Clinical trial results:
A MULTINATIONAL, MULTICENTRE, RANDOMISED, DOUBLE BLIND, PLACEBO-CONTROLLED , 2-WAY CROSSOVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF GLYCOPYRROLATE BROMIDE ADMINISTERED VIA PMDI (CHF 5259), FOR THE TREATMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-005268-25
Trial protocol	GB DE BG
Global end of trial date	06 February 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	CCD-05993AA1-09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02189577
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici SpA
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, CHIESI FARMACEUTICI SPA, +39 0521 2791, ClinicalTrial_info@chiesi.com
Scientific contact	Clinical Trial Transparency, CHIESI FARMACEUTICI SPA, +39 0521 2791, ClinicalTrial_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	06 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2015
Global end of trial reached?	Yes
Global end of trial date	06 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of CHF 5259 pMDI versus placebo in terms of change from baseline in pre-dose morning FEV1 on Day 28.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy:

The background medication (Qvar, extrafine BDP at 100 µg per actuation) was administered to all patients via inhalation by pMDI from V1 until V5. During the two treatment periods, the background medication was administered concomitantly and always after the study medication.
The dose was adjusted by the Investigator according to the patient's previous treatment based on the reference table; this dose remained unchanged throughout the entire study.

Evidence for comparator: -

Actual start date of recruitment	27 June 2014
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: 43
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Germany: 39
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	64
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 98 patients (49 patients per sequence) were planned to be randomised to obtain 78 completed and evaluable patients.
The study involved a run-in period of 2 weeks (±2 days) followed by a treatment phase consisting of two 4-week (±2 days) treatment period (P1 and P2) separated by 1-week (+2 days) wash-out period.

Pre-assignment

Screening details:

A total of 161 patients were screened, of whom 100 were randomised to one of the two treatment sequences:
• CHF 5259 pMDI/placebo: n=50;
• Placebo/CHF 5259 pMDI: n=50.
Only 8 (8.0%) patients discontinued the study due to AEs (5 patients), death (1 patient), protocol violation (1 patient) and withdrawal of consent (1 patient).

Pre-assignment period milestones

Number of subjects started	100
Number of subjects completed	100

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:

The randomisation list was prepared by a specialised external provider and the whole study team, the Investigators and the patients were blind to sequence assignment. To maintain the blind, during the treatment periods, patients inhaled study medication from two canisters daily, regardless of treatment period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence CHF 5259 pMDI - placebo

Arm description:

CHF 5259 pMDI or Test Treatment or Treatment T: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Placebo or Reference therapy: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Arm type	experimental - placebo
Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	GB
Other name	Glycopyrronium bromide
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

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

Dosage and administration details:

Reference product: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Arm title	Sequence Placebo - CHF 5259 pMDI

Arm description:

Placebo or Reference therapy: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

CHF 5259 pMDI or Tests Treatment or Treatment T: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

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

Dosage and administration details:

Reference product: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator

Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	GB
Other name	Glycopyrronium bromide
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Number of subjects in period 1	Sequence CHF 5259 pMDI - placebo	Sequence Placebo - CHF 5259 pMDI
Started	50	50
Completed	46	46
Not completed	4	4
Adverse event, serious fatal	1	-

protocol violation	1	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	4

Baseline characteristics

Reporting groups

Reporting group title	Sequence CHF 5259 pMDI - placebo

Reporting group description:

CHF 5259 pMDI or Test Treatment or Treatment T: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Placebo or Reference therapy: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Reporting group title	Sequence Placebo - CHF 5259 pMDI

Reporting group description:

Placebo or Reference therapy: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

CHF 5259 pMDI or Tests Treatment or Treatment T: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Reporting group values	Sequence CHF 5259 pMDI - placebo	Sequence Placebo - CHF 5259 pMDI	Total
Number of subjects	50	50	100
Age categorical Units: Subjects			
Adults (18-64 years)	30	34	64
From 65-84 years	20	16	36
Age continuous Units: years			
arithmetic mean	62.3	62.4	
standard deviation	± 8.5	± 7.2	-
Gender categorical Units: Subjects			
Female	23	17	40
Male	27	33	60

End points

End points reporting groups

Reporting group title	Sequence CHF 5259 pMDI - placebo

Reporting group description:

CHF 5259 pMDI or Test Treatment or Treatment T: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Placebo or Reference therapy: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Reporting group title	Sequence Placebo - CHF 5259 pMDI

Reporting group description:

Placebo or Reference therapy: Placebo of CHF 5259 administered via pMDI.
Dose: 2 puffs, bid.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

CHF 5259 pMDI or Tests Treatment or Treatment T: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.
Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.
Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Subject analysis set title	CHF 5259 pMDI - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after baseline.
One patient was allocated to the treatment sequence placebo-CHF 5259 pMDI, received a placebo kit in both treatment
periods. He was counted only in the placebo column in the Safety population (i.e. actual treatment) and in both the CHF 5259
pMDI column and the placebo column in the ITT population (i.e. planned treatment).

Subject analysis set title	CHF 5259 pMDI - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population: all randomised patients who received at least one dose of the study medication.
Patient 202302 was allocated to the treatment sequence placebo-CHF 5259 pMDI, received a placebo kit in both treatment
periods. He was counted only in the placebo column in the Safety population (i.e. actual treatment) and in both the CHF 5259
pMDI column and the placebo column in the ITT population (i.e. planned treatment).

Subject analysis set title	CHF 5259 pMDI - Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol (PP) population: all patients from the ITT population without any major protocol deviations;

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

Subject analysis set description:

Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after baseline;

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population: all randomised patients who received at least one dose of the study medication.

Patient 202302 was allocated to the treatment sequence placebo-CHF 5259 pMDI, received a placebo kit in both treatment
periods. He was counted only in the placebo column in the Safety population (i.e. actual treatment) and in both the CHF 5259
pMDI column and the placebo column in the ITT population (i.e. planned treatment).

Subject analysis set title	Placebo - Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol (PP) population: all patients from the ITT population without any major protocol deviations;

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

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

End point description:

All pulmonary function tests (FEV1, FVC and IC) were carried out under medical supervision at either a clinic or hospital and were recorded using a computer-operated spirometer. At screening (V1), the post-bronchodilator FEV1 values (30 minutes after administration of 4 x 100 µg salbutamol for reversibility testing) were considered for eligibility.
Lung function measurements and daily calibration of the spirometer were done according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society. For FEV1 (L) and FVC (L) measurements, the highest value from three technically satisfactory attempts (irrespective of the curve they were derived from) was recorded. The chosen value should have not exceeded the next one by more than 150 mL. If the difference was larger, up to 8 measurements were performed and the largest value was reported.

End point type	Primary

End point timeframe:

Pre-dose morning spirometry was performed at screening (Visit 1), Visit 2 (Period 1 Day 1), Visit 3 (Period 1 Day 28), Visit 4 (Period 2 Day 1), Visit 5 (Period 2 Day 28). FEV1 value at baseline is the mean of measures at 45- and 10-min predose on Day 1.

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[1]	95[2]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.067 (0.023 to 0.11)	-0.024 (-0.082 to 0.034)		

Notes:

[1] - number of subjects of the ITT population actually analysed

[2] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=192 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.088

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.137

Notes:

[3] - The primary variable was analysed using an Analysis of Covariance (ANCOVA) model, including treatment, patient and period as fixed effects and baseline FEV1 (mean of the two measurements at 45- and 10-minute pre-dose on Day 1 in each treatment period) as covariate. The adjusted mean change from baseline for each treatment and the adjusted mean difference between CHF 5259 pMDI and placebo with their 95% CIs and p-values were estimated by the model. Superiority was demonstrated.

Secondary: FEV1 AUC0-12h normalised by time on day 28

End point title	FEV1 AUC0-12h normalised by time on day 28

End point description:

FEV1 AUC0-12h normalised by time on Day 28 was a key secondary efficacy variable .
All pulmonary function tests (FEV1, FVC and IC) were carried out under medical supervision at either a clinic or hospital and were recorded using a computer-operated spirometer. At screening (V1), the post-bronchodilator FEV1 values (30 minutes after administration of 4 x 100 µg salbutamol for reversibility testing) were considered for eligibility.
Lung function measurements and daily calibration of the spirometer were done according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society. For FEV1 (L) and FVC (L) measurements, the highest value from three technically satisfactory attempts (irrespective of the curve they were derived from) was recorded. The chosen value should have not exceeded the next one by more than 150 mL. If the difference was larger, up to 8 measurements were performed and the largest value was reported.

End point type	Secondary

End point timeframe:

On day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[4]	94[5]		
Units: liters				
arithmetic mean (confidence interval 95%)	1.473 (1.358 to 1.588)	1.344 (1.236 to 1.452)		

Notes:

[4] - number of subjects of the ITT population actually analysed

[5] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=187 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.079
upper limit	0.162

Notes:

[6] - The key secondary efficacy variable was FEV1 AUC0-12h normalised by time on Day 28 and was analysed using an ANCOVA model, including treatment, patient and period as fixed effects and baseline FEV1 as covariate. The adjusted mean for each treatment and the adjusted mean difference between CHF 5259 pMDI and placebo with their 95% CIs and p-values were estimated by the model.

Secondary: FEV1 response on Day 28

End point title	FEV1 response on Day 28

End point description:

A patient was considered a responder if he/she had a change from baseline in pre-dose morning FEV1 on Day 28 ≥ 100 mL. If a patient had a change from baseline in pre-dose morning FEV1 on Day 28 < 100 mL or missing, he/she was considered as non-responder.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	96		
Units: number of responders				
number (not applicable)	39	25		

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.036
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.871

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	7.708

Notes:

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

Secondary: FEV1 AUC0-12h normalized by time on Day 1

End point title	FEV1 AUC0-12h normalized by time on Day 1

End point description:

FEV1 AUC0-12h normalised by time on Day 1 is one of the secondary efficacy variables of the study.

End point type	Secondary

End point timeframe:

On day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96[8]	94[9]		
Units: liters				
arithmetic mean (confidence interval 95%)	1.423 (1.316 to 1.53)	1.356 (1.242 to 1.47)		

Notes:

[8] - number of subjects of the ITT population actually analysed

[9] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=190 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.118

Notes:

[10] - Change from baseline in trough FEV1 at 12 hours on Day 1 and Day 28 (mean of the two measurements at 11.5 and 12-hour post-dose), were all analysed using the same model used for the primary efficacy variable.

Secondary: FEV1 AUC0-4h normalized by time on Day 1

End point title	FEV1 AUC0-4h normalized by time on Day 1

End point description:

FEV1 AUC0-4h normalised by time on Day 1 is one of the secondary efficacy variables of the study.

End point type	Secondary

End point timeframe:

on Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[11]	95[12]		
Units: liters				
arithmetic mean (confidence interval 95%)	1.48 (1.369 to 1.592)	1.375 (1.262 to 1.489)		

Notes:

[11] - number of subjects of the ITT population actually analysed

[12] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=192 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.118

Notes:

[13] - Change from baseline in FEV1 AUC0-4h normalised by time on Day 1 and Day 28 were all analysed using the same model used for the primary efficacy variable.

Secondary: FEV1 AUC 0-4h normalized by time on Day 28

End point title	FEV1 AUC 0-4h normalized by time on Day 28

End point description:

FEV1 AUC0-4h normalised by time on Day 28 is one of the secondary efficacy variables of the study.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[14]	94[15]		
Units: liters				
arithmetic mean (confidence interval 95%)	1.523 (1.409 to 1.637)	1.355 (1.274 to 1.463)		

Notes:

[14] - number of subjects of the ITT population actually analysed

[15] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=188 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.112
upper limit	0.2

Notes:

[16] - Change from baseline in FEV1 AUC0-4h normalised by time on Day 1 and Day 28 were all analysed using the same model used for the primary efficacy variable.

Secondary: Change from baseline in trough FEV1 at 12 hours on Day 1

End point title	Change from baseline in trough FEV1 at 12 hours on Day 1

End point description:

Change from baseline in trough FEV1 at 12 hours on Day 1 was the mean of the two measurements at 11.5 and 12-hour post-dose.

End point type	Secondary

End point timeframe:

on Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[17]	95[18]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.052 (0.007 to 0.097)	-0.01 (-0.05 to 0.03)		

Notes:

[17] - number of subjects of the ITT population actually analysed

[18] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a Cross-over study, groups examined should not be added. The number N=192 (subject analysis set) is an
innate error of the EudraCT database system

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.006
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.107

Notes:

[19] - Change from baseline in through FEV1 at 12 hours on Day 1 was analysed using the same model used for the primary efficacy variable.

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

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

End point description:

Change from baseline in trough FEV1 at 12 hours on Day 28 was the mean of the two measurements at 11.5 and 12-hour post-dose.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[20]	94[21]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.047 (-0.011 to 0.105)	-0.012 (-0.062 to 0.039)		

Notes:

[20] - number of subjects of the ITT population actually analysed

[21] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a Cross-over study, groups examined should not be added. The number N=187 (subject analysis set) is an
innate error of the EudraCT database system

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.017
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.11

Notes:

[22] - Change from baseline in trough FEV1 at 12 hours on Day 28 was analysed using the same model used for the primary efficacy variable.

Secondary: Change from baseline in trough FVC at 12 hours on Day 1

End point title	Change from baseline in trough FVC at 12 hours on Day 1

End point description:

Change from baseline in trough FVC at 12 hours on Day 1 was calculated as the mean of the two measurements at 11.5 and 12-hour post-dose.

End point type	Secondary

End point timeframe:

on Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[23]	95[24]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.041 (-0.041 to 0.122)	-0.019 (-0.081 to 0.044)		

Notes:

[23] - number of subjects of the ITT population actually analysed

[24] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=192 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.193
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.123

Notes:

[25] - Change from baseline in trough FVC at 12 hours on Day 1 (mean of the two measurements at 11.5 and 12-hour post-dose) was analysed using the same model used for the primary efficacy variable, including baseline FVC instead of baseline FEV1 as covariate.

Secondary: Change from baseline in trough FVC at 12 hours on Day 28

End point title	Change from baseline in trough FVC at 12 hours on Day 28

End point description:

Change from baseline in trough FVC at 12 hours on Day 28 was calculated as the mean of the two measurements at 11.5 and 12-hour post-dose.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[26]	94[27]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.084 (-0.022 to 0.19)	-0.012 (-0.082 to 0.057)		

Notes:

[26] - number of subjects of the ITT population actually analysed

[27] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=187 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.052
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.159

Notes:

[28] - Change from baseline in trough FVC at 12 hours on Day 28 (mean of the two measurements at 11.5 and 12-hour post-dose) was analysed using the same model used for the primary efficacy variable, including baseline FVC instead of baseline FEV1 as covariate.

Secondary: Change from baseline in peak FEV1 over 12 hours on Day 1

End point title	Change from baseline in peak FEV1 over 12 hours on Day 1

End point description:

The maximum value obtained between 15 min and 12h post-dose assessments.

End point type	Secondary

End point timeframe:

on Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98[29]	96[30]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.28 (0.236 to 0.324)	0.187 (0.15 to 0.225)		

Notes:

[29] - number of subjects of the ITT population actually analysed

[30] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.133

Notes:

[31] - Peak FEV1 over 12 hours on Day 1 was analysed using the same model used for the primary efficacy variable.

Secondary: Change from baseline in peak FEV1 over 12 hours on Day 28

End point title	Change from baseline in peak FEV1 over 12 hours on Day 28

End point description:

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[32]	94[33]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.294 (0.239 to 0.349)	0.179 (0.127 to 0.231)		

Notes:

[32] - number of subjects of the ITT population actually analysed

[33] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=188 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	0.156

Notes:

[34] - Peak FEV1 over 12 hours on Day 1 and Day 28, were analysed using the same model used for the primary efficacy variable.

Secondary: Change from baseline in peak FVC over 12 hours on Day 1

End point title	Change from baseline in peak FVC over 12 hours on Day 1

End point description:

The maximum value obtained between 15 min and 12h post-dose assessments.

End point type	Secondary

End point timeframe:

on Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	96		
Units: liters				
arithmetic mean (confidence interval 95%)	0.435 (0.362 to 0.508)	0.311 (0.259 to 0.364)		

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.107

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.172

Notes:

[35] - Peak FVC over 12 hours on Day 1 was analysed using the same model used for the primary efficacy variable, including baseline FVC as covariate.

Secondary: Change from baseline in peak FVC over 12 hours on Day 28

End point title	Change from baseline in peak FVC over 12 hours on Day 28

End point description:

The maximum value obtained between 15 min and 12h post-dose assessments.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[36]	94[37]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.469 (0.371 to 0.567)	0.282 (0.21 to 0.354)		

Notes:

[36] - number of subjects of the ITT population actually analysed

[37] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=188 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.242

Notes:

[38] - Peak FVC over 12 hours on Day 28 was analysed using the same model used for the primary efficacy variable, including baseline FVC as covariate.

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

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

End point description:

For IC, at Day 1 (both Visits 2 and 4), the measurement performed 45 min pre-dose was considered as the baseline value for the period.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[39]	94[40]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.106 (0.04 to 0.171)	-0.031 (-0.107 to 0.044)		

Notes:

[39] - number of subjects of the ITT population actually analysed

[40] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=188 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.076
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.144

Notes:

[41] - Change from baseline in pre-dose morning IC on Day 28 was analysed using the same model used for the primary efficacy
variable, including baseline IC instead of baseline FEV1 as covariate.

Secondary: Change from baseline in 2-hour post-dose IC on Day 1

End point title	Change from baseline in 2-hour post-dose IC on Day 1

End point description:

For IC, at Day 1 (both Visits 2 and 4), the measurement performed 45 min pre-dose was considered as the baseline value for the period.

End point type	Secondary

End point timeframe:

on Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	96		
Units: liters				
arithmetic mean (confidence interval 95%)	0.19 (0.127 to 0.254)	0.066 (0.008 to 0.124)		

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a Cross-over study, groups examined should not be added. The number N=194 (subject analysis set) is an
innate error of the EudraCT database system

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.011
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.157

Notes:

[42] - Change from baseline in 2h post-dose IC on Day 1 was analysed using the same model used for the primary efficacy
variable, including baseline IC instead of baseline FEV1 as covariate.

Secondary: Change from baseline in 2-hour post-dose IC on Day 28

End point title	Change from baseline in 2-hour post-dose IC on Day 28

End point description:

For IC, at Day 1 (both Visits 2 and 4), the measurement performed 45 min pre-dose was considered as the baseline value for the period.

End point type	Secondary

End point timeframe:

on Day 28

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[43]	94[44]		
Units: liters				
arithmetic mean (confidence interval 95%)	0.225 (0.15 to 0.3)	0.058 (-0.02 to 0.136)		

Notes:

[43] - number of subjects of the ITT population actually analysed

[44] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=188 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.003
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.036
upper limit	0.176

Notes:

[45] - Change from baseline in 2h post-dose IC on Day 28 was analysed using the same model used for the primary efficacy
variable, including baseline IC instead of baseline FEV1 as covariate.

Secondary: Change from baseline in SGRQ total score on day 28

End point title	Change from baseline in SGRQ total score on day 28

End point description:

The St George’s Respiratory Questionnaire (SGRQ) was filled by the patient at all visits during the treatment phase. This questionnaire comprised 50 items, with 76 weighted responses, developed to measure health in chronic airflow limitation. Three component scores were calculated: symptoms, activity and impacts on daily life and a total score was then calculated, with lower scores corresponding to a better health.

End point type	Secondary

End point timeframe:

At all visits from Visit 1 (screening) until the last day of the second treatment period (Visit 5).

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[46]	92[47]		
Units: integer				
arithmetic mean (confidence interval 95%)	-0.53 (-2.68 to 1.62)	1.37 (-0.04 to 2.79)		

Notes:

[46] - number of subjects of the ITT population actually analysed

[47] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a Cross-over study, groups examined should not be added. The number N=186 (subject analysis set) is an
innate error of the EudraCT database system

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.029
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.08
upper limit	-0.23

Notes:

[48] - Change from baseline in SGRQ total score Day 28 was analysed using the same model used for the primary efficacy variable, including baseline SGRQ total score (score on Day 1) instead of baseline FEV1 as covariate.

Secondary: Change from baseline in SGRQ symptoms score on Day 28

End point title	Change from baseline in SGRQ symptoms score on Day 28

End point description:

The St George’s Respiratory Questionnaire (SGRQ) was filled by the patient at all visits during the treatment phase. This questionnaire comprised 50 items, with 76 weighted responses, developed to measure health in chronic airflow limitation. Three component scores were calculated: symptoms, activity and impacts on daily life and a total score was then calculated, with lower scores corresponding to a better health.

End point type	Secondary

End point timeframe:

At all visits from Visit 1 (screening) until the last day of the second treatment period (Visit 5).

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95[49]	94[50]		
Units: integer				
arithmetic mean (confidence interval 95%)	-3.14 (-6.62 to 0.35)	1.6 (-1 to 4.2)		

Notes:

[49] - number of subjects of the ITT population actually analysed

[50] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=189 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	-3.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.75
upper limit	-0.59

Notes:

[51] - Change from baseline in the SGRQ total score and domain scores on Day 28 was analysed using the same model used for the primary efficacy variable, including baseline
SGRQ total/domain score (score on Day 1) instead of baseline FEV1 as covariate.

Secondary: Change from baseline in SGRQ activity score on Day 28

End point title	Change from baseline in SGRQ activity score on Day 28

End point description:

The St George’s Respiratory Questionnaire (SGRQ) was filled by the patient at all visits during the treatment phase. This questionnaire comprised 50 items, with 76 weighted responses, developed to measure health in chronic airflow limitation. Three component scores were calculated: symptoms, activity and impacts on daily life and a total score was then calculated, with lower scores corresponding to a better health.

End point type	Secondary

End point timeframe:

At all visits from Visit 1 (screening) until the last day of the second treatment period (Visit 5).

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96[52]	93[53]		
Units: integer				
arithmetic mean (confidence interval 95%)	0.21 (-2.09 to 2.5)	2.35 (-0.02 to 4.72)		

Notes:

[52] - number of subjects of the ITT population actually analysed

[53] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=189 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.064
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	-2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.89
upper limit	0.14

Notes:

[54] - Change from baseline in the SGRQ activity score was analysed using the same model used for the primary efficacy variable, including baseline
SGRQ total/domain score (score on Day 1) instead of baseline FEV1 as covariate.

Secondary: Change from baseline in SGRQ impact score on Day 28

End point title	Change from baseline in SGRQ impact score on Day 28

End point description:

The St George’s Respiratory Questionnaire (SGRQ) was filled by the patient at all visits during the treatment phase. This questionnaire comprised 50 items, with 76 weighted responses, developed to measure health in chronic airflow limitation. Three component scores were calculated: symptoms, activity and impacts on daily life and a total score was then calculated, with lower scores corresponding to a better health.

End point type	Secondary

End point timeframe:

At all visits from Visit 1 (screening) until the last day of the second treatment period (Visit 5).

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[55]	94[56]		
Units: integer				
arithmetic mean (confidence interval 95%)	0.1 (-2.41 to 2.62)	0.38 (-1.34 to 2.11)		

Notes:

[55] - number of subjects of the ITT population actually analysed

[56] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=191 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.427
Method	ANCOVA
Parameter estimate	adjusted mean differencej
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.55
upper limit	1.52

Notes:

[57] - Change from baseline in the SGRQ impact score on Day 28 was analysed using the same model used for the primary efficacy variable, including baseline
SGRQ total/domain score (score on Day 1) instead of baseline FEV1 as covariate.

Secondary: Percentage of days without intake of rescue medication

End point title	Percentage of days without intake of rescue medication

End point description:

Use of rescue medication was evaluated by treatment in terms of percentage of days without intake of rescue medication (secondary efficacy variable), average use of rescue medication (number of puffs/day) (secondary efficacy variable) and average number of times rescue medication used per day (secondary efficacy variable).

End point type	Secondary

End point timeframe:

Dispensation of rescue medication has been at each visit from Visit 1 (screening) to Visit 4; collection of rescue medication has been at Visit 5. Information on rescue medication was collected through all the study using a diary.

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89[58]	89[59]		
Units: percent				
arithmetic mean (confidence interval 95%)	48.17 (39.48 to 56.87)	45.94 (37.42 to 54.46)		

Notes:

[58] - number of subjects of the ITT population actually analysed

[59] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=178 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.056
Method	ANOVA
Parameter estimate	adjusted mean differencej
Point estimate	4.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	9.89

Notes:

[60] - Percentage of days without intake of rescue medication will be analysed using an ANOVA model with treatment, period and patient as fixed effects.

Secondary: Average use of rescue medication (number of puffs/day)

End point title	Average use of rescue medication (number of puffs/day)

End point description:

Use of rescue medication was evaluated by treatment in terms of percentage of days without intake of rescue medication (secondary efficacy variable), average use of rescue medication (number of puffs/day) (secondary efficacy variable) and average number of times rescue medication used per day (secondary efficacy variable).

End point type	Secondary

End point timeframe:

Dispensation of rescue medication has been at each visit from Visit 1 (screening) to Visit 4; collection of rescue medication has been at Visit 5.

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90[61]	89[62]		
Units: number				
arithmetic mean (confidence interval 95%)	1.88 (1.44 to 2.33)	2.12 (1.6 to 2.64)		

Notes:

[61] - number of subjects of the ITT population actually analysed

[62] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=179 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.021
Method	ANOVA
Parameter estimate	adjusted mean differencej
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.05

Notes:

[63] - Average use of rescue medication will be analysed using an ANOVA model with treatment, period and patient as fixed effects.

Secondary: Average number of times rescue medication used per day

End point title	Average number of times rescue medication used per day

End point description:

Use of rescue medication was evaluated by treatment in terms of percentage of days without intake of rescue medication (secondary efficacy variable), average use of rescue medication (number of puffs/day) (secondary efficacy variable) and average number of times rescue medication used per day (secondary efficacy variable). The average number of times rescue medication as used per day was statistically significantly lower with CHF 5259 pMDI than with placebo.

End point type	Secondary

End point timeframe:

Dispensation of rescue medication has been at each visit from Visit 1 (screening) to Visit 4; collection of rescue medication has been at Visit 5.

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90[64]	90[65]		
Units: integer				
arithmetic mean (confidence interval 95%)	1.18 (0.89 to 1.47)	1.29 (0.98 to 1.59)		

Notes:

[64] - number of subjects of the ITT population actually analysed

[65] - number of subjects of the ITT population actually analysed

Statistical analyses

Statistical analysis title	CHF 5259 pMDI vs Placebo

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=180 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF 5259 pMDI - ITT v Placebo - ITT population
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.035
Method	ANOVA
Parameter estimate	adjusted mean differencej
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	-0.01

Notes:

[66] - Average number of times rescue medication is used per day will be analysed using an ANOVA model with treatment, period and patient as fixed effects.

Secondary: Change from baseline in SBP post-dose Day 1

End point title	Change from baseline in SBP post-dose Day 1

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	96		
Units: mmHg				
arithmetic mean (standard deviation)	0 (± 8.4)	0.1 (± 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SBP pre-dose Day 28

End point title	Change from baseline in SBP pre-dose Day 28

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96[67]	95[68]		
Units: mmHg				
arithmetic mean (standard deviation)	-1.5 (± 12.1)	-0.4 (± 9.4)		

Notes:

[67] - number of subjects of the safety population actually analysed

[68] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SBP post-dose Day 28

End point title	Change from baseline in SBP post-dose Day 28

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[69]	94[70]		
Units: mmHg				
arithmetic mean (standard deviation)	-2.3 (± 13.2)	-0.1 (± 12.6)		

Notes:

[69] -
number of subjects of the safety population actually analysed

[70] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SBP Day 28 post-dose from Day 28 pre-dose

End point title	Change in SBP Day 28 post-dose from Day 28 pre-dose

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[71]	94[72]		
Units: mmHg				
arithmetic mean (standard deviation)	-0.9 (± 10.4)	0.2 (± 10.9)		

Notes:

[71] - number of subjects of the safety population actually analysed

[72] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in DBP post-dose Day 1

End point title	Change from baseline in DBP post-dose Day 1

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	96		
Units: mmHg				
arithmetic mean (standard deviation)	-0.2 (± 7.1)	-0.2 (± 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in DBP pre-dose Day 28

End point title	Change from baseline in DBP pre-dose Day 28

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96[73]	95		
Units: mmHg				
arithmetic mean (standard deviation)	-0.8 (± 8.3)	1 (± 8.6)		

Notes:

[73] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in DBP post-dose Day 28

End point title	Change from baseline in DBP post-dose Day 28

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[74]	94[75]		
Units: mmHg				
arithmetic mean (standard deviation)	-2.2 (± 8.4)	0.2 (± 8.5)		

Notes:

[74] - number of subjects of the safety population actually analysed

[75] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DBP Day 28 post-dose from Day 28 pre-dose

End point title	Change in DBP Day 28 post-dose from Day 28 pre-dose

End point description:

SBP and DBP measurement are made after a 10-minute rest in sitting position. Measurements were performed at pre-dose at V1 and at pre- and
2-hour post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[76]	94		
Units: mmHg				
arithmetic mean (standard deviation)	-1.3 (± 6)	-1 (± 7.3)		

Notes:

[76] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HR Day 28 post-dose from Day 28 pre-dose

End point title	Change in HR Day 28 post-dose from Day 28 pre-dose

End point description:

The 12-lead ECG was performed in triplicate at pre-dose at V1 and at pre- and 1 hour-45 minute post-

dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	92		
Units: bpm				
arithmetic mean (standard deviation)	-2.2 (± 7.1)	-2.4 (± 7.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in QTcF Day 28 post-dose from Day 28 pre-dose

End point title	Change in QTcF Day 28 post-dose from Day 28 pre-dose

End point description:

The 12-lead ECG was performed in triplicate at pre-dose at V1 and at pre- and 1 hour-45 minute post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	92		
Units: ms				
arithmetic mean (standard deviation)	0.2 (± 10.5)	2.8 (± 8.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PR Day 28 post-dose from Day 28 pre-dose

End point title	Change in PR Day 28 post-dose from Day 28 pre-dose

End point description:

The 12-lead ECG was performed in triplicate at pre-dose at V1 and at pre- and 1 hour-45 minute post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	92		
Units: ms				
arithmetic mean (standard deviation)	1.3 (± 7.6)	0.6 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in QRS Day 28 post-dose from Day 28 pre-dose

End point title	Change in QRS Day 28 post-dose from Day 28 pre-dose

End point description:

The 12-lead ECG was performed in triplicate at pre-dose at V1 and at pre- and 1 hour-45 minute post-dose from V2 to V5.

End point type	Secondary

End point timeframe:

At each visit, from visit 1 (screening) to visit 5.

End point values	Sequence CHF 5259 pMDI - placebo	Sequence Placebo - CHF 5259 pMDI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: ms				
arithmetic mean (standard deviation)	94 (± 9.9)	93.6 (± 9.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Males with abnormalities in QTcF values (>450 ms)

End point title	Males with abnormalities in QTcF values (>450 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;

• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males
and 470 ms for females).

End point type	Secondary

End point timeframe:

post- dose on Day 1 and on Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59[77]	57[78]		
Units: unit	0	1		

Notes:

[77] - number of subjects of the safety population actually analysed

[78] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Males with abnormalities in QTcF values (>480 ms)

End point title	Males with abnormalities in QTcF values (>480 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;
• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males and 470 ms for females).

End point type	Secondary

End point timeframe:

Post-dose on Day 1 and Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59[79]	57[80]		
Units: unit	0	0		

Notes:

[79] - number of subjects of the safety population actually analysed

[80] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Males with abnormalities in QTcF values (>500 ms)

End point title	Males with abnormalities in QTcF values (>500 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;
• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males and 470 ms for females).

End point type	Secondary

End point timeframe:

Post-dose on Day 1 and Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59[81]	57[82]		
Units: unit	0	0		

Notes:

[81] - number of subjects of the safety population actually analysed

[82] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Females with abnormalities in QTcF values (>470 ms)

End point title	Females with abnormalities in QTcF values (>470 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;
• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males and 470 ms for females).

End point type	Secondary

End point timeframe:

Post-dose on Day 1 and Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[83]	39[84]		
Units: unit	1	1		

Notes:

[83] - number of subjects of the safety population actually analysed

[84] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Females with abnormalities in QTcF values (>500 ms)

End point title	Females with abnormalities in QTcF values (>500 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;
• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males and 470 ms for females).

End point type	Secondary

End point timeframe:

Post-dose on Day 1 and Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[85]	39[86]		
Units: unit	0	0		

Notes:

[85] - number of subjects of the safety population actually analysed

[86] - number of subjects of the safety population actually analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with abnormalities in change from baseline QTcF values (>30 ms)

End point title	Patients with abnormalities in change from baseline QTcF values (>30 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;
• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1

(1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males and 470 ms for females).

End point type	Secondary

End point timeframe:

Post-dose on Day 1 and Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	96		
Units: unit	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with abnormalities in change from baseline QTcF values (>60 ms)

End point title	Patients with abnormalities in change from baseline QTcF values (>60 ms)

End point description:

The following QTcF abnormalities were reported:
• 1 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms at post-dose on Day 1. No other abnormalities were reported in male patients;
• 1 (2.6%) female patient during treatment with CHF 5259 pMDI had a QTcF value > 470 ms at post-dose on Day 1 and at post- dose on Day 28 and the same patient had a QTcF value > 470 ms at post-dose on Day 1 and at post-dose on Day 28 during treatment with placebo;
• 4 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo. In all cases, QTcF value was below the normal threshold (i.e. 450 ms for males and 470 ms for females).

End point type	Secondary

End point timeframe:

Post-dose on Day 1 and Day 28

End point values	CHF 5259 pMDI - safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	96		
Units: unit	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: BDI focal score on Day 1

End point title	BDI focal score on Day 1

End point description:

BDI was collected at Visits 1, 2 and 4.
BDI focal score on Day 1 and TDI focal score on Day 28 are presented by treatment

End point type	Secondary

End point timeframe:

On Day 1

End point values	CHF 5259 pMDI - ITT	Placebo - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	91		
Units: score				
arithmetic mean (confidence interval 95%)	6.16 (5.73 to 6.59)	5.99 (5.51 to 6.46)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
At each Visit from visit 1 (screening) to Visit 6 (follow-up call)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	CHF 5259 pMDI - safety population
Reporting group description: -	
Reporting group title	Placebo - safety population

Reporting group description:

The Safety population was defined as all randomised patients who received at least one dose of the study medication.
Patient 202302 was allocated to the treatment sequence placebo-CHF 5259 pMDI, received a placebo kit in both treatment
periods. He was counted only in the placebo column in the Safety population (i.e. actual treatment) and in both the CHF 5259
pMDI column and the placebo column in the ITT population (i.e. planned treatment).

Serious adverse events	CHF 5259 pMDI - safety population	Placebo - safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 97 (3.09%)	1 / 96 (1.04%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
COPD	Additional description: One Patient experienced 1 serious TEAE of COPD exacerbation during treatment with CHF 5259 pMDI and another patient experienced 1 serious TEAE of COPD exacerbation (and 1 serious TEAE of malignant lung neoplasm) during treatment with placebo.		
subjects affected / exposed	1 / 97 (1.03%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	CHF 5259 pMDI - safety population	Placebo - safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 97 (20.62%)	17 / 96 (17.71%)	
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 97 (1.03%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 97 (3.09%)	1 / 96 (1.04%)	
occurrences (all)	3	1	
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 97 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
COPD	Additional description: These are non serious cases of COPD		
subjects affected / exposed	2 / 97 (2.06%)	3 / 96 (3.13%)	
occurrences (all)	2	3	
Cough			
subjects affected / exposed	1 / 97 (1.03%)	3 / 96 (3.13%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	0 / 97 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	2	
Dysphonia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Sputum increased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Ecchymosis	Additional description: For one patient, one AE (ecchymosis) was allocated to both treatments/periods due to partially missing onset date		
subjects affected / exposed	1 / 97 (1.03%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 97 (5.15%)	1 / 96 (1.04%)	
occurrences (all)	6	1	
Oral candidiasis			

subjects affected / exposed	1 / 97 (1.03%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
Fungal skin infection			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There are no limitation or caveats to this summary of results

Notes: