Clinical trial results:
A 52 week, randomized, double blind, multinational, multicentre, active controlled, 2-arm parallel group trial comparing CHF 5993 100/6/12.5 µg pMDI (fixed combination of extrafine beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 100/6 µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) in patients with asthma uncontrolled on medium doses of inhaled corticosteroids in combination with long-acting ß2-agonists.

Summary

EudraCT number	2015-000716-18
Trial protocol	GB CZ PT SK HU LT ES PL
Global end of trial date	17 May 2018

Results information

Result version number	v1 (current)
This version publication date	13 June 2019
First version publication date	13 June 2019

Trial information

Trial identification

Sponsor protocol code	CCD-05993AB1-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02676076
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2018
Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate the superiority of CHF 5993 pressurised metered dose inhaler (pMDI) 100/6/12.5 µg compared to CHF 1535 pMDI 100/6 µg in terms of change from baseline in pre-dose forced expiratory volume in the 1st second (FEV1) at Week 26;
- To demonstrate the reduction of moderate and severe asthma exacerbations rate with CHF 5993 pMDI 100/6/12.5 µg compared to CHF 1535 pMDI 100/6 µg during the entire 52-week treatment period.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and following all other requirements of local laws.
From screening to end of treatment, vital signs were recorded pre-dose at screening and pre- and post-dose at all visits during the treatment period; physical examination was performed at all visits; concomitant medications and adverse events (AEs) were recorded, and asthma exacerbations were assessed at all visits; lung function tests were performed (pre-dose for FEV1 and forced vital capacity from screening to end of treatment visits, pre-dose for inspiratory capacity and vital capacity and post-dose serial spirometry at all visits during the treatment period); 12-lead single electrocardiograms were recorded pre-dose at screening and pre- and post-dose at all visits during the treatment period (parameters evaluated included heart rate, PR interval, QRS interval and Fridericia-corrected QT interval).
Patients completed the electronic diary from home twice daily from screening until the end of treatment to record asthma symptoms, treatment compliance and use of rescue medication, and used the electronic peakflowmeter to record peak expiratory flow twice daily from home from screening until the end of treatment.
The Asthma Control Questionnaire© (ACQ)-7 was completed at screening and all visits during the treatment period. The EuroQuality of Life-5-Dimensional-3-Level questionnaire, and health economic and outcome assessments were competed at all visits during the treatment period.
Blood samplings for haematology and blood chemistry were performed at screening, Week 26 and Week 52.
Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).
An independent Data Safety Monitoring Board was established for independent scrutiny of the study and impartial safety insurance of patients.

Background therapy: -

Evidence for comparator:

In this study, CHF 1535 pMDI 100/6 µg (beclometasone dipropionate [BDP]/formoterol fumarate [FF] 100/6 µg, total daily dose BDP/FF 400/24 µg, which is the marketed dose) was chosen as control treatment. The approved asthma indication of CHF 1535 pMDI 100/6 µg is in "patients not adequately controlled with inhaled corticosteroids (ICS) and 'as needed' inhaled rapid-acting ß2-agonist or patients already adequately controlled on both ICS and long-acting ß2-agonists (LABAs)". In this study, although the population included patients with uncontrolled asthma while on medium doses of ICS in combination with LABAs, no safety risks were foreseen for this population as they were allowed to use inhaled salbutamol as rescue medication and they were closely and medically monitored during the entire study. The choice of comparator is in line with the scientific advice for the clinical development of CHF 5993 provided by the EMA.

Actual start date of recruitment	17 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 131
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Bulgaria: 96
Country: Number of subjects enrolled	Czech Republic: 107
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 83
Country: Number of subjects enrolled	Argentina: 21
Country: Number of subjects enrolled	Belarus: 13
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Russian Federation: 361
Country: Number of subjects enrolled	Ukraine: 242
Worldwide total number of subjects	1155
EEA total number of subjects	518

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)	950
From 65 to 84 years	205
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 1628 patients were screened according to inclusion and exclusion criteria; of these, 1155 patients were randomised.

Pre-assignment

Screening details:

At screening, within 7 days of a pre-screening visit, inclusion/exclusion criteria were assessed. There were 473 screening failures (failure to meet randomisation criteria [389 patients], consent withdrawal [58 patients], other reasons [17 patients], adverse events [4 patients], asthma exacerbations [4 patients], lost to follow-up [1 patient]).

Period 1

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

Blinding implementation details:

An Interactive Response Technology (IRT) system was used to assign patients to the treatment arms. The randomisation list was provided to the labelling facility. An additional copy of the Master Randomisation List was provided to the analytical laboratory performing the pharmacokinetic analyses on biological samples, that was unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	CHF 5993 pMDI 100/6/12.5 µg

Arm description:

Patients were randomised to receive CHF 5993 pMDI 100/6/12.5 µg 2 puffs twice daily (BID) (total daily dose: BDP/FF/glycopyrronium bromide [GB] 400/24/50 µg) for 52 weeks following a 2-week ± 2 days open-label run-in period of CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg). Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).

Arm type	Experimental
Investigational medicinal product name	CHF 5993 pMDI 100/6/12.6 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: CHF 5993 pMDI, fixed-dose combination of BDP/FF/GB.
Dose: BDP 100 µg, FF 6 µg, GB 12.5 µg per actuation, 2 puffs BID.
Total daily dose: BDP/FF/GB 400/24/50 µg.
Mode of administration: pMDI using a standard actuator.
Patients were trained in the proper use of the pMDI device.
At Week 0, Week 12, Week 26 and Week 40, 2 kits of study treatment were dispensed to each patient, each consisting of one box containing two inhalers (numbered 1 and 2) which were to be used in the morning and in the evening. Each day during the 52-week treatment period, patients administered 1 puff from each pMDI inhaler in the morning and in the evening.
If patients were used to inhaling their pMDI asthma medications with a spacer device, they used the AeroChamber Plus™ for inhaling the study treatment. Patients were trained in the proper use of this device, which was dispensed at screening, Week 0 and Week 26.

Arm title	CHF 1535 pMDI 100/6 µg

Arm description:

Patients were randomised to receive CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg) for 52 weeks following a 2-week ± 2 days open-label run-in period of CHF 1535 pMDI 100/6

µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg). Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).

Arm type	Active comparator
Investigational medicinal product name	CHF 1535 pMDI 100/6 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

CHF 1535 pMDI 100/6 µg containing BDP 100 µg and FF 6 µg.
Dose: BDP 100 µg and FF 6 µg per actuation, 2 puffs BID.
Total daily dose: BDP/FF 400/24 µg.
Mode of administration: pMDI using a standard actuator.
Patients were trained in the proper use of the pMDI device.
At Week 0, Week 12, Week 26 and Week 40, 2 kits of study treatment were dispensed to each patient, each kit consisting of one box containing two inhalers (numbered 1 and 2) which were to be used in the morning and in the evening. Each day during the 52-week treatment period, patients administered 1 puff from each pMDI inhaler in the morning and in the evening.
If patients were used to inhaling their pMDI asthma medications with a spacer device, they used the AeroChamber Plus™ for inhaling the study treatment. Patients were trained in the use of the AeroChamber Plus™ device, and this was dispensed at screening, Week 0 and Week 26.

Number of subjects in period 1	CHF 5993 pMDI 100/6/12.5 µg	CHF 1535 pMDI 100/6 µg
Started	579	576
Completed	542	539
Not completed	37	37
Adverse event, serious fatal	3	-
Consent withdrawn by subject	22	26
Asthma exacerbation	1	-
Protocol violation	7	4
Adverse event, non-fatal	-	5
Lost to follow-up	2	2
Reason not specified	2	-

Baseline characteristics

Reporting groups

Reporting group title	CHF 5993 pMDI 100/6/12.5 µg

Reporting group description:

Patients were randomised to receive CHF 5993 pMDI 100/6/12.5 µg 2 puffs twice daily (BID) (total daily dose: BDP/FF/glycopyrronium bromide [GB] 400/24/50 µg) for 52 weeks following a 2-week ± 2 days open-label run-in period of CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg). Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).

Reporting group title	CHF 1535 pMDI 100/6 µg

Reporting group description:

Patients were randomised to receive CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg) for 52 weeks following a 2-week ± 2 days open-label run-in period of CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg). Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).

Reporting group values	CHF 5993 pMDI 100/6/12.5 µg	CHF 1535 pMDI 100/6 µg	Total
Number of subjects	579	576	1155
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)	473	477	950
From 65-84 years	106	99	205
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.6	52.4	
standard deviation	± 12.3	± 12.3	-
Gender categorical Units: Subjects			
Female	358	355	713
Male	221	221	442

Subject analysis sets

Subject analysis set title	CHF 5993 pMDI 100/6/12.5 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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

Subject analysis set title	CHF 1535 pMDI 100/6 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population 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	CHF 5993 pMDI 100/6/12.5 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Subject analysis set title	CHF 1535 pMDI 100/6 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Subject analysis set title	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A pre-specified pooled analysis of the rate of severe asthma exacerbations over the 52-week treatment period was performed in the ITT population in two pivotal studies - CCD-05993AB1-03 (TRIMARAN) and CCD-05993AB2-02 (TRIGGER). The ITT population in each study 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 variables) after baseline. The present analysis set included patients from the CHF 5993 pMDI 100/6/12.5 µg (“CHF 5993 pMDI”) arm in Study CCD-05993AB1-03 (ITT population) and the CHF 5993 pMDI 200/6/12.5 µg (“CHF 5993 pMDI high strength [HS]") arm in Study CCD-05993AB2-02 (ITT population).

Subject analysis set title	CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A pre-specified pooled analysis of severe asthma exacerbations over the 52-week treatment period was performed in the ITT populations of two pivotal studies - CCD-05993AB1-03 (TRIMARAN) and CCD-05993AB2-02 (TRIGGER). The ITT population in each study 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 variables) after baseline. The present analysis set included the CHF 1535 pMDI 100/6 µg ("CHF 1535 pMDI”) arm in Study CCD-05993AB1-03 (ITT population) and the CHF 1535 pMDI 200/6 µg (“CHF 1535 pMDI HS”) arm in Study CCD-05993AB2-02 (ITT population).

Reporting group values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT	CHF 5993 pMDI 100/6/12.5 µg - Safety
Number of subjects	575	574	576
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	52.6	52.5	52.6
standard deviation	± 12.4	± 12.2	± 12.4

Gender categorical Units: Subjects			
Female	354	353	355
Male	221	221	221

Reporting group values	CHF 1535 pMDI 100/6 µg - Safety	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT
Number of subjects	574	1146	1145
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	52.5		
standard deviation	± 12.2	±	±
Gender categorical Units: Subjects			
Female	353		
Male	221		

End points

End points reporting groups

Reporting group title	CHF 5993 pMDI 100/6/12.5 µg

Reporting group description:

Patients were randomised to receive CHF 5993 pMDI 100/6/12.5 µg 2 puffs twice daily (BID) (total daily dose: BDP/FF/glycopyrronium bromide [GB] 400/24/50 µg) for 52 weeks following a 2-week ± 2 days open-label run-in period of CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg). Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).

Reporting group title	CHF 1535 pMDI 100/6 µg

Reporting group description:

Patients were randomised to receive CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg) for 52 weeks following a 2-week ± 2 days open-label run-in period of CHF 1535 pMDI 100/6 µg 2 puffs BID (total daily dose: BDP/FF 400/24 µg). Rescue medication (salbutamol 100 µg per inhalation) was used throughout the treatment period in case of absolute need; the maximum allowed dose was 8 inhalations/day (800 µg).

Subject analysis set title	CHF 5993 pMDI 100/6/12.5 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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

Subject analysis set title	CHF 1535 pMDI 100/6 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population 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	CHF 5993 pMDI 100/6/12.5 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Subject analysis set title	CHF 1535 pMDI 100/6 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Subject analysis set title	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A pre-specified pooled analysis of the rate of severe asthma exacerbations over the 52-week treatment period was performed in the ITT population in two pivotal studies - CCD-05993AB1-03 (TRIMARAN) and CCD-05993AB2-02 (TRIGGER). The ITT population in each study 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 variables) after baseline. The present analysis set included patients from the CHF 5993 pMDI 100/6/12.5 µg ("CHF 5993 pMDI") arm in Study CCD-05993AB1-03 (ITT population) and the CHF 5993 pMDI 200/6/12.5 µg ("CHF 5993 pMDI high strength [HS]") arm in Study CCD-05993AB2-02 (ITT population).

Subject analysis set title	CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A pre-specified pooled analysis of severe asthma exacerbations over the 52-week treatment period was performed in the ITT populations of two pivotal studies - CCD-05993AB1-03 (TRIMARAN) and CCD-05993AB2-02 (TRIGGER). The ITT population in each study 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 variables) after baseline. The present analysis set included the CHF 1535 pMDI

100/6 µg ("CHF 1535 pMDI") arm in Study CCD-05993AB1-03 (ITT population) and the CHF 1535 pMDI 200/6 µg ("CHF 1535 pMDI HS") arm in Study CCD-05993AB2-02 (ITT population).

Primary: Change from baseline in pre-dose FEV1 at Week 26

End point title	Change from baseline in pre-dose FEV1 at Week 26

End point description:

FEV1 is the forced expiratory volume in the first second. Change from baseline (CFB) in pre-dose morning FEV1 at Week 26 was analysed. Data are presented as adjusted means (least squares means) with their 95% confidence intervals (CIs).

End point type	Primary

End point timeframe:

Baseline to Week 26.

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	557[1]	553[2]		
Units: Litres				
least squares mean (confidence interval 95%)	0.185 (0.155 to 0.214)	0.127 (0.098 to 0.157)		

Notes:

[1] - Number of patients in the ITT population = 575;
Number of patients with available data = 557.
[2] - Number of patients in the ITT population = 574;
Number of patients with available data = 553.

Statistical analyses

Statistical analysis title	Adj. mean difference, CFB in pre-dose FEV1 Week 26

Statistical analysis description:

The CFB in pre-dose FEV1 at Week 26 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and country as fixed effects, and baseline value (Week 0, pre-dose) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted means in each treatment group, adjusted mean difference between treatments with 95% CIs and p-values were estimated.

Comparison groups	CHF 1535 pMDI 100/6 µg - ITT v CHF 5993 pMDI 100/6/12.5 µg - ITT
Number of subjects included in analysis	1110
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.008
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.099

Notes:

[3] - Comparisons between treatments were conducted according to a hierarchical testing procedure to test the co-primary and key secondary efficacy endpoints. At step 1, both superiority tests on the co-primary endpoints had to be significant. For this endpoint, superiority of CHF 5993 pMDI 100/6/12.5 µg over CHF 1535 pMDI 100/6 µg was demonstrated if the lower limit of the confidence interval for the adjusted mean difference between treatments was > 0.

Primary: Moderate and severe asthma exacerbation rate over the 52-week treatment period

End point title	Moderate and severe asthma exacerbation rate over the 52-week treatment period

End point description:

Severe asthma exacerbation - asthma worsening requiring initiation of treatment with systemic corticosteroids for at least 3 days (courses of corticosteroids separated by ≥ 1 week treated as separate severe exacerbations); requirement of an emergency room (ER) visit or hospitalisation was documented. Moderate asthma exacerbation - defined as ≥ 1 of the following criteria fulfilled and leading to a change in treatment (sustained increase of ≥ 1 puff of short acting β2-agonist [SABA] for 2 consecutive days): nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights/increase of ≥ 0.75 from baseline in daily symptom score on 2 consecutive days; increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase 4 puffs/day); ≥ 20% decrease in peak expiratory flow from baseline on at least 2 consecutive mornings/evenings or ≥ 20% decrease in FEV1 from baseline; visit to the ER/trial site for asthma treatment not requiring systemic corticosteroids.

End point type	Primary

End point timeframe:

52-week treatment period.

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	575	574		
Units: Adjusted exacerbation rate/patient/year				
number (confidence interval 95%)	1.825 (1.634 to 2.037)	2.157 (1.937 to 2.402)		

Statistical analyses

Statistical analysis title	Adjusted rate ratio, moderate/severe exacerbations

Statistical analysis description:

The number of moderate and severe exacerbations during the 52-week treatment period was analysed using a negative binomial model including treatment, country, and number of exacerbations in the previous year (1 or > 1) as fixed effects, and log-time on study as an offset. Adjusted asthma exacerbation rates in each treatment group, adjusted rate ratios with their 95% CIs and p-values were estimated by the model.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg - ITT

Number of subjects included in analysis	1149
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.033
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.725
upper limit	0.987

Notes:

[4] - Comparisons between treatments were conducted according to a hierarchical testing procedure to test the co-primary and key secondary efficacy endpoints. At step 1, both superiority tests on the co-primary endpoints had to be significant. For this endpoint, superiority of CHF 5993 pMDI 100/6/12.5 µg over CHF 1535 pMDI 100/6 µg was demonstrated if the upper limit of the CI for the adjusted rate ratio between treatments was < 1.

Secondary: Change from baseline in peak0-3h FEV1 at Week 26

End point title	Change from baseline in peak0-3h FEV1 at Week 26

End point description:

Peak0-3h FEV1 is the peak forced expiratory volume in the first second within 3 hours post-dose. The change from baseline in peak0-3h FEV1 at Week 26 was analysed. This was a key secondary efficacy endpoint. Data are presented as adjusted means (least squares means) with their 95% CIs.

End point type	Secondary

End point timeframe:

Baseline to Week 26.

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	553[5]	553[6]		
Units: Litres				
least squares mean (confidence interval 95%)	0.485 (0.453 to 0.516)	0.401 (0.369 to 0.432)		

Notes:

[5] - Number of patients in the ITT population = 575;
Number of patients with available data = 553.

[6] - Number of patients in the ITT population = 574;
Number of patients with available data = 553.

Statistical analyses

Statistical analysis title	Adj. mean difference in CFB, peak0-3h FEV1 Week 26

Statistical analysis description:

The CFB in peak0-3h FEV1 at Week 26 was analysed using a linear MMRM including treatment, visit, treatment by visit interaction and country as fixed effects; baseline value (Week 0, pre-dose) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted means in each treatment group, adjusted mean difference between treatments, their 95% CIs and p-values were estimated.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg - ITT

Number of subjects included in analysis	1106
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.129

Notes:

[7] - The comparisons between treatments were conducted according to a hierarchical testing procedure.
At step 1, both superiority tests on the two co-primary endpoints had to be significant.
At step 2, superiority of CHF 5993 pMDI 100/6/12.5 µg over CHF 1535 pMDI 100/6 µg had to be demonstrated for the present key secondary efficacy endpoint. Superiority was demonstrated if the lower limit of the CI for the adjusted mean difference between treatments was > 0.
Steps 3 and 4 followed in sequence.

Secondary: Change from baseline in the average morning PEF measured by patients at home over the 26-week treatment period

End point title	Change from baseline in the average morning PEF measured by patients at home over the 26-week treatment period

End point description:

Patients monitored peak expiratory flow (PEF, litres/minute) twice a day (morning and evening) during the run-in period (baseline measurement) and the entire treatment period at home, using a portable ePeakflowmeter which was customised with a specific program according to the parameters required by the study protocol. Patients were trained on the purpose and technique of PEF home monitoring. During each measurement session, patients performed three blows before intake of run-in or study medication (as applicable), data were recorded on the device and automatically transmitted from home to the Vitalograph database on a daily basis.
The change from baseline in the average morning PEF over the 26-week treatment period was analysed. This was a key secondary efficacy endpoint.
Data are presented as adjusted means (least squares mean) with their 95% CIs.

End point type	Secondary

End point timeframe:

26-week treatment period from Weeks 1 to 26.

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	566[8]	569[9]		
Units: Litres/minute				
least squares mean (confidence interval 95%)	5.325 (1.921 to 8.729)	-3.131 (-6.533 to 0.271)		

Notes:

[8] - Number of patients in the ITT population = 575;
Number of patients with available data = 566.
[9] - Number of patients in the ITT population = 574;
Number of patients with available data = 569.

Statistical analyses

Statistical analysis title	Adj. mean difference, CFB in average morning PEF

Statistical analysis description:

The CFB in average morning PEF over the 26-week treatment period was analysed using a linear MMRM which included treatment, inter-visit period, treatment by inter-visit period interaction and country as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates. Adjusted means in each treatment group, adjusted mean difference between treatments, 95% CIs and p-values were estimated.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg - ITT
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	8.456
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.643
upper limit	13.269

Notes:

[10] - Comparisons between treatments were conducted according to a hierarchical testing procedure.
Step 1: both superiority (sup) tests on the co-primary endpoints had to be significant;
Step 2: sup of CHF 5993 pMDI 100/6/12.5 µg over CHF 1535 pMDI 100/6 µg had to be demonstrated for CFB in peak0-3h FEV1 at Week 26;
Step 3: sup (as in step 2) had to be demonstrated for the present endpoint (lower limit of the CI for the adjusted mean difference between treatments had to be > 0);
Step 4 followed.

Secondary: Severe asthma exacerbation rate over 52 weeks of treatment in a pre-specified pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02

End point title	Severe asthma exacerbation rate over 52 weeks of treatment in a pre-specified pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02

End point description:

A pre-specified pooled analysis of the rate of severe asthma exacerbations over the 52-week treatment period was performed in the ITT populations of two pivotal studies CCD-05993AB1-03 (present study, TRIMARAN) and CCD-05993AB2-02 (TRIGGER).
The pooled analysis of the two studies was based on the following treatment groups:
1. CHF 5993 pMDI + CHF 5993 pMDI High Strength (HS), for which data from the CHF 5993 pMDI 100/6/12.5 µg ("CHF 5993 pMDI") arm in Study CCD-05993AB1-03 and the CHF 5993 pMDI 200/6/12.5 µg ("CHF 5993 pMDI HS") arm in Study CCD-05993AB2-02 were pooled;
2. CHF 1535 pMDI + CHF 1535 pMDI HS, for which data from the CHF 1535 pMDI 100/6 µg ("CHF 1535 pMDI") arm in Study CCD-05993AB1-03 and the CHF 1535 pMDI 200/6 µg ("CHF 1535 pMDI HS") arm in Study CCD-05993AB2-02 were pooled.
This was a key secondary efficacy endpoint.

End point type	Secondary

End point timeframe:

52-week treatment period.

End point values	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg	CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1146	1145		
Units: Adjusted exacerbation rate/patient/year				
number (confidence interval 95%)	0.239 (0.206 to 0.276)	0.310 (0.271 to 0.354)		

Statistical analyses

Statistical analysis title	Adj. exacerbation rate ratio (severe exacerbation)

Statistical analysis description:

The number of severe asthma exacerbations during the 52-week treatment period was analysed in the pooled data of the two pivotal studies using a negative binomial model including treatment, country, and number of exacerbations in the previous year (1 or > 1) as fixed effects, and log-time on study as an offset. The adjusted asthma exacerbation rates in each treatment group and the adjusted rate ratios with their 95% CIs and p-values were estimated by the model.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT
Number of subjects included in analysis	2291
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.008
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.636
upper limit	0.933

Notes:

[11] - Comparisons between treatments were conducted according to a hierarchical testing procedure.
Step 1: superiority (sup) tests on the co-primary endpoints had to be significant;
Steps 2, 3: sup of CHF 5993 pMDI 100/6/12.5 µg over CHF 1535 pMDI 100/6 µg had to be demonstrated for CFB in peak0-3h FEV1 (Week 26), then CFB in morning PEF over 26 weeks;
Step 4 (present endpoint): sup of CHF 5993 pMDI over CHF 1535 pMDI was demonstrated if the upper limit of the CI for the adj. rate ratio was < 1.

Secondary: Asthma Control Questionnaire©-7 response at Week 52

End point title	Asthma Control Questionnaire©-7 response at Week 52

End point description:

An ACQ-7 response was defined as change from baseline (Week 0, pre-dose) in ACQ-7 score ≤ -0.5; non-response was defined as change from baseline in ACQ-7 score >-0.5 or missing data.
The ACQ-7 allows the identification of the adequacy of asthma control in individual patients. The first 6 items of the questionnaire refer to symptoms and rescue use in the previous 7 days (patients were asked to recall how their asthma had been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale with 0 = no impairment and 6 = maximum impairment); the 7th item (related to FEV1, completed by the clinical staff) was populated with the value of FEV1 % of predicted when reversibility was met at screening (Week -2) and considering the pre-dose FEV1 % of predicted taken at -15 minutes at visits during the treatment period.
The ACQ-7 was completed at screening, and during the treatment period from Week 0 to Week 52.

End point type	Secondary
End point timeframe:	
Baseline to Week 52.	

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	575	574		
Units: Patients				
number (not applicable)	350	340		

Statistical analyses

Statistical analysis title	Odds ratio, ACQ-7 response at Week 52
Statistical analysis description:	
ACQ-7 response was compared between treatment groups using a logistic model including treatment and country as factors and the baseline value (Week 0) as covariate. The odds ratio for the treatment effects with their 95% CIs and corresponding p-values were estimated by the model.	
Comparison groups	CHF 5993 pMDI 100/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg - ITT
Number of subjects included in analysis	1149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.843
upper limit	1.362

Secondary: Time to first moderate or severe asthma exacerbation

End point title	Time to first moderate or severe asthma exacerbation
End point description:	
The number of patients at risk of a moderate or severe asthma exacerbation is presented.	
End point type	Secondary
End point timeframe:	
Baseline to Week 52.	

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	575[12]	574[13]		
Units: Patients	337	379		

Notes:

[12] - Of 575 patients in the ITT population, 337 had a moderate/severe exacerbation.

[13] - Of 574 patients in the ITT population, 379 had a moderate/severe exacerbation.

Statistical analyses

Statistical analysis title	Hazard ratio (time to 1st mod/severe exacerbation)

Statistical analysis description:

Time to first moderate or severe asthma exacerbation was analysed using a Cox proportional hazards model including treatment, country and number of exacerbations in the previous year (1 or > 1) as factors.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg - ITT
Number of subjects included in analysis	1149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Cox proportional hazards analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	0.975

Secondary: Time to first severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02

End point title	Time to first severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02

End point description:

The number of patients at risk of a severe asthma exacerbation is presented.

End point type	Secondary

End point timeframe:

Baseline to 52 weeks for both studies in the pooled analysis.

End point values	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg	CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1146[14]	1145[15]		
Units: Patients	209	257		

Notes:

[14] - Of 1146 patients in the ITT population, 209 had a severe exacerbation.

[15] - Of 1145 patients in the ITT population, 257 had a severe exacerbation.

Statistical analyses

Statistical analysis title	Hazard ratio (time to 1st severe exacerbation)

Statistical analysis description:

Time to first severe asthma exacerbation in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 was analysed using a Cox proportional hazards model including treatment, country and number of exacerbations in the previous year (1 or > 1) as factors.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg and 200/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg and 200/6 µg - ITT
Number of subjects included in analysis	2291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Cox proportional hazards analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.788
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	0.946

Secondary: Change from baseline in the percentage of asthma control days in each inter-visit period, over the 52-week treatment period

End point title	Change from baseline in the percentage of asthma control days in each inter-visit period, over the 52-week treatment period

End point description:

Patients recorded asthma symptom scores and use of rescue medication in the eDiary twice a day at home during the run-in (baseline values) and treatment periods; data were automatically transmitted daily to the Vitalograph database.
Asthma symptoms (i.e. overall symptoms, cough, wheeze, chest tightness and breathlessness) were scored as follows:
Morning (night-time asthma symptoms): 0 (no symptoms), 1 (mild - symptoms not causing awakening), 2 (moderate - discomfort enough to cause awakenings) and 3 (severe - causing awakenings for most of the night/did not sleep at all);
Evening (daytime asthma symptoms): 0 (no symptoms), 1 (mild - aware of symptoms which could be easily tolerated), 2 (moderate - discomfort enough to cause interference with daily activity),
3 (severe - incapacitating with inability to work/take part in usual activity).
Asthma control days were calculated as days (i.e. night-time + daytime) with a total asthma score of 0 and no rescue medication use.

End point type	Secondary

End point timeframe:

52-week treatment period.

End point values	CHF 5993 pMDI 100/6/12.5 µg - ITT	CHF 1535 pMDI 100/6 µg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574[16]	574[17]		
Units: Percentage				
least squares mean (confidence interval 95%)	16.395 (14.154 to 18.635)	15.109 (12.863 to 17.355)		

Notes:

[16] - Number of patients in the ITT population = 575;
Number of patients with available data = 574.

[17] - Number of patients in the ITT population = 574;
Number of patients with available data = 574.

Statistical analyses

Statistical analysis title	Adjusted mean difference - CFB over 52 weeks

Statistical analysis description:

The CFB in percentage of asthma control days over the entire treatment period (Weeks 1-52) was analysed using a linear MMRM including treatment, inter-visit period, treatment by inter-visit period interaction and country as fixed effects, and baseline value (run-in period) and baseline by inter-visit period interaction and country as covariates.

Comparison groups	CHF 5993 pMDI 100/6/12.5 µg - ITT v CHF 1535 pMDI 100/6 µg - ITT
Number of subjects included in analysis	1148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.427
Method	Linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	1.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.887
upper limit	4.459

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time of patient informed consent until study completion or discontinuation.

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs) were defined as AEs with date of first randomised study treatment intake ≤ AE onset date ≤ date of completion/discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	CHF 5993 pMDI 100/6/12.5 µg - Safety

Reporting group description:

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

Reporting group title	CHF 1535 pMDI 100/6 µg - Safety

Reporting group description:

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

Serious adverse events	CHF 5993 pMDI 100/6/12.5 µg - Safety	CHF 1535 pMDI 100/6 µg - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 576 (4.86%)	22 / 574 (3.83%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	3	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mantle cell lymphoma stage IV			

subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 576 (1.22%)	4 / 574 (0.70%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tonsillar inflammation			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Limb crushing injury			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 576 (0.35%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 576 (0.17%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Myocardial infarction			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 576 (0.17%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	2 / 576 (0.35%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 576 (0.00%)	2 / 574 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bursitis infective			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 576 (0.17%)	0 / 574 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 576 (0.00%)	3 / 574 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 576 (0.00%)	1 / 574 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CHF 5993 pMDI 100/6/12.5 µg - Safety	CHF 1535 pMDI 100/6 µg - Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	429 / 576 (74.48%)	451 / 574 (78.57%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	12 / 576 (2.08%)	7 / 574 (1.22%)	
occurrences (all)	20	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 576 (2.78%)	9 / 574 (1.57%)	
occurrences (all)	22	12	
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 576 (6.60%)	46 / 574 (8.01%)	
occurrences (all)	49	52	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	334 / 576 (57.99%)	377 / 574 (65.68%)	
occurrences (all)	1179	1348	
Oropharyngeal pain			
subjects affected / exposed	9 / 576 (1.56%)	12 / 574 (2.09%)	
occurrences (all)	9	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 576 (1.39%)	14 / 574 (2.44%)	
occurrences (all)	8	15	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	71 / 576 (12.33%)	78 / 574 (13.59%)	
occurrences (all)	85	98	
Respiratory tract infection viral			
subjects affected / exposed	15 / 576 (2.60%)	26 / 574 (4.53%)	
occurrences (all)	17	30	
Bronchitis			
subjects affected / exposed	18 / 576 (3.13%)	22 / 574 (3.83%)	
occurrences (all)	22	26	
Pharyngitis			
subjects affected / exposed	12 / 576 (2.08%)	16 / 574 (2.79%)	
occurrences (all)	12	17	
Viral upper respiratory tract infection			
subjects affected / exposed	12 / 576 (2.08%)	16 / 574 (2.79%)	
occurrences (all)	14	20	
Rhinitis			
subjects affected / exposed	8 / 576 (1.39%)	12 / 574 (2.09%)	
occurrences (all)	8	13	
Sinusitis			
subjects affected / exposed	6 / 576 (1.04%)	12 / 574 (2.09%)	
occurrences (all)	6	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2016	There was one substantial general amendment (protocol version 2.0, dated 12 May 2016) to clarify the nature of long-acting β2-agonist (LABA) daily doses in inclusion criterion #4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported