF 5993 DPI - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Treatment A=CHF 5993 DPI; the Per protocol (PP) set was defined as all patients from the ITT set without any major protocol deviations (i.e. wrong inclusions, poor compliance, non-permitted medications).	
Subject analysis set title	B) CHF 5993 pMDI - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Treatment B=CHF 5993 pMDI; the ITT set was defined as all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after baseline.	
Subject analysis set title	B) CHF 5993 pMDI - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Treatment B=CHF 5993 pMDI; the PP set was defined as all patients from the ITT set without any major protocol deviations (i.e. wrong inclusions, poor compliance, non-permitted medications).	

Subject analysis set title	C) CHF 1535 pMDI - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Treatment C=CHF 1535 pMDI; the ITT set was defined as all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after baseline.

Subject analysis set title	C) CHF 1535 pMDI - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Treatment C=CHF 1535 pMDI; the PP set was defined as all patients from the ITT set without any major protocol deviations (i.e. wrong inclusions, poor compliance, non-permitted medications).

Primary: Change from baseline in FEV1 AUC0-12h normalised by time (L) on Day 28 - ITT set

End point title	Change from baseline in FEV1 AUC0-12h normalised by time (L) on Day 28 - ITT set

End point description:

FEV1 AUC0-12h normalised by time on Day 28 was calculated based on the actual times using the linear trapezoidal rule. The corresponding change from baseline in FEV1 AUC0-12h normalised by time on Day 28 was analysed using an analysis of covariance (ANCOVA) model with treatment, period and patient as fixed effects, and baseline FEV1 value as a covariate.

End point type	Primary

End point timeframe:

Baseline (pre-dose on Day 1 of each treatment period) to Day 28. FEV1 was assessed at 45 and 10 minutes pre-dose and 10, 30 minutes and 1, 2, 4, 6, 8, 10 and 12 hours post-dose on Day 1 and Day 28 (and also at 23.5 and 24 hours post-dose on Day 28).

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	351[1]	351[2]	353[3]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.146 (0.136 to 0.157)	0.167 (0.156 to 0.177)	0.062 (0.051 to 0.072)	

Notes:

[1] - Number of patients in the ITT set = 354; Number of patients with available data = 351.

[2] - Number of patients in the ITT set = 357; Number of patients with available data = 351.

[3] - Number of patients in the ITT set = 357; Number of patients with available data = 353.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=702, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	-0.006

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=704, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.12

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=704, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.099

Primary: Change from baseline in FEV1 AUC0-12h normalised by time (L) on Day 28 - PP set

End point title	Change from baseline in FEV1 AUC0-12h normalised by time

	(L) on Day 28 - PP set

End point description:

FEV1 AUC0-12h normalised by time on Day 28 was calculated based on the actual times using the linear trapezoidal rule. The corresponding change from baseline in FEV1 AUC0-12h normalised by time on Day 28 was analysed using an ANCOVA model with treatment, period and patient as fixed effects, and baseline FEV1 value as a covariate.

End point type	Primary

End point timeframe:

Baseline (pre-dose on Day 1 of each treatment period) to Day 28. FEV1 was assessed at 45 and 10 minutes pre-dose and 10, 30 minutes and 1, 2, 4, 6, 8, 10 and 12 hours post-dose on Day 1 and Day 28 (and also at 23.5 and 24 hours post-dose on Day 28).

End point values	A) CHF 5993 DPI - PP	B) CHF 5993 pMDI - PP	C) CHF 1535 pMDI - PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	342[4]	342[5]	351[6]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.151 (0.140 to 0.162)	0.173 (0.162 to 0.184)	0.067 (0.056 to 0.077)	

Notes:

[4] - Number of patients in the PP set = 345; Number of patients with available data = 342.

[5] - Number of patients in the PP set = 346; Number of patients with available data = 342.

[6] - Number of patients in the PP set = 354; Number of patients with available data = 351.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI PP

Statistical analysis description:

The value N=684, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - PP v B) CHF 5993 pMDI - PP
Number of subjects included in analysis	684
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	-0.007

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI PP

Statistical analysis description:

The value N=693, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - PP v C) CHF 1535 pMDI - PP

Number of subjects included in analysis	693
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	0.091
upper limit	0.121

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI PP

Statistical analysis description:

The value N=693, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - PP v C) CHF 1535 pMDI - PP
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.099

Primary: Change from baseline in trough FEV1 at 24 hours (L) on Day 28 - ITT set

End point title	Change from baseline in trough FEV1 at 24 hours (L) on Day 28 - ITT set

End point description:

Trough FEV1 at 24 hours on Day 28 was defined as the mean of 23.5 and 24 hour post-dose measurements. Baseline was defined as the mean of 45 and 10 minute pre-dose measurements on Day 1. Change from baseline in trough FEV1 at 24 hours on Day 28 was analysed using the same model as for FEV1 AUC0-12h normalised by time on Day 28.

End point type	Primary

End point timeframe:

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

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	351[7]	350[8]	351[9]	
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.006 (-0.019 to 0.006)	-0.009 (-0.021 to 0.003)	-0.063 (-0.076 to -0.051)	

Notes:

[7] - Number of patients in the ITT set = 354; Number of patients with available data = 351.

[8] - Number of patients in the ITT set = 357; Number of patients with available data = 350.

[9] - Number of patients in the ITT set = 357; Number of patients with available data = 351.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=701, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT
Number of subjects included in analysis	701
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.749
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.02

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=701, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.072

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=702, shown below, is generated automatically and is due to innate error of the EudraCT database system

Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.074

Primary: Change from baseline in trough FEV1 at 24 hours (L) on Day 28 - PP set

End point title	Change from baseline in trough FEV1 at 24 hours (L) on Day 28 - PP set

End point description:

Trough FEV1 at 24 hours on Day 28 was defined as the mean of 23.5 and 24 hour post-dose measurements. Baseline was defined as the mean of 45 and 10 minute pre-dose measurements on Day 1. Change from baseline in trough FEV1 at 24 hours on Day 28 was analysed using the same model as for FEV1 AUC0-12h normalised by time on Day 28.

End point type	Primary

End point timeframe:

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

End point values	A) CHF 5993 DPI - PP	B) CHF 5993 pMDI - PP	C) CHF 1535 pMDI - PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	341[10]	341[11]	348[12]	
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.003 (-0.015 to 0.010)	-0.006 (-0.018 to 0.007)	-0.060 (-0.072 to -0.047)	

Notes:

[10] - Number of patients in the PP set = 345; Number of patients with available data = 341.

[11] - Number of patients in the PP set = 346; Number of patients with available data = 341.

[12] - Number of patients in the PP set = 354; Number of patients with available data = 348.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI PP

Statistical analysis description:

The value N=682, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - PP v B) CHF 5993 pMDI - PP
Number of subjects included in analysis	682
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.753
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.02

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI PP

Statistical analysis description:

The value N=689, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - PP v C) CHF 1535 pMDI - PP
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.072

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI PP

Statistical analysis description:

The value N=689, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - PP v C) CHF 1535 pMDI - PP

Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.074

Secondary: Change from baseline in pre-dose morning FEV1 (L) on Day 28 - ITT set

End point title	Change from baseline in pre-dose morning FEV1 (L) on Day 28 - ITT set

End point description:

Pre-dose morning FEV1 on Day 28 was defined as the mean of 45 and 10 minute pre-dose measurements. Baseline was defined as the mean of 45 and 10 minute pre-dose measurements on Day 1. Change from baseline in pre-dose morning FEV1 on Day 28 was analysed using the same model as for FEV1 AUC0-12h normalised by time on Day 28.

End point type	Secondary

End point timeframe:

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

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	351[13]	352[14]	354[15]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.047 (0.034 to 0.060)	0.056 (0.043 to 0.069)	-0.025 (-0.038 to -0.012)	

Notes:

[13] - Number of patients in the ITT set = 354; Number of patients with available data = 351.

[14] - Number of patients in the ITT set = 357; Number of patients with available data = 352.

[15] - Number of patients in the ITT set = 357; Number of patients with available data = 354.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=703, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT

Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.363
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.01

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT
Statistical analysis description:	
The value N=706, shown below, is generated automatically and is due to innate error of the EudraCT database system.	
Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	0.099

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT
Statistical analysis description:	
The value N=705, shown below, is generated automatically and is due to innate error of the EudraCT database system.	
Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.072

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.09

Secondary: Change from baseline in FEV1 AUC0-4h normalised by time (L) on Day 28 - ITT set

End point title	Change from baseline in FEV1 AUC0-4h normalised by time (L) on Day 28 - ITT set

End point description:

FEV1 AUC0-4h normalised by time on Day 28 was calculated based on the actual times using the linear trapezoidal rule. The corresponding change from baseline in FEV1 AUC0-4h normalised by time on Day 28 was analysed using the same model as for FEV1 AUC0-12h normalised by time on Day 28.

End point type	Secondary

End point timeframe:

The change from baseline in FEV1 AUC0-4h normalised by time was analysed on Day 28.

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	351[16]	352[17]	353[18]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.215 (0.204 to 0.227)	0.241 (0.230 to 0.253)	0.131 (0.120 to 0.143)	

Notes:

[16] - Number of patients in the ITT set = 354; Number of patients with available data = 351.

[17] - Number of patients in the ITT set = 357; Number of patients with available data = 352.

[18] - Number of patients in the ITT set = 357; Number of patients with available data = 353.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=703, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043
upper limit	-0.01

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=705, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.127

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=704, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	0.101

Secondary: Change from baseline in FEV1 AUC0-12h normalised by time (L) on Day

1 - ITT set	
End point title	Change from baseline in FEV1 AUC0-12h normalised by time (L) on Day 1 - ITT set

End point description:

FEV1 AUC0-12h normalised by time on Day 1 was calculated based on the actual times using the linear trapezoidal rule. The corresponding change from baseline in FEV1 AUC0-12h normalised by time on Day 1 was analysed using the same model as for FEV1 AUC0-12h normalised by time on Day 28.

End point type	Secondary

End point timeframe:

The change from baseline in FEV1 AUC0-12h normalised by time was analysed on Day 1.

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	351[19]	356[20]	354[21]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.162 (0.153 to 0.170)	0.160 (0.151 to 0.169)	0.086 (0.077 to 0.095)	

Notes:

[19] - Number of patients in the ITT set = 354; Number of patients with available data = 351.

[20] - Number of patients in the ITT set = 357; Number of patients with available data = 356.

[21] - Number of patients in the ITT set = 357; Number of patients with available data = 354.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=707, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.782
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.014

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=710, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT

Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.086

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=705, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.063
upper limit	0.088

Secondary: Responder analysis on the change from baseline in pre-dose morning FEV1 on Day 28 - ITT set

End point title	Responder analysis on the change from baseline in pre-dose morning FEV1 on Day 28 - ITT set

End point description:

Responders were patients with a change from baseline in pre-dose morning FEV1 ≥ 100 mL on Day 28. Real non-responders were patients with a change from baseline in pre-dose morning FEV1 < 100 mL on Day 28. Non-responders due to missing values were patients with missing baseline values or missing data pre-dose on Day 28.

FEV1 response on Day 28 was analysed using a conditional logistic regression model with treatment and period as fixed effects, patient as strata and baseline FEV1 as covariate.

End point type	Secondary

End point timeframe:

FEV1 response was analysed on Day 28.

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	354[22]	357[23]	357[24]	
Units: patients				
Responders	128	125	67	
Real non-responders	223	227	287	
Non-responders due to missing values	3	5	3	

Notes:

[22] - Number of patients in the ITT set.

[23] - Number of patients in the ITT set.

[24] - Number of patients in the ITT set.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=711, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT
Number of subjects included in analysis	711
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.89
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.533

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=714, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	714
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.126

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.002
upper limit	4.88

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=711, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	711
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.216
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.064
upper limit	5.01

Secondary: Change from baseline in SGRQ total score on Day 28 - ITT set

End point title	Change from baseline in SGRQ total score on Day 28 - ITT set

End point description:

SGRQ is a questionnaire developed to measure health in chronic airflow limitation. The total score for SGRQ was calculated from several domains (symptoms, impacts and activity). Lower scores correspond to better health.

The change from baseline in SGRQ total score on Day 28 was analysed using the same model as for FEV1 AUC0-12h normalised by time on Day 28, except that SGRQ total score was included as a covariate instead of baseline FEV1.

End point type	Secondary

End point timeframe:

The change from baseline in SGRQ total score was analysed on Day 28.

End point values	A) CHF 5993 DPI - ITT	B) CHF 5993 pMDI - ITT	C) CHF 1535 pMDI - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	337[25]	340[26]	333[27]	
Units: points				
least squares mean (confidence interval 95%)	-0.82 (-1.56 to -0.08)	-1.26 (-1.99 to -0.53)	0.26 (-0.49 to 1.00)	

Notes:

[25] - Number of patients in the ITT set = 354; Number of patients with available data = 337.

[26] - Number of patients in the ITT set = 357; Number of patients with available data = 340.

[27] - Number of patients in the ITT set = 357; Number of patients with available data = 333.

Statistical analyses

Statistical analysis title	CHF 5993 DPI v CHF 5993 pMDI ITT

Statistical analysis description:

The value N=677, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	A) CHF 5993 DPI - ITT v B) CHF 5993 pMDI - ITT
Number of subjects included in analysis	677
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.41
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.47

Statistical analysis title	CHF 5993 pMDI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=673, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	B) CHF 5993 pMDI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	-0.48

Statistical analysis title	CHF 5993 DPI v CHF 1535 pMDI ITT

Statistical analysis description:

The value N=670, shown below, is generated automatically and is due to innate error of the EudraCT

database system.

Comparison groups	A) CHF 5993 DPI - ITT v C) CHF 1535 pMDI - ITT
Number of subjects included in analysis	670
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	-0.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs) were defined as all AEs that started on or after date of first randomised study treatment intake and on or before 14 days after the date of the last randomised study treatment intake. TEAEs were assigned to the last study treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	A) CHF 5993 DPI - Safety

Reporting group description:

Treatment A=CHF 5993 DPI; the Safety set was defined as all randomised patients who received at least one dose of study treatment.

Reporting group title	B) CHF 5993 pMDI - Safety

Reporting group description:

Treatment B=CHF 5993 pMDI; the Safety set was defined as all randomised patients who received at least one dose of study treatment.

Reporting group title	C) CHF 1535 pMDI - Safety

Reporting group description:

Treatment C=CHF 1535 pMDI; the Safety set was defined as all randomised patients who received at least one dose of study treatment.

Serious adverse events	A) CHF 5993 DPI - Safety	B) CHF 5993 pMDI - Safety	C) CHF 1535 pMDI - Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 354 (1.13%)	6 / 358 (1.68%)	1 / 357 (0.28%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 357 (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
Injury, poisoning and procedural complications			
Patella fracture			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	0 / 357 (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
Rib fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	0 / 357 (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			
Pancreatitis chronic			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	0 / 357 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	1 / 357 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	0 / 357 (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
Pulmonary haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 357 (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
Respiratory failure			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 357 (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
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 354 (0.28%)	2 / 358 (0.56%)	0 / 357 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 357 (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
Gastrointestinal infection			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	0 / 357 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1.5 %

Non-serious adverse events	A) CHF 5993 DPI - Safety	B) CHF 5993 pMDI - Safety	C) CHF 1535 pMDI - Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 354 (14.97%)	62 / 358 (17.32%)	55 / 357 (15.41%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 354 (1.13%)	7 / 358 (1.96%)	2 / 357 (0.56%)
occurrences (all)	4	7	2
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	12 / 354 (3.39%)	11 / 358 (3.07%)	6 / 357 (1.68%)
occurrences (all)	12	11	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 354 (2.82%)	9 / 358 (2.51%)	11 / 357 (3.08%)
occurrences (all)	10	10	11

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