Clinical trial results:
A 52 week, randomized, double blind, multinational, multicentre, active controlled, 3-arm parallel group trial comparing CHF 5993 200/6/12.5 µg pMDI (fixed combination of extrafine beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 200/6 µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) alone or on top of open-label tiotropium 2.5 µg Respimat® in patients with asthma uncontrolled on high doses of inhaled corticosteroids in combination with long-acting ß2-agonists.

Summary

EudraCT number	2015-000717-40
Trial protocol	GB CZ SK DE PT HU LT ES PL IT
Global end of trial date	28 May 2018

Results information

Result version number	v1 (current)
This version publication date	15 June 2019
First version publication date	15 June 2019

Trial information

Trial identification

Sponsor protocol code	CCD-05993AB2-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02676089
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 05212791, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 05212791, clinicaltrials_info@chiesi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2018
Global end of trial reached?	Yes
Global end of trial date	28 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:
- To demonstrate the superiority of CHF 5993 pressurised metered dose inhaler (pMDI) 200/6/12.5 µg compared to CHF 1535 pMDI 200/6 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 exacerbation rate with CHF 5993 pMDI 200/6/12.5 µg compared to CHF 1535 pMDI 200/6 µg during the entire 52-week treatment period.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and all other requirements of local laws.
At all visits from screening onwards, concomitant medications and adverse events were recorded, physical examination of patients was carried out and asthma exacerbations were assessed. Vital signs and 12-lead electrocardiograms (ECGs) were recorded at all visits (pre-dose at screening, pre- and post-dose during the treatment period). 24-hour Holter ECGs were recorded at screening, Week 0, Week 12 , Week 26 and Week 52 on a subset of at least 10% of randomised patients. Spirometry was performed at all visits (pre-dose FEV1 and forced vital capacity from screening to Week 52,
pre-dose inspiratory capacity and vital capacity, and serial post-dose spirometry [FEV1, FVC] from randomisation to Week 52).
Subjects were provided with salbutamol as rescue medication.
Patients completed the electronic diary (eDiary)/electronic peak flow meter (ePeakflowmeter) (same device) twice daily at home from screening to Week 52, recording asthma symptoms, treatment compliance, rescue intake and peak expiratory flow (PEF). The Asthma Control Questionnaire© (ACQ)-7 was completed at all visits from screening to Week 52. The EuroQuality of Life-5-Dimensional-3-Level (EQ-5D-3L™) questionnaire was completed at all visits from randomisation to Week 52. Health economic information was collected during the study.
Blood collection for routine haematology and blood chemistry was performed at screening, Week 26 and Week 52. Heart rate, Fridericia-corrected QT interval, PR interval and QRS interval were evaluated on 12-lead ECGs. Electrocardiographic and arrhythmia analyses were performed on 24-hour Holter ECGs.
An independent Data Safety Monitoring Board was established for independent scrutiny of the study and impartial safety insurance of patients. An Adjudication Committee was established to evaluate Major Adverse Cardiovascular Events.

Background therapy: -

Evidence for comparator:

CHF 5993 pMDI 200/6/12.5 µg was compared to CHF 1535 pMDI 200/6 µg alone and to the free combination CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg.
CHF 1535 pMDI 200/6 µg was chosen as control treatment, as it is currently marketed for the treatment of asthmatic patients (used at the marketed dose in this study).
The free combination CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg (a long-acting muscarinic antagonist [LAMA]) was considered a suitable comparator to test the superiority of CHF 5993 pMDI 200/6/12.5 µg in terms of pulmonary function, as CHF 5993 pMDI 200/6/12.5 µg derives from the combination of CHF 1535 pMDI 200/6 µg and the LAMA glycopyrronium bromide.

Actual start date of recruitment	06 April 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	Argentina: 60
Country: Number of subjects enrolled	Belarus: 29
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Russian Federation: 325
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Ukraine: 215
Country: Number of subjects enrolled	Poland: 289
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 119
Country: Number of subjects enrolled	Slovakia: 24
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 171
Country: Number of subjects enrolled	Czech Republic: 91
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Hungary: 69
Country: Number of subjects enrolled	Lithuania: 1
Worldwide total number of subjects	1437
EEA total number of subjects	803

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)	1173
From 65 to 84 years	264
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 2100 patients were screened according to inclusion/exclusion criteria, and 1437 patients were randomised.

Pre-assignment

Screening details:

At screening, within 7 days of a pre-screening visit, inclusion/exclusion criteria were assessed. There were 663 screening failures (579, 63, 13, 4, 3 and 1 patient due to failure to meet inclusion/exclusion criteria, withdrawal of consent, other reasons, adverse events, lost to follow-up and asthma exacerbations, respectively).

Period 1

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

Blinding implementation details:

An Interactive Response Technology (IRT) system was used to generate the randomisation list. This was a double-blind study with an open-label arm (CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg arm).

Arms

Are arms mutually exclusive?	Yes
Arm title	CHF 5993 pMDI 200/6/12.5 µg

Arm description:

Patients were randomised to receive CHF 5993 pMDI 200/6/12.5 µg, 2 inhalations twice daily (BID) (total daily dose: 800 µg beclometasone dipropionate [BDP]/24 µg formoterol fumarate [FF]/50 µg glycopyrronium bromide [GB]) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Arm type	Experimental
Investigational medicinal product name	CHF 5993 pMDI 200/6/12.5 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 containing 200 µg BDP/6 µg FF/12.5 µg GB per metered dose.
Double-blind study design: During study visits patients randomised to the CHF 5993 pMDI 200/6/12.5 µg treatment group received two kits of study treatment at randomisation, Week 12, Week 26 and Week 40, each consisting of one box containing two CHF 5993 pMDI inhalers numbered 1 and 2. Patients administered 1 puff from each inhaler in the morning and evening.
Dose: 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF/50 µg GB).

Arm title	CHF 1535 pMDI 200/6 µg

Arm description:

Patients were randomised to receive CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Arm type	Control
Investigational medicinal product name	CHF 1535 pMDI 200/6 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: CHF 1535 pMDI containing 200 µg BDP/6 µg FF per metered dose.
Double-blind study design: During study visits patients randomised to the CHF 1535 pMDI 200/6 µg treatment group received two kits of study treatment at randomisation, Week 12, Week 26 and Week 40, each consisting of one box containing two CHF 1535 pMDI inhalers numbered 1 and 2. Patients administered 1 puff from each inhaler in the morning and evening.
Dose: 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Arm title	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg

Arm description:

This was an open-label arm. Patients were randomised to receive CHF 1535 pMDI 200/6 µg (2 inhalations BID) + tiotropium 2.5 µg (2 inhalations once a day [OD]) (total daily dose: 800 µg BDP/24 µg FF + 5 µg tiotropium) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Arm type	Active comparator
Investigational medicinal product name	CHF 1535 pMDI 200/6 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: CHF 1535 pMDI containing 200 µg BDP/6 µg FF per metered dose.
During study visits patients randomised to the CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg treatment group received two kits of pMDI at randomisation, Week 12, Week 26 and Week 40, each consisting of one box containing two CHF 1535 pMDI inhalers numbered 1 and 2. Patients administered 1 puff from each inhaler in the morning and evening.
Dose: 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).
Patients randomised to this arm also received SPIRIVA® Respimat® for administration of tiotropium 2.5 µg.

Investigational medicinal product name	Tiotropium 2.5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: Tiotropium 2.5 µg per dose equivalent to 3.124 µg tiotropium bromide.
During study visits patients randomised to the CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg treatment group received 2 kits of SPIRIVA® Respimat® at randomisation, Week 12, Week 26 and Week 40, each consisting of one box containing two tiotropium inhalers. These inhalers were to be used in the morning only; patients administered 1 puff from each SPIRIVA® Respimat® in the morning.
Dose: 2 inhalations OD (total daily dose: 5 µg tiotropium).
Patients randomised to this arm also received CHF 1535 pMDI inhalers for administration of CHF 1535 pMDI 200/6 µg.

Number of subjects in period 1	CHF 5993 pMDI 200/6/12.5 µg	CHF 1535 pMDI 200/6 µg	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg
Started	573	576	288
Completed	534	533	262
Not completed	39	43	26
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	26	25	20
Patient departure	1	-	-
Patient decision	-	1	-

Adverse event, non-fatal	3	7	2
Safety concern	-	-	1
Unblinding code broken	1	-	-
Lost to follow-up	-	1	1
Pregnancy	2	-	1
Lack of efficacy	2	-	-
Protocol deviation	3	8	1

Baseline characteristics

Reporting groups	
Reporting group title	CHF 5993 pMDI 200/6/12.5 µg
Reporting group description:	
Patients were randomised to receive CHF 5993 pMDI 200/6/12.5 µg, 2 inhalations twice daily (BID) (total daily dose: 800 µg beclometasone dipropionate [BDP]/24 µg formoterol fumarate [FF]/50 µg glycopyrronium bromide [GB]) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).	
Reporting group title	CHF 1535 pMDI 200/6 µg
Reporting group description:	
Patients were randomised to receive CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).	
Reporting group title	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg
Reporting group description:	
This was an open-label arm. Patients were randomised to receive CHF 1535 pMDI 200/6 µg (2 inhalations BID) + tiotropium 2.5 µg (2 inhalations once a day [OD]) (total daily dose: 800 µg BDP/24 µg FF + 5 µg tiotropium) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).	

Reporting group values	CHF 5993 pMDI 200/6/12.5 µg	CHF 1535 pMDI 200/6 µg	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg
Number of subjects	573	576	288
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)	474	452	247
From 65-84 years	99	124	41
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	53.2	54.0	51.5
standard deviation	± 12.2	± 11.9	± 12.3
Gender categorical			
Units: Subjects			
Female	361	329	185
Male	212	247	103

Reporting group values	Total		
Number of subjects	1437		
Age categorical			
Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	1173		
From 65-84 years	264		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	875		
Male	562		

Subject analysis sets

Subject analysis set title	CHF 5993 pMDI 200/6/12.5 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 200/6 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 1535 pMDI 200/6 µg + tiotropium 2.5 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 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 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT
Number of subjects	571	571	287
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	53.1	54.0	51.6
standard deviation	± 12.2	± 11.8	± 12.3
Gender categorical Units: Subjects			
Female	359	327	184
Male	212	244	103

Reporting group values	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	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			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female			

Male			

End points

End points reporting groups

Reporting group title	CHF 5993 pMDI 200/6/12.5 µg

Reporting group description:

Patients were randomised to receive CHF 5993 pMDI 200/6/12.5 µg, 2 inhalations twice daily (BID) (total daily dose: 800 µg beclometasone dipropionate [BDP]/24 µg formoterol fumarate [FF]/50 µg glycopyrronium bromide [GB]) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Reporting group title	CHF 1535 pMDI 200/6 µg

Reporting group description:

Patients were randomised to receive CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Reporting group title	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg

Reporting group description:

This was an open-label arm. Patients were randomised to receive CHF 1535 pMDI 200/6 µg (2 inhalations BID) + tiotropium 2.5 µg (2 inhalations once a day [OD]) (total daily dose: 800 µg BDP/24 µg FF + 5 µg tiotropium) for 52 weeks after a 2-week open-label run-in period during which they received CHF 1535 pMDI 200/6 µg, 2 inhalations BID (total daily dose: 800 µg BDP/24 µg FF).

Subject analysis set title	CHF 5993 pMDI 200/6/12.5 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 200/6 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 1535 pMDI 200/6 µg + tiotropium 2.5 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 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 volume of air that can be forced out in the first second after taking a deep breath. Change from baseline (CFB) in pre-dose morning FEV1 at Week 26 was analysed. Data are presented as adjusted means (least square means) with their 95% confidence intervals (CIs).

End point type	Primary

End point timeframe:

Baseline (pre-dose at the randomisation visit, Week 0) to Week 26.

End point values	CHF 5993 pMDI 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	551[1]	547[2]	275[3]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.229 (0.196 to 0.263)	0.157 (0.123 to 0.190)	0.274 (0.227 to 0.321)	

Notes:

[1] - Number of patients in the ITT population=571;
Number of patients with available data=551.
[2] - Number of patients in the ITT population=571;
Number of patients with available data=547.
[3] - Number of patients in the ITT population=287;
Number of patients with available data=275.

Statistical analyses

Statistical analysis title	Adj. mean difference, CFB pre-dose FEV1 at 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 (pre-dose, Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. The adjusted (adj.) means in each treatment group, adj. mean differences between treatments, their 95% CIs and p-values were estimated by the model.

Comparison groups	CHF 5993 pMDI 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT
Number of subjects included in analysis	1098
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.003
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.12

Notes:

[4] - 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 statistically (stat.) significant. For this endpoint, superiority of CHF 5993 pMDI 200/6/12.5 µg over CHF 1535 pMDI 200/6 µg was demonstrated if the lower limit of the CI for the adj. mean difference was > 0. Steps 2 to 4 followed in sequence.

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:

The rate of moderate and severe asthma exacerbations (defined below) was evaluated over 52 weeks of treatment.
Severe: asthma worsening requiring initiation of treatment with systemic corticosteroids for at least 3 days (corticosteroid courses separated by ≥ 1 week treated as separate exacerbations).
Moderate: ≥ 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 (minimum: 4 puffs/day) in occasions of SABA use on 2 consecutive days;
- ≥ 20% decrease in PEF from baseline on at least 2 consecutive mornings/evenings or ≥ 20% decrease in FEV1 from baseline;
- Visit to Emergency Room/study site, no corticosteroids.

End point type	Primary

End point timeframe:

Baseline to 52 weeks.

End point values	CHF 5993 pMDI 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	571	571	287	
Units: Adjusted exacerbation rate/patient/year				
number (confidence interval 95%)	1.726 (1.543 to 1.932)	1.963 (1.757 to 2.192)	1.613 (1.373 to 1.897)	

Statistical analyses

Statistical analysis title	Adjusted exacerbation rate ratio

Statistical analysis description:

The number of moderate and severe asthma exacerbations over 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. The adj. asthma exacerbation rates in each treatment group and the adj. rate ratios with their 95% CIs and p-values were estimated by the model.

Comparison groups	CHF 5993 pMDI 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT

Number of subjects included in analysis	1142
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.11
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.751
upper limit	1.03

Notes:

[5] - The comparisons between treatments in terms of co-primary and key secondary efficacy endpoints were conducted according to a hierarchical testing procedure. At step 1, both superiority tests on the two co-primary endpoints had to be statistically significant. For this endpoint, superiority of CHF 5993 pMDI 200/6/12.5 µg over CHF 1535 pMDI 200/6 µg was demonstrated if the upper limit of the CI for the adj. rate ratio between treatments was < 1. Steps 2 to 4 followed in sequence.

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 CFB 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 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	547[6]	540[7]	272[8]	
Units: Litres				
least squares mean (confidence interval 95%)	0.522 (0.488 to 0.556)	0.417 (0.383 to 0.451)	0.555 (0.507 to 0.603)	

Notes:

[6] - Number of patients in the ITT population=571;
Number of patients with available data=547.

[7] - Number of patients in the ITT population=571;
Number of patients with available data=540.

[8] - Number of patients in the ITT population=287;
Number of patients with available data=272.

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. Adj. means in each treatment group, adj. mean difference between treatments, their 95% CIs and p-values were estimated.

Comparison groups	CHF 5993 pMDI 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT
Number of subjects included in analysis	1087
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.153

Notes:

[9] - 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 stat. significant.
At step 2, superiority of CHF 5993 pMDI 200/6/12.5 µg over CHF 1535 pMDI 200/6 µg had to be demonstrated for the present key secondary efficacy endpoint. Superiority was demonstrated if the lower limit of the CI for the adj. 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 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 CFB 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.

End point values	CHF 5993 pMDI 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	563[10]	562[11]	287	
Units: Litres/minute				
least squares mean (confidence interval 95%)	10.102 (6.717 to 13.487)	2.297 (-1.091 to 5.684)	10.286 (5.540 to 15.032)	

Notes:

[10] - Number of patients in the ITT population=571;
Number of patients with available data=563.
[11] - Number of patients in the ITT population = 571;

Number of patients with available data = 562.

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 (run-in) and baseline by inter-visit period interaction as covariates. Adj. means in each treatment group, adj. mean difference between treatments, their 95% CIs and p-values were estimated.

Comparison groups	CHF 5993 pMDI 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT
Number of subjects included in analysis	1125
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.001
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	7.805
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.016
upper limit	12.594

Notes:

[12] - 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 stat. significant;
Step 2: sup of CHF 5993 pMDI 200/6/12.5 µg over CHF 1535 pMDI 200/6 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 adj. 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 (TRIMARAN) and CCD-05993AB2-02 (present study, 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 adj. asthma exacerbation rates in each treatment group and the adj. 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[13]
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:

[13] - 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 200/6/12.5 µg over CHF 1535 pMDI 200/6 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© (ACQ)-7 response at Week 52

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

End point description:

An ACQ-7 response was defined as CFB (Week 0, pre-dose) in ACQ-7 score ≤ -0.5. Non-response was defined as CFB 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 from screening to Week 52.

End point type	Secondary

End point timeframe:

Baseline to Week 52.

End point values	CHF 5993 pMDI 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	536[14]	538[15]	263[16]	
Units: Patients				
number (not applicable)	356	332	168	

Notes:

[14] - Number of patients in the ITT population=571;
Number of patients with available data=536.
[15] - Number of patients in the ITT population=571;
Number of patients with available data=538.
[16] - Number of patients in the ITT population=287;
Number of patients with available data=168.

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 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT
Number of subjects included in analysis	1074
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Logistic model
Parameter estimate	Odds ratio
Point estimate	1.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.912
upper limit	1.478

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 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	571[17]	571[18]	287[19]	
Units: Patients	323	364	162	

Notes:

[17] - Of 571 patients in the ITT population, 323 patients had a moderate/severe exacerbation.

[18] - Of 571 patients in the ITT population, 364 patients had a moderate/severe exacerbation.

[19] - Of 287 patients in the ITT population, 162 patients 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 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT
Number of subjects included in analysis	1142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cox proportional hazards analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.688
upper limit	0.929

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[20]	1145[21]		
Units: Patients	209	257		

Notes:

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

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

Statistical analyses

Statistical analysis title	Hazard ratio (time to first 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 (puffs/day) 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 200/6/12.5 µg - ITT	CHF 1535 pMDI 200/6 µg - ITT	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	571	568[22]	287	
Units: Percentage				
least squares mean (confidence interval 95%)	15.601 (13.389 to 17.813)	12.088 (9.870 to 14.307)	12.530 (9.401 to 15.658)	

Notes:

[22] - Number of patients in the ITT population=571;
Number of patients with available data=568.

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 200/6/12.5 µg - ITT v CHF 1535 pMDI 200/6 µg - ITT
Number of subjects included in analysis	1139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	linear MMRM
Parameter estimate	Adjusted mean difference
Point estimate	3.513
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.379
upper limit	6.646

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 200/6/12.5 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 200/6 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 200/6 µg + tiotropium 2.5 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 200/6/12.5 µg - Safety	CHF 1535 pMDI 200/6 µg - Safety	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 571 (4.90%)	33 / 573 (5.76%)	15 / 287 (5.23%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst torsion			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine cervical erosion			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	11 / 571 (1.93%)	11 / 573 (1.92%)	6 / 287 (2.09%)
occurrences causally related to treatment / all	0 / 12	0 / 11	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac hypertrophy			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia vitamin B12 deficiency			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastritis			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric stenosis			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back disorder			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 571 (0.18%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	1 / 571 (0.18%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 571 (0.00%)	0 / 573 (0.00%)	1 / 287 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	3 / 571 (0.53%)	5 / 573 (0.87%)	2 / 287 (0.70%)
occurrences causally related to treatment / all	0 / 3	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 571 (0.00%)	1 / 573 (0.17%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 571 (0.18%)	0 / 573 (0.00%)	0 / 287 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CHF 5993 pMDI 200/6/12.5 µg - Safety	CHF 1535 pMDI 200/6 µg - Safety	CHF 1535 pMDI 200/6 µg + tiotropium 2.5 µg - Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	406 / 571 (71.10%)	437 / 573 (76.27%)	207 / 287 (72.13%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 571 (1.75%)	6 / 573 (1.05%)	7 / 287 (2.44%)
occurrences (all)	11	6	7
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 571 (4.38%)	27 / 573 (4.71%)	13 / 287 (4.53%)
occurrences (all)	36	31	16
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	320 / 571 (56.04%)	361 / 573 (63.00%)	159 / 287 (55.40%)
occurrences (all)	1088	1226	510
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 571 (2.10%)	5 / 573 (0.87%)	7 / 287 (2.44%)
occurrences (all)	14	5	7
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	46 / 571 (8.06%)	63 / 573 (10.99%)	34 / 287 (11.85%)
occurrences (all)	55	80	38
Respiratory tract infection viral			
subjects affected / exposed	17 / 571 (2.98%)	28 / 573 (4.89%)	14 / 287 (4.88%)
occurrences (all)	23	36	16
Bronchitis			
subjects affected / exposed	18 / 571 (3.15%)	18 / 573 (3.14%)	12 / 287 (4.18%)
occurrences (all)	25	23	14
Upper respiratory tract infection			
subjects affected / exposed	8 / 571 (1.40%)	15 / 573 (2.62%)	7 / 287 (2.44%)
occurrences (all)	11	18	8
Pharyngitis			
subjects affected / exposed	10 / 571 (1.75%)	12 / 573 (2.09%)	4 / 287 (1.39%)
occurrences (all)	10	14	4
Rhinitis			
subjects affected / exposed	7 / 571 (1.23%)	12 / 573 (2.09%)	4 / 287 (1.39%)
occurrences (all)	7	14	5
Respiratory tract infection			
subjects affected / exposed	5 / 571 (0.88%)	12 / 573 (2.09%)	5 / 287 (1.74%)
occurrences (all)	5	16	6
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	3 / 571 (0.53%)	3 / 573 (0.52%)	6 / 287 (2.09%)
occurrences (all)	3	3	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 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 daily doses in inclusion criterion #4. This was first approved by the Czech Republic Regulatory Authority (on 09 June 2016).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported