Clinical trial results:
A 52-week, double blind, double dummy, randomized, multinational, multicentre, 3-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrrolate bromide administered via pMDI (CHF 5993) versus tiotropium bromide and versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI and tiotropium bromide in patients with chronic obstructive pulmonary disease

Summary

EudraCT number	2013-000063-91
Trial protocol	HU IT GB SK BG PL HR
Global end of trial date	18 March 2016

Results information

Result version number	v1 (current)
This version publication date	14 April 2017
First version publication date	14 April 2017

Trial information

Trial identification

Sponsor protocol code	CCD-1208-PR-0090

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01911364
WHO universal trial number (UTN)	-
Other trial identifiers	TRINITY: Trinity

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
Demonstrate superiority of CHF 5993 pMDI over tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment.

Key secondary objectives:
Demonstrate superiority of CHF 5993 pMDI over Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning forced expiratory volume in the 1st second [FEV1] at Week 52);

Demonstrate non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning FEV1 at Week 52).

CHF 5993=Fixed combination of BDP and FF and GB
CHF 1535=Fixed combination of BDP and FF
BDP=Beclometasone dipropionate
FF=Formoterol fumarate
GB=Glycopyrronium bromide
pMDI=Pressurised metered dose inhaler

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices (GCP) guidelines, and national legal requirements.

At all visits, from screening onwards, concomitant medication, AEs and vital signs were recorded, COPD exacerbations were assessed, pre-dose spirometry (including inspiratory capacity [IC], FEV1 and forced vital capacity [FVC]), and physical examinations were carried out. From screening, the electronic diary (eDiary) was completed to record rescue medication use, compliance with treatment and EXAcerbations of Chronic pulmonary disease Tool (EXACT)-Patient-Reported Outcome (PRO) questionnaire.

Furthermore, 12-lead electrocardiogram (ECG) parameters: heart rate (HR), Fridericia-corrected QT interval (QTcF), PR interval (PR), and QRS interval (QRS) were evaluated at screening, week 26, and week 52 of treatment. At screening, 12-lead ECG measurements were done pre-bronchodilator, while at week 26, and week 52, they were done pre-dose and 10 minutes post-dose.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2014
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: 275
Country: Number of subjects enrolled	Romania: 219
Country: Number of subjects enrolled	Russian Federation: 658
Country: Number of subjects enrolled	Slovakia: 48
Country: Number of subjects enrolled	Turkey: 60
Country: Number of subjects enrolled	Ukraine: 816
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Argentina: 50
Country: Number of subjects enrolled	Belarus: 65
Country: Number of subjects enrolled	Bulgaria: 181
Country: Number of subjects enrolled	Croatia: 18
Country: Number of subjects enrolled	Germany: 143
Country: Number of subjects enrolled	Hungary: 126
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Mexico: 12
Worldwide total number of subjects	2691
EEA total number of subjects	1030

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)	1500
From 65 to 84 years	1188
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Overall, 3433 patients were screened according to inclusion and exclusion criteria; of these, 2691 patients were randomized.

Pre-assignment

Screening details:

At the screening visit, inclusion/exclusion criteria were assessed. The screening visit was followed by a 2-week, open-label, run-in period during which patients self-administered Tiotropium (18µg daily) as 1 capsule once daily.

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:

Interactive Response Technology (IRT) was used to assign study medication kits to have an inventory control and patient dosing tracking. The IRT maintained quantities, kit numbers, drug types,batch/code number, expiration dates and it monitored inventory levels at all sites and managed the drug re-supply.

Double dummy design of the study was ensured; patients randomised to CHF 5993 pMDI received Tiotropium matched placebo and patients randomised to Tiotropium received pMDI placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A: CHF 5993 pMDI (100/6/12.5µg)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	CHF 5993 pMDI (100/6/12.5µg)
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 400 µg, FF 24 µg, GB 50 µg.

Mode of administration:
pMDI using a standard actuator. If patients inhaled their usual COPD pMDI medications with a spacer device, they were provided with the AeroChamber Plus™ Flow-Vu antistatic valved holding chamber (simply referred to as AeroChamber Plus™) to be used when taking the pMDI study treatments.

CHF 5993=Fixed combination of BDP and FF and GB
BDP=Beclometasone dipropionate
bid=Twice daily
FF=Formoterol fumarate
GB=Glycopyrronium bromide
pMDI=Pressurised metered dose inhaler

Arm title	Treatment B: Tiotropium (18µg)

Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tiotropium (18µg)
Investigational medicinal product code	
Other name	Spiriva®, Tiotropium bromide
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Reference product:
Tiotropium Bromide (Spiriva®) inhalation powder, hard capsule.

Dose:
18 µg per capsule, one capsule, once daily.
Total daily dose: 18 µg.

Mode of administration:
Dry powder inhaler, HandiHaler® inhaler.

Arm title	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

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

Dosage and administration details:

Reference product:
CHF 1535 pMDI, FDC of BDP + FF

Dose:
BDP 100 µg, FF 6 µg per actuation, 2 puffs, bid
Total daily dose: BDP 400 µg, FF 24 µg

Mode of administration:
pMDI (for CHF 1535), using a standard actuator. If patients inhaled their usual COPD pMDI medications with a spacer device, they were provided with the AeroChamber Plus™ to be used when taking the pMDI study treatments.

CHF 1535=Fixed combination of BDP and FF
BDP = Beclometasone dipropionate
bid=Twice daily
FF=Formoterol fumarate
pMDI=Pressurised metered dose inhaler

Investigational medicinal product name	Tiotropium (18µg)
Investigational medicinal product code	
Other name	Spiriva®, Tiotropium bromide
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Reference product:
Tiotropium Bromide (Spiriva®) inhalation powder, hard capsule.

Dose:
18 µg per capsule, one capsule, once daily.
Total daily dose: 18 µg.

Mode of administration:
Dry powder inhaler, HandiHaler® inhaler.

Number of subjects in period 1	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Started	1078	1075	538
Completed	986	914	496
Not completed	92	161	42
Consent withdrawn by subject	49	92	19
Adverse event, non-fatal	13	26	5
Protocol violation	2	1	3
Death	19	29	8
Other	1	1	-
Lost to follow-up	7	2	5
Lack of efficacy	1	10	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A: CHF 5993 pMDI (100/6/12.5µg)
Reporting group description: -	
Reporting group title	Treatment B: Tiotropium (18µg)
Reporting group description: -	
Reporting group title	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Reporting group description: -	

Reporting group values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects	1078	1075	538
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)	594	600	306
From 65-84 years	482	475	231
85 years and over	2	0	1
Age continuous Units: years			
arithmetic mean	63.4	63.3	62.6
standard deviation	± 8.7	± 8.4	± 8.9
Gender categorical Units: Subjects			
Female	249	246	140
Male	829	829	398
Race Units: Subjects			
Black or African American	1	0	0
White	1068	1070	533
Other	9	5	5

Reporting group values	Total		
Number of subjects	2691		
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)	1500		
From 65-84 years	1188		
85 years and over	3		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	635		
Male	2056		
Race			
Units: Subjects			
Black or African American	1		
White	2671		
Other	19		

End points

End points reporting groups

Reporting group title	Treatment A: CHF 5993 pMDI (100/6/12.5µg)
Reporting group description: -	
Reporting group title	Treatment B: Tiotropium (18µg)
Reporting group description: -	
Reporting group title	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Reporting group description: -	

Primary: 1_Moderate and severe COPD exacerbation rate over 52 weeks of treatment, CHF 5993 vs Tiotropium

End point title	1_Moderate and severe COPD exacerbation rate over 52 weeks of treatment, CHF 5993 vs Tiotropium

End point description:

Rate of moderate or severe COPD exacerbation.

Evaluate the rate of moderate or severe COPD exacerbation over 52 weeks of treatment.
Data are presented as Adjusted Exacerbation Rate per Patient per Year (95% CI).

Shown are the number of subjects included in the model and the number of subjects with available results.

A COPD exacerbation was defined as treated with systemic corticosteroids if this treatment was recorded.

COPD=Chronic obstructive pulmonary disease

End point type	Primary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[1]	1074[2]	538[3]	
Units: exacerbation/patient/year				
number (confidence interval 95%)	0.457 (0.412 to 0.508)	0.571 (0.517 to 0.632)	0.452 (0.389 to 0.524)	

Notes:

[1] - ITT population

[2] - ITT population

[3] - ITT population

Statistical analyses

Statistical analysis title	1_Adj rate ratio mod & sev exacerbations; A vs B

Statistical analysis description:

Adjusted rate ratio for moderate and severe exacerbations.
Primary efficacy analysis.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.003
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.801
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.693
upper limit	0.925

Notes:

[4] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

Superiority of CHF 5993 pMDI over Tiotropium was demonstrated by a statistically significant adjusted rate ratio (defined as $p<0.05$) favouring CHF 5993 pMDI.

Statistical analysis title	2_Adj rate ratio mod & sev exacerbations; A vs C

Statistical analysis description:

Adjusted rate ratio for moderate and severe exacerbations.
Secondary efficacy analysis.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.887
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	1.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.846
upper limit	1.214

Notes:

[5] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

Statistical analysis title	3_Adj rate ratio mod & sev exacerbations; C vs B

Statistical analysis description:

Adjusted rate ratio for moderate and severe exacerbations.
Secondary efficacy analysis.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v

	Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.01
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	0.944

Notes:

[6] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

Secondary: 2_Change from baseline in pre-dose morning FEV1 at week 52

End point title	2_Change from baseline in pre-dose morning FEV1 at week 52

End point description:

Key secondary endpoint.
Change from baseline in pre-dose morning FEV1, at Week 52.

FEV1=Forced expiratory volume in the 1st second. It is the volume of air that can be forced out in one second after taking a deep breath.

End point type	Secondary

End point timeframe:

Baseline to Week 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	985[7]	921[8]	495[9]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.082 (0.065 to 0.1)	0.021 (0.003 to 0.039)	0.085 (0.061 to 0.11)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	1_Adj mean difference between treatment; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1906
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.086

Notes:

[10] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Superiority of CHF 5993 pMDI over Tiotropium was demonstrated by a statistically significant adjusted mean difference between treatments favouring CHF 5993 pMDI.

Statistical analysis title	2_Adj mean difference between treatments; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

Non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium was demonstrated by a 95% confidence interval of the adjusted mean difference between treatments lying entirely to the right of the pre-defined non inferiority margin of -50 mL.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1480
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.852
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.027

Notes:

[11] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium was demonstrated.

Statistical analysis title	3_Adj mean difference between treatments; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1416
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.094

Notes:

[12] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 3_Time to first moderate or severe COPD exacerbation

End point title	3_Time to first moderate or severe COPD exacerbation

End point description:

Time to first moderate or severe COPD exacerbation.

Shown are the number of subjects included in the model and the number of subjects with available results.

COPD=Chronic obstructive pulmonary disease

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[13]	1074[14]	538[15]	
Units: Subjects, at least 1 mod or sev exacerbt	351	383	167	

Notes:

[13] - ITT population

[14] - ITT population

[15] - ITT population

Statistical analyses

Statistical analysis title	1_Time to first mod or sev COPD exacerbation; AvsB

Statistical analysis description:

Time to first moderate or severe COPD exacerbation.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.015
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.836
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.723
upper limit	0.966

Notes:

[16] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

Statistical analysis title	2_Time to first mod or sev COPD exacerbation; AvsC

Statistical analysis description:

Time to first moderate or severe COPD exacerbation.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.569
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.877
upper limit	1.269

Notes:

[17] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

Statistical analysis title	3_Time to first mod or sev COPD exacerbation; CvsB

Statistical analysis description:

Time to first moderate or severe COPD exacerbation.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.012
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.792

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	0.951

Notes:

[18] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

Secondary: 4_Rate of severe COPD exacerbations over 52 weeks of treatment

End point title	4_Rate of severe COPD exacerbations over 52 weeks of treatment

End point description:

Rate of severe COPD exacerbations over 52 weeks of treatment.

Data are presented as Adjusted Exacerbation Rate per Patient per Year (95% CI).

Shown are the number of subjects included in the model and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[19]	1074[20]	538[21]	
Units: exacerbation/patient/year				
number (confidence interval 95%)	0.067 (0.052 to 0.086)	0.098 (0.078 to 0.123)	0.057 (0.039 to 0.082)	

Notes:

[19] - ITT population

[20] - ITT population

[21] - ITT population

Statistical analyses

Statistical analysis title	1_Adj rate ratio of severe exacerbations; A vs B

Statistical analysis description:

Adjusted rate ratio for severe exacerbations.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.017
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.495
upper limit	0.935

Notes:

[22] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, and smoking status at screening as fixed effects, and log-time on study as an offset.

Statistical analysis title	2_Adj rate ratio of severe exacerbations; A vs C

Statistical analysis description:

Adjusted rate ratio for severe exacerbations.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.447
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	1.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.771
upper limit	1.804

Notes:

[23] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, and smoking status at screening as fixed effects, and log-time on study as an offset.

Statistical analysis title	3_Adj rate ratio of severe exacerbations; C vs B

Statistical analysis description:

Adjusted rate ratio for severe exacerbations.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.009
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.577

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.382
upper limit	0.87

Notes:

[24] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, and smoking status at screening as fixed effects, and log-time on study as an offset.

Secondary: 5_Time to first severe COPD exacerbation

End point title	5_Time to first severe COPD exacerbation

End point description:

Time to first severe COPD exacerbation.

Shown are the number of subjects included in the model and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[25]	1074[26]	538[27]	
Units: Subjects, at least 1 severe exacerbation	75	99	35	

Notes:

[25] - ITT population

[26] - ITT population

[27] - ITT population

Statistical analyses

Statistical analysis title	1_Time to first sev COPD exacerbation; A vs B

Statistical analysis description:

Time to first severe COPD exacerbation.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.021
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.702

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.948

Notes:

[28] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

Statistical analysis title	2_Time to first sev COPD exacerbation; A vs C

Statistical analysis description:

Time to first severe COPD exacerbation.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.822
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.701
upper limit	1.565

Notes:

[29] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

Statistical analysis title	3_Time to first sev COPD exacerbation; C vs B

Statistical analysis description:

Time to first severe COPD exacerbation.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.042
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.456
upper limit	0.986

Notes:

[30] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

Secondary: 6_Rate of moderate COPD exacerbations over 52 weeks of treatment

End point title	6_Rate of moderate COPD exacerbations over 52 weeks of treatment

End point description:

Rate of moderate COPD exacerbations over 52 weeks of treatment.

Data are presented as Adjusted Exacerbation Rate per Patient per Year (95% CI).

Shown are the number of subjects included in the model and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[31]	1074[32]	538[33]	
Units: exacerbation/patient/year				
number (confidence interval 95%)	0.37 (0.329 to 0.416)	0.442 (0.395 to 0.495)	0.376 (0.32 to 0.443)	

Notes:

[31] - ITT population (analysed)

[32] - ITT population (analysed)

[33] - ITT population (analysed)

Statistical analyses

Statistical analysis title	1_Adj rate ratio of moderate exacerbations; A vs B

Statistical analysis description:

Adjusted rate ratio for moderate exacerbations.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.03
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.713
upper limit	0.983

Notes:

[34] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

Statistical analysis title	2_Adj rate ratio of moderate exacerbation; A vs C

Statistical analysis description:

Adjusted rate ratio for moderate exacerbations.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.871
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.806
upper limit	1.2

Notes:

[35] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

Statistical analysis title	3_Adj rate ratio of moderate exacerbation; C vs B

Statistical analysis description:

Adjusted rate ratio for moderate exacerbations.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.108
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.036

Notes:

[36] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

Secondary: 7_Change from baseline in pre-dose morning FEV1 at all other clinic visits

End point title	7_Change from baseline in pre-dose morning FEV1 at all other clinic visits

End point description:

Change from baseline in pre-dose morning FEV1 at all other study visits.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Baseline and study visit (Week 4, 12, 26, 40).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1068[37]	1055[38]	536[39]	
Units: litre(s)				
least squares mean (confidence interval 95%)				
Week 4	0.081 (0.067 to 0.095)	0.012 (-0.002 to 0.026)	0.091 (0.071 to 0.111)	
Week 12	0.082 (0.066 to 0.097)	0.03 (0.015 to 0.046)	0.101 (0.08 to 0.123)	
Week 26	0.075 (0.059 to 0.092)	0.024 (0.007 to 0.041)	0.086 (0.063 to 0.109)	
Week 40	0.08 (0.063 to 0.097)	0.025 (0.007 to 0.042)	0.093 (0.069 to 0.117)	

Notes:

[37] - ITT (available for change from baseline)
Wk 04 n=1067
Wk 12 n=1047
Wk 26 n=1027
Wk 40 n=998

[38] - ITT (available for change from baseline)
Wk 04 n=1052
Wk 12 n=1019
Wk 26 n=977
Wk 40 n=944

[39] - ITT (available for change from baseline)
Wk 04 n=536
Wk 12 n=526
Wk 26 n=510
Wk 40 n=502

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, wk 4; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (2123) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2123
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.089

Notes:

[40] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, wk 4; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (1604) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1604
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.443
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.015

Notes:

[41] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, wk 4; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (1591) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1591
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.103

Notes:

[42] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	4_Adj mean diffr btw treatment, wk 12; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (2123) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2123
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.073

Notes:

[43] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	5_Adj mean diffr btw treatment, wk 12; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (1604) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1604
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.145
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.007

Notes:

[44] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	6_Adj mean diffr btw treatment, wk 12; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (1591) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1591
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.098

Notes:

[45] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	7_Adj mean diffr btw treatment, wk 26; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (2123) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2123
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.075

Notes:

[46] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	8_Adj mean diffr btw treatment, wk 26; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1604) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1604
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.461
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.018

Notes:

[47] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	9_Adj mean diffr btw treatment, wk 26; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1591) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1591
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.091

Notes:

[48] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	10_Adj mean diffr btw treatment, wk 40; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (2123) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2123
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.08

Notes:

[49] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	11_Adj mean diffr btw treatment, wk 40; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (1604) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1604
Analysis specification	Pre-specified
Analysis type	other[50]
P-value	= 0.384
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.016

Notes:

[50] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	12_Adj mean diffr btw treatment, wk 40; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (1591) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1591
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.098

Notes:

[51] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 8_Change from baseline to the average over the treatment period in pre-dose morning FEV1

End point title	8_Change from baseline to the average over the treatment period in pre-dose morning FEV1

End point description:

Change from baseline to the average over the treatment period in pre-dose morning FEV1.

Shown are the number of subjects included in the model and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to the overall treatment period (Week 4 to Week 52).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1068[52]	1055[53]	536[54]	
Units: litre(s)				
least squares mean (confidence interval 95%)	0.08 (0.067 to 0.093)	0.022 (0.009 to 0.036)	0.091 (0.073 to 0.11)	

Notes:

[52] - ITT (available for change from baseline)

[53] - ITT (available for change from baseline)

[54] - ITT (available for change from baseline)

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, average; A vs B

Statistical analysis description:

Adjusted mean difference between treatments - average over treatment period.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2123
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.077

Notes:

[55] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, average; A vs C

Statistical analysis description:

Adjusted mean difference between treatments - average over treatment period.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1604
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	= 0.337
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.012

Notes:

[56] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, average; C vs B

Statistical analysis description:

Adjusted mean difference between treatments - average over treatment period.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1591
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.092

Notes:

[57] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 9_FEV1 response (change from baseline in pre-dose morning FEV1 ≥ 100 mL) at Week 26 and Week 52

End point title	9_FEV1 response (change from baseline in pre-dose morning FEV1 ≥ 100 mL) at Week 26 and Week 52

End point description:

FEV1 response is defined as a change from baseline in pre-dose morning FEV1 ≥100 mL.
If the change from baseline was <100 mL, the patient was classed as a non-responder in terms of FEV1. Subjects with missing pre-dose morning FEV1 value at the relevant time points were also classified as non-responders.

Results are shown as the number of responders at Week 26 and Week 52.

End point type	Secondary

End point timeframe:

Baseline to study visit at Week 26, Week 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[58]	1074[59]	538[60]	
Units: subject				
Week 26	421	306	204	
Week 52	408	295	210	

Notes:

[58] - ITT population

[59] - ITT population

[60] - ITT population

Statistical analyses

Statistical analysis title	1_Btw grp analysis, FEV1 ≥100 mL, Wk 26; A vs B

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, at Week 26).

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	1.93

Notes:

[61] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Statistical analysis title	2_Btw grp analysis, FEV1 ≥100 mL, Wk 26; A vs C

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, at Week 26).

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[62]
P-value	= 0.694
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.3

Notes:

[62] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Statistical analysis title	3_Btw grp analysis, FEV1 ≥100 mL, Wk 26; C vs B

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, at Week 26).

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	1.92

Notes:

[63] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Statistical analysis title	4_Btw grp analysis, FEV1 ≥100 mL, Wk 52; A vs B

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, at Week 52).

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	1.95

Notes:

[64] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Statistical analysis title	5_Btw grp analysis, FEV1 ≥100 mL, Wk 26; A vs C

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, at Week 26).

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	= 0.627
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.18

Notes:

[65] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Statistical analysis title	6_Btw grp analysis, FEV1 ≥100 mL, Wk 52; C vs B

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, at Week 52).

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	2.13

Notes:

[66] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Secondary: 10_Change from baseline in pre-dose morning inspiratory capacity (IC)

at all clinic visits

End point title	10_Change from baseline in pre-dose morning inspiratory capacity (IC) at all clinic visits

End point description:

Change from baseline in pre-dose morning inspiratory capacity (IC) at all clinic visits.

IC is the volume change recorded at the mouth when taking a slow full inspiration with no hesitation, from a position of passive end-tidal expiration (i.e. functional residual capacity [FRC]), to a position to maximum inspiration. The average of at least 3 acceptable slow vital capacity manoeuvres was recorded for IC.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (W).

End point type	Secondary

End point timeframe:

Baseline and study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1063[67]	1054[68]	533[69]	
Units: litre(s)				
least squares mean (confidence interval 95%)				
Week 4	0.068 (0.047 to 0.09)	-0.002 (-0.023 to 0.019)	0.088 (0.059 to 0.118)	
Week 12	0.07 (0.047 to 0.093)	0.012 (-0.011 to 0.035)	0.128 (0.096 to 0.16)	
Week 26	0.078 (0.054 to 0.102)	0.039 (0.014 to 0.063)	0.083 (0.049 to 0.117)	
Week 40	0.072 (0.047 to 0.096)	0.033 (0.008 to 0.058)	0.082 (0.047 to 0.117)	
Week 52	0.071 (0.046 to 0.096)	0.012 (-0.014 to 0.037)	0.072 (0.037 to 0.108)	

Notes:

[67] - ITT (avail for change from baseline)
W 04 n=1060
W 12 n=1043
W 26 n=1022
W 40 n=991
W 52 n=975

[68] - ITT (avail for change from baseline)
W 04 n=1051
W 12 n=1016
W 26 n=973
W 40 n=943
W 52 n=918

[69] - ITT (avail for change from baseline)
W 04 n=533
W 12 n=521
W 26 n=507
W 40 n=500
W 52 n=492

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, wk 4; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (2117) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2117
Analysis specification	Pre-specified
Analysis type	other[70]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.1

Notes:

[70] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, wk 4; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (1596) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1596
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.284
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	0.017

Notes:

[71] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, wk 4; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (1587) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1587
Analysis specification	Pre-specified
Analysis type	other[72]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	0.127

Notes:

[72] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	4_Adj mean diffr btw treatment, wk 12; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (2117) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2117
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.09

Notes:

[73] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	5_Adj mean diffr btw treatment, wk 12; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (1596) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1596
Analysis specification	Pre-specified
Analysis type	other[74]
P-value	= 0.004
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.098
upper limit	-0.019

Notes:

[74] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	6_Adj mean diffr btw treatment, wk 12; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (1587) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1587
Analysis specification	Pre-specified
Analysis type	other[75]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.076
upper limit	0.156

Notes:

[75] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	7_Adj mean diffr btw treatment, wk 26; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (2117) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2117
Analysis specification	Pre-specified
Analysis type	other[76]
P-value	= 0.025
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.074

Notes:

[76] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	8_Adj mean diffr btw treatment, wk 26; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1596) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1596
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.808
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.037

Notes:

[77] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	9_Adj mean diffr btw treatment, wk 26; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1587) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1587
Analysis specification	Pre-specified
Analysis type	other[78]
P-value	= 0.038
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.086

Notes:

[78] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	10_Adj mean diffr btw treatment, wk 40; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (2117) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2117
Analysis specification	Pre-specified
Analysis type	other[79]
P-value	= 0.03
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.074

Notes:

[79] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	11_Adj mean diffr btw treatment, wk 40; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (1596) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1596
Analysis specification	Pre-specified
Analysis type	other[80]
P-value	= 0.642
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.033

Notes:

[80] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	12_Adj mean diffr btw treatment, wk 40; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (1587) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1587
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.025
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.092

Notes:

[81] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	13_Adj mean diffr btw treatment, wk 52; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (2117) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2117
Analysis specification	Pre-specified
Analysis type	other[82]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.095

Notes:

[82] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	14_Adj mean diffr btw treatment, wk 52; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1596) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1596
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	= 0.961
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.042

Notes:

[83] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	15_Adj mean diffr btw treatment, wk 52; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1587) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1587
Analysis specification	Pre-specified
Analysis type	other[84]
P-value	= 0.006
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.104

Notes:

[84] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 11_Change from baseline in SGRQ at all study visits: Total Score

End point title	11_Change from baseline in SGRQ at all study visits: Total Score

End point description:

SGRQ Total Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patients at all study visits (Week 0=baseline, 4, 12, 26, 40, 52).

The Total Score for SGRQ was calculated, whereby lower scores correspond to better health.
Moreover, 3 component scores of SGRQ were also calculated and include the domains:
i) Symptoms, ii) Activity, and iii) Impacts on daily life.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (W).

SGRQ=Saint George's Respiratory Questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1012[85]	1018[86]	519[87]	
Units: score				
least squares mean (confidence interval 95%)				
Week 4	-4.27 (-4.96 to -3.59)	-2.12 (-2.8 to -1.43)	-4.73 (-5.69 to -3.77)	
Week 12	-5.58 (-6.33 to -4.82)	-3.75 (-4.51 to -2.99)	-6.19 (-7.25 to -5.13)	

Week 26	-5.44 (-6.26 to -4.62)	-4.41 (-5.24 to -3.59)	-7.2 (-8.35 to -6.05)	
Week 40	-5.87 (-6.71 to -5.02)	-4.05 (-4.91 to -3.2)	-6.89 (-8.08 to -5.71)	
Week 52	-5.74 (-6.6 to -4.88)	-4.14 (-5.01 to -3.27)	-7.32 (-8.51 to -6.12)	

Notes:

[85] - ITT (avail for change from baseline)
W 04 n=982
W 12 n=954
W 26 n=944
W 40 n=915
W 52 n=899

[86] - ITT (avail for change from baseline)
W 04 n=983
W 12 n=949
W 26 n=919
W 40 n=877
W 52 n=860

[87] - ITT (avail for change from baseline)
W 04 n=497
W 12 n=494
W 26 n=474
W 40 n=467
W 52 n=463

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, wk 4; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (2030) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2030
Analysis specification	Pre-specified
Analysis type	other[88]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	-1.19

Notes:

[88] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, wk 4; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (1531) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the

footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	other[89]
P-value	= 0.451
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	1.64

Notes:

[89] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, wk 4; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 4.

The number of subjects in this analysis (1537) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1537
Analysis specification	Pre-specified
Analysis type	other[90]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-1.43

Notes:

[90] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	4_Adj mean diffr btw treatment, wk 12; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (2030) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B:

	Tiotropium (18µg)
Number of subjects included in analysis	2030
Analysis specification	Pre-specified
Analysis type	other[91]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-0.75

Notes:

[91] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	5_Adj mean diffr btw treatment, wk 12; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (1531) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	other[92]
P-value	= 0.352
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	1.92

Notes:

[92] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	6_Adj mean diffr btw treatment, wk 12; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 12.

The number of subjects in this analysis (1537) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1537
Analysis specification	Pre-specified
Analysis type	other[93]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	-1.14

Notes:

[93] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	7_Adj mean diffr btw treatment, wk 26; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (2030) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2030
Analysis specification	Pre-specified
Analysis type	other[94]
P-value	= 0.083
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	0.14

Notes:

[94] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	8_Adj mean diffr btw treatment, wk 26; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1531) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	other[95]
P-value	= 0.014
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	3.17

Notes:

[95] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	9_Adj mean diffr btw treatment, wk 26; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1537) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1537
Analysis specification	Pre-specified
Analysis type	other[96]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.21
upper limit	-1.37

Notes:

[96] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	10_Adj mean diffr btw treatment, wk 40; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (2030) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2030
Analysis specification	Pre-specified
Analysis type	other[97]
P-value	= 0.003
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.02
upper limit	-0.61

Notes:

[97] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	11_Adj mean diffr btw treatment, wk 40; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (1531) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	other[98]
P-value	= 0.166
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	2.48

Notes:

[98] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	12_Adj mean diffr btw treatment, wk 40; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 40.

The number of subjects in this analysis (1537) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	1537
Analysis specification	Pre-specified
Analysis type	other[99]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	-1.38

Notes:

[99] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	13_Adj mean diffr btw treatment, wk 52; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (2030) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2030
Analysis specification	Pre-specified
Analysis type	other[100]
P-value	= 0.01
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	-0.38

Notes:

[100] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	14_Adj mean diffr btw treatment, wk 52; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1531) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	other[101]
P-value	= 0.036
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	3.05

Notes:

[101] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	15_Adj mean diffr btw treatment, wk 52; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1537) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1537
Analysis specification	Pre-specified
Analysis type	other[102]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.66
upper limit	-1.69

Notes:

[102] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 12_Change from baseline in SGRQ at all study visits: Symptoms Score

End point title	12_Change from baseline in SGRQ at all study visits: Symptoms Score

End point description:

SGRQ Symptoms Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patients at all study visits (Week 0=baseline, 4, 12, 26, 40, 52).

The Total Score for SGRQ was calculated, whereby lower scores correspond to better health.
Moreover, 3 component scores of SGRQ were also calculated and include the domains:

i) Symptoms, ii) Activity, and iii) Impacts on daily life.

Shown are the number of subjects included in the model and the number of subjects with available results at week (Wk).

SGRQ=Saint George's Respiratory Questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52); data shown are for Week 26 and Week 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1045[103]	1047[104]	533[105]	
Units: score				
least squares mean (confidence interval 95%)				
Week 26	-7.65 (-8.69 to -6.62)	-5.41 (-6.46 to -4.36)	-9.87 (-11.33 to -8.41)	
Week 52	-9.07 (-10.14 to -7.99)	-6.65 (-7.74 to -5.55)	-11.07 (-12.58 to -9.57)	

Notes:

[103] - ITT (available for change from baseline)
Wk 26 n=994
Wk 52 n=947
[104] - ITT (available for change from baseline)
Wk 26 n=967
Wk 52 n=900
[105] - ITT (available for change from baseline)
Wk 26 n=497
Wk 52 n=483

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, wk 26; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (2092) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2092
Analysis specification	Pre-specified
Analysis type	other[106]
P-value	= 0.003
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.72
upper limit	-0.77

Notes:

[106] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, wk 26; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1578) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1578
Analysis specification	Pre-specified
Analysis type	other[107]
P-value	= 0.015
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	4.01

Notes:

[107] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, wk 26; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1580) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1580
Analysis specification	Pre-specified
Analysis type	other[108]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-4.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.26
upper limit	-2.66

Notes:

[108] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	4_Adj mean diffr btw treatment, wk 52; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (2092) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2092
Analysis specification	Pre-specified
Analysis type	other[109]
P-value	= 0.002
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.95
upper limit	-0.88

Notes:

[109] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	5_Adj mean diffr btw treatment, wk 52; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1578) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1578
Analysis specification	Pre-specified
Analysis type	other[110]
P-value	= 0.034
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	2.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	3.86

Notes:

[110] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	6_Adj mean diffr btw treatment, wk 52; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1580) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1580
Analysis specification	Pre-specified
Analysis type	other[111]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.29
upper limit	-2.56

Notes:

[111] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 13_Change from baseline in SGRQ at all study visits: Activity Score

End point title	13_Change from baseline in SGRQ at all study visits: Activity Score

End point description:

SGRQ Activity Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patients at all study visits (Week 0=baseline, 4, 12, 26, 40, 52).

The Total Score for SGRQ was calculated, whereby lower scores correspond to better health.
Moreover, 3 component scores of SGRQ were also calculated and include the domains:
i) Symptoms, ii) Activity, and iii) Impacts on daily life.

Shown are the number of subjects included in the model and the number of subjects with available results at week (Wk).

SGRQ=Saint George’s Respiratory Questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52); data shown are for Week 26 and Week 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1036[112]	1026[113]	527[114]	
Units: score				
least squares mean (confidence interval 95%)				
Week 26	-3.74 (-4.76 to -2.73)	-3.51 (-4.55 to -2.48)	-5.93 (-7.36 to -4.5)	
Week 52	-4.43 (-5.46 to -3.41)	-2.64 (-3.69 to -1.59)	-6.04 (-7.48 to -4.6)	

Notes:

[112] - ITT (available for change from baseline)
Wk 26 n=976
Wk 52 n=940

[113] - ITT (available for change from baseline)
Wk 26 n=933
Wk 52 n=889

[114] - ITT (available for change from baseline)
Wk 26 n=493
Wk 52 n=481

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, wk 26; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (2062) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2062
Analysis specification	Pre-specified
Analysis type	other[115]
P-value	= 0.755
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	1.22

Notes:

[115] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, wk 26; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1563) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1563
Analysis specification	Pre-specified
Analysis type	other[116]
P-value	= 0.015
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	3.94

Notes:

[116] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, wk 26; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1553) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1553
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.18
upper limit	-0.65

Statistical analysis title	4_Adj mean diffr btw treatment, wk 52; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (2062) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2062
Analysis specification	Pre-specified
Analysis type	other[117]
P-value	= 0.017
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.26
upper limit	-0.32

Notes:

[117] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	5_Adj mean diffr btw treatment, wk 52; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1563) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1563
Analysis specification	Pre-specified
Analysis type	other[118]
P-value	= 0.075
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	3.37

Notes:

[118] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	6_Adj mean diffr btw treatment, wk 52; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1553) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1553
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.18
upper limit	-1.61

Secondary: 14_Change from baseline in SGRQ at all study visits: Impact on daily life Score

End point title	14_Change from baseline in SGRQ at all study visits: Impact on daily life Score

End point description:

SGRQ Impact on daily life Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patients at all study visits (Week 0=baseline, 4, 12, 26, 40, 52).

The Total Score for SGRQ was calculated, whereby lower scores correspond to better health.
Moreover, 3 component scores of SGRQ were also calculated and include the domains:
i) Symptoms, ii) Activity, and iii) Impacts on daily life.

Shown are the number of subjects included in the model and the number of subjects with available results at week (Wk).

SGRQ=Saint George's Respiratory Questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52); data shown are for Week 26 and Week 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1041[119]	1032[120]	527[121]	
Units: score				
least squares mean (confidence interval 95%)				
Week 26	-5.73 (-6.66 to -4.81)	-4.67 (-5.61 to -3.72)	-7.04 (-8.34 to -5.73)	
Week 52	-5.58 (-6.55 to -4.61)	-4.29 (-5.29 to -3.3)	-7.23 (-8.59 to -5.86)	

Notes:

[119] - ITT (available for change from baseline)
Wk 26 n=991
Wk 52 n=951
[120] - ITT (available for change from baseline)
Wk 26 n=943
Wk 52 n=890
[121] - ITT (available for change from baseline)
Wk 26 n=496
Wk 52 n=483

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treatment, wk 26; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (2073) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2073
Analysis specification	Pre-specified
Analysis type	other[122]
P-value	= 0.115
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	0.26

Notes:

[122] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treatment, wk 26; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1568) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1568
Analysis specification	Pre-specified
Analysis type	other[123]
P-value	= 0.112
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.91

Notes:

[123] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treatment, wk 26; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 26.

The number of subjects in this analysis (1559) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1559
Analysis specification	Pre-specified
Analysis type	other[124]
P-value	= 0.004
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	-0.75

Notes:

[124] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	4_Adj mean diffr btw treatment, wk 52; A vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (2073) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2073
Analysis specification	Pre-specified
Analysis type	other[125]
P-value	= 0.07
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	0.11

Notes:

[125] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	5_Adj mean diffr btw treatment, wk 52; A vs C

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1568) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1568
Analysis specification	Pre-specified
Analysis type	other[126]
P-value	= 0.054
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	3.32

Notes:

[126] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	6_Adj mean diffr btw treatment, wk 52; C vs B

Statistical analysis description:

Adjusted mean difference between treatments at week 52.

The number of subjects in this analysis (1559) is due to an innate validation error within the EudraCT database. The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1559
Analysis specification	Pre-specified
Analysis type	other[127]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.62
upper limit	-1.24

Notes:

[127] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 15_SGRQ response (change from baseline in Total score ≤-4) at Week 26 and Week 52

End point title	15_SGRQ response (change from baseline in Total score ≤-4) at Week 26 and Week 52

End point description:

SGRQ response is defined as a change from baseline in SGRQ total score ≤ -4. If the change from baseline was > -4, the patient was classed as a non-responder in terms of SGRQ. Patients with missing value for the change from baseline at the relevant time points were also classified as non-responders.

Results are shown as the number of subjects Included in model and the number of responders in each of the treatment groups.

SGRQ=Saint George's respiratory questionnaire

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[128]	1074[129]	538[130]	
Units: subject				
Week 26	508	438	276	
Week 52	494	423	254	

Notes:

[128] - ITT population

[129] - ITT population

[130] - ITT population

Statistical analyses

Statistical analysis title	1_Btw grp analysis, SGRQ score ≤-4, Wk 26; A vs B

Statistical analysis description:

Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 26).

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 26.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)

Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[131]
P-value	= 0.002
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.57

Notes:

[131] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Statistical analysis title	2_Btw grp analysis, SGRQ score ≤-4, Wk 26; A vs C

Statistical analysis description:

Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 26).

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 26.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[132]
P-value	= 0.049
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1

Notes:

[132] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Statistical analysis title	3_Btw grp analysis, SGRQ score ≤-4, Wk 26; C vs B

Statistical analysis description:

Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 26).

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 26.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[133]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	2.02

Notes:

[133] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Statistical analysis title	4_Btw grp analysis, SGRQ score ≤-4, Wk 52; A vs B

Statistical analysis description:

Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 52).

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 52.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2151
Analysis specification	Pre-specified
Analysis type	other[134]
P-value	= 0.002
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.59

Notes:

[134] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Statistical analysis title	5_Btw grp analysis, SGRQ score ≤-4, Wk 52; A vs C

Statistical analysis description:

Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 52).

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 52.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	other[135]
P-value	= 0.373
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.13

Notes:

[135] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Statistical analysis title	6_Btw grp analysis, SGRQ score ≤-4, Wk 52; C vs B

Statistical analysis description:

Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 52).

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 52.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	other[136]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	1.83

Notes:

[136] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Secondary: 16_Change from baseline for percentage of days without intake of rescue medication

End point title	16_Change from baseline for percentage of days without intake of rescue medication

End point description:

Days without intake of rescue medication.

Change from baseline to each inter-visit period and for the entire treatment period (Week 1-52) in the percentage of days without intake of rescue medication.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (W) interval.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 26, 40, 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1038[137]	1015[138]	513[139]	
Units: days				
least squares mean (confidence interval				

95%)				
Week 1-4	13.89 (12.14 to 15.63)	5.81 (4.05 to 7.57)	13.08 (10.6 to 15.56)	
Week 5-12	14.51 (12.6 to 16.42)	6.22 (4.28 to 8.16)	14.48 (11.76 to 17.19)	
Week 13-26	14.14 (12.12 to 16.17)	5.47 (3.41 to 7.53)	15.03 (12.16 to 17.9)	
Week 27-40	14.23 (12.12 to 16.33)	5.06 (2.91 to 7.22)	15.62 (12.63 to 18.61)	
Week 41-52	12.89 (10.77 to 15.01)	4.11 (1.94 to 6.29)	14.13 (11.12 to 17.14)	
Week 1-52	13.91 (12.04 to 15.79)	5.19 (3.28 to 7.1)	14.75 (12.08 to 17.41)	

Notes:

[137] - ITT
W 1-4 n=1034
W 5-12 n=1018
W 13-26 n=1004
W 27-40 n=978
W 41-52 n=964
W 1-52 n=1038

[138] - ITT
W 1-4 n=1009
W 5-12 n=970
W 13-26 n=954
W 27-40 n=907
W 41-52 n=894
W 1-52 n=1015

[139] - ITT
W 1-4 n=509
W 5-12 n=507
W 13-26 n=497
W 27-40 n=486
W 41-52 n=480
W 1-52 n=513

Attachments (see zip file)	Figure 15_Trinity_without rescue med.pdf

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treat groups W 1-52; A vs B

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.

The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Adjusted mean change from baseline in percentage of days without rescue medication use for each inter-visit period in the ITT population, is shown in the attached Figure.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2053
Analysis specification	Pre-specified
Analysis type	other[140]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	8.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.05
upper limit	11.4

Notes:

[140] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

Statistical analysis title	2_Adj mean diffr btw treat groups W 1-52; A vs C

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.

The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Adjusted mean change from baseline in percentage of days without rescue medication use for each inter-visit period in the ITT population, is shown in the attached Figure.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)
Number of subjects included in analysis	1551
Analysis specification	Pre-specified
Analysis type	other[141]
P-value	= 0.616
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.09
upper limit	2.42

Notes:

[141] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

Statistical analysis title	3_Adj mean diffr btw treat groups W 1-52; C vs B

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.

The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Adjusted mean change from baseline in percentage of days without rescue medication use for each inter-visit period in the ITT population, is shown in the attached Figure.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1528
Analysis specification	Pre-specified
Analysis type	other[142]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	9.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.28
upper limit	12.83

Notes:

[142] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

Secondary: 17_Change from baseline for the average use of rescue medication

End point title	17_Change from baseline for the average use of rescue medication

End point description:

Average use of rescue medication.

Change from baseline to each inter-visit period and for the entire treatment period (Week 1-52) in the average use of rescue medication (number of puffs/day).

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (W) interval.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 26, 40, 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1038[143]	1015[144]	513[145]	
Units: puffs/day				
least squares mean (confidence interval 95%)				
Week 1-4	-0.53 (-0.62 to -0.45)	-0.03 (-0.11 to 0.06)	-0.56 (-0.68 to -0.44)	
Week 5-12	-0.51 (-0.61 to -0.41)	0 (-0.1 to 0.1)	-0.59 (-0.73 to -0.45)	
Week 13-26	-0.5 (-0.61 to -0.4)	0.06 (-0.05 to 0.16)	-0.57 (-0.71 to -0.42)	
Week 27-40	-0.47 (-0.59 to -0.36)	0.14 (0.02 to 0.25)	-0.54 (-0.7 to -0.38)	
Week 41-52	-0.42 (-0.53 to -0.3)	0.2 (0.08 to 0.32)	-0.46 (-0.63 to -0.3)	
Week 1-52	-0.48 (-0.58 to -0.38)	0.1 (-0.01 to 0.2)	-0.54 (-0.68 to -0.4)	

Notes:

[143] - ITT
W 1-4 n=1034
W 5-12 n=1018
W 13-26 n=1004
W 27-40 n=978
W 41-52 n=964
W 1-52 n=1038

[144] - ITT
W 1-4 n=1009
W 5-12 n=970
W 13-26 n=954
W 27-40 n=907
W 41-52 n=894
W 1-52 n=1015
[145] - ITT
W 1-4 n=509
W 5-12 n=507
W 13-26 n=497
W 27-40 n=486
W 41-52 n=480
W 1-52 n=513

Attachments (see zip file)	Figure 16_Trinity_with rescue med.pdf

Statistical analyses

Statistical analysis title	1_Adj mean diffr btw treat groups W 1-52; A vs B

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.

The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Adjusted mean change from baseline in average use of rescue medication (puffs/day) for each inter-visit period in the ITT population, is shown in the attached Figure.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	2053
Analysis specification	Pre-specified
Analysis type	other[146]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	-0.43

Notes:

[146] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	2_Adj mean diffr btw treat groups W 1-52; A vs C

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.

The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Adjusted mean change from baseline in average use of rescue medication (puffs/day) for each inter-visit period in the ITT population, is shown in the attached Figure.

Comparison groups	Treatment A: CHF 5993 pMDI (100/6/12.5µg) v Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)

Number of subjects included in analysis	1551
Analysis specification	Pre-specified
Analysis type	other[147]
P-value	= 0.495
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.23

Notes:

[147] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	3_Adj mean diffr btw treat groups W 1-52; C vs B

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.

The correct number of participating subjects for this statistical comparison is shown in the footnote of the table containing 'End point values'.

Adjusted mean change from baseline in average use of rescue medication (puffs/day) for each inter-visit period in the ITT population, is shown in the attached Figure.

Comparison groups	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg) v Treatment B: Tiotropium (18µg)
Number of subjects included in analysis	1528
Analysis specification	Pre-specified
Analysis type	other[148]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.46

Notes:

[148] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Secondary: 18_Vital signs: Systolic blood pressure

End point title	18_Vital signs: Systolic blood pressure

End point description:

Systolic Blood Pressure.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 0, Week 26, and Week 52).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[149]	1075[150]	537[151]	
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Week 0, 10 min post-dose	0.3 (0 to 0.7)	0.4 (0 to 0.8)	0.4 (-0.1 to 0.9)	
Week 26, pre-dose	0.2 (-0.5 to 0.8)	0.5 (-0.2 to 1.2)	-0.1 (-1 to 0.8)	
Week 26, 10 min post-dose	0.3 (-0.4 to 0.9)	0.4 (-0.3 to 1.1)	0.1 (-0.8 to 1)	
Week 52, pre-dose	0.5 (-0.2 to 1.2)	0.1 (-0.6 to 0.9)	-0.2 (-1.2 to 0.8)	
Week 52, 10 min post-dose	0.4 (-0.3 to 1.1)	0.3 (-0.5 to 1)	0.1 (-0.9 to 1.1)	

Notes:

[149] - Safety pop
W 0 post n=1069
W 26 pre n=1028
W 26 post n=1018
W 52 pre n=988
W 52 post n=986

[150] - Safety pop N=1076
W 0 post n=1071
W 26 pre n=978
W 26 post n=954
W 52 pre n=923
W 52 post n=911

[151] - Safety pop
W 0 post n=536
W 26 pre n=512
W 26 post n=507
W 52 pre n=497
W 52 post n=495

Statistical analyses

No statistical analyses for this end point

Secondary: 19_Vital signs: Diastolic blood pressure

End point title	19_Vital signs: Diastolic blood pressure

End point description:

Diastolic Blood Pressure.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and

10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 0, Week 26, and Week 52).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[152]	1075[153]	537[154]	
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Week 0, 10 min post-dose	-0.2 (-0.5 to 0.1)	0 (-0.3 to 0.3)	0.4 (-0.1 to 0.8)	
Week 26, pre-dose	-0.1 (-0.6 to 0.4)	0.3 (-0.2 to 0.8)	-0.5 (-1.2 to 0.2)	
Week 26, 10 min post-dose	-0.1 (-0.6 to 0.3)	0.1 (-0.4 to 0.6)	-0.4 (-1.1 to 0.3)	
Week 52, pre-dose	0 (-0.5 to 0.5)	0.4 (-0.2 to 0.9)	0.1 (-0.7 to 0.8)	
Week 52, 10 min post-dose	-0.5 (-1 to 0)	0.1 (-0.4 to 0.6)	-0.2 (-1 to 0.5)	

Notes:

[152] - Safety pop
W 0 post n=1069
W 26 pre n=1028
W 26 post n=1018
W 52 pre n=988
W 52 post n=986

[153] - Saf pop N=1076
W 0 post n=1071
W 26 pre n=978
W 26 post n=954
W 52 pre n=923
W 52 post n=911

[154] - Safety pop
W 0 post n=536
W 26 pre n=512
W 26 post n=507
W 52 pre n=497
W 52 post n=495

Statistical analyses

No statistical analyses for this end point

Secondary: 20_Vital signs: Body mass index

End point title	20_Vital signs: Body mass index

End point description:

Body Mass Index.

Results represent changes from baseline (Week 0), on Week 26 and Week 52.

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[155]	1075[156]	537[157]	
Units: kg/m2				
arithmetic mean (confidence interval 95%)				
Week 26	0.04 (-0.02 to 0.1)	0.05 (-0.02 to 0.12)	0.02 (-0.06 to 0.11)	
Week 52	0.01 (-0.07 to 0.09)	0.06 (-0.01 to 0.14)	-0.04 (-0.16 to 0.08)	

Notes:

[155] - Safety population
Wk 26 n=1028
Wk 52 n=988

[156] - Safety population actual N=1076
Wk 26 n=976
Wk 52 n=923

[157] - Safety population
Wk 26 n=512
Wk 52 n=497

Statistical analyses

No statistical analyses for this end point

Secondary: 21_Electrocardiogram parameters: Heart rate

End point title	21_Electrocardiogram parameters: Heart rate

End point description:

Electrocardiogram parameter: Heart Rate.

Results represent changes from screening (Week -2), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Screening (Week -2) to Week 26, 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[158]	1075[159]	537[160]	
Units: bpm				
arithmetic mean (standard deviation)				
Week 26, pre-dose	-1.42 (± 11.59)	1.54 (± 11.81)	-0.11 (± 11.31)	
Week 26, 10 min post-dose	-3.4 (± 11.41)	-1.3 (± 11.93)	-2.03 (± 12)	
Week 52, pre-dose	-0.6 (± 11.61)	2.5 (± 12.21)	0.63 (± 12.25)	
Week 52, 10 min post-dose	-1.9 (± 11.65)	0.42 (± 12.21)	-1.25 (± 12.28)	

Notes:

[158] - Safety population
W 26 pre n=1015
W 26 post n=983
W 52 pre n=963
W 52 post n=958

[159] - Safety population actual N=1076
W 26 pre n=978
W 26 post n=911
W 52 pre n=903
W 52 post n=880

[160] - Safety population
W 26 pre n=504
W 26 post n=491
W 52 pre n=486
W 52 post n=485

Statistical analyses

No statistical analyses for this end point

Secondary: 22_Electrocardiogram parameters: QTcF interval

End point title	22_Electrocardiogram parameters: QTcF interval

End point description:

Electrocardiogram parameter: QTcF (Fridericia's Corrected QT Interval).

Results represent changes from screening (Week -2), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Screening (Week -2) to Week 26, 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[161]	1075[162]	537[163]	
Units: msec				
arithmetic mean (standard deviation)				
Week 26, pre-dose	-0.54 (± 17.17)	0.85 (± 16.24)	-0.63 (± 17.3)	
Week 26, 10 min post-dose	-0.14 (± 18.93)	-0.95 (± 17.55)	-0.64 (± 19.47)	
Week 52, pre-dose	0.1 (± 17.08)	-0.51 (± 17.68)	-1.83 (± 19.89)	
Week 52, 10 min post-dose	0.23 (± 17.63)	-0.58 (± 17.65)	-1.19 (± 17.84)	

Notes:

[161] - Safety population
W 26 pre n=1015
W 26 post n=983
W 52 pre n=963
W 52 post n=958

[162] - Safety population actual N=1076
W 26 pre n=977
W 26 post n=911
W 52 pre n=903
W 52 post n=880

[163] - Safety population
W 26 pre n=503
W 26 post n=490
W 52 pre n=486
W 52 post n=485

Statistical analyses

No statistical analyses for this end point

Secondary: 23_Electrocardiogram parameters: PR interval

End point title	23_Electrocardiogram parameters: PR interval

End point description:

Electrocardiogram parameter: PR interval

Results represent changes from screening (Week -2), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Screening (Week -2) to Week 26, 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[164]	1075[165]	537[166]	
Units: msec				
arithmetic mean (standard deviation)				
Week 26, pre-dose	0.56 (± 15.23)	0.25 (± 13.72)	1 (± 14.79)	
Week 26, 10 min post-dose	0.31 (± 14.67)	0.53 (± 13.57)	0.78 (± 15.38)	
Week 52, pre-dose	1.46 (± 14.92)	0.39 (± 15.84)	2.27 (± 15.96)	
Week 52, 10 min post-dose	0.35 (± 15.19)	0.5 (± 16.13)	1.94 (± 15.6)	

Notes:

[164] - Safety population
W 26 pre n=1014
W 26 post n=982
W 52 pre n=962
W 52 post n=958

[165] - Safety population actual N=1076
W 26 pre n=976
W 26 post n=910
W 52 pre n=901
W 52 post n=878

[166] - Safety population
W 26 pre n=502
W 26 post n=490
W 52 pre n=486
W 52 post n=485

Statistical analyses

No statistical analyses for this end point

Secondary: 24_Electrocardiogram parameters: QRS interval

End point title	24_Electrocardiogram parameters: QRS interval

End point description:

Electrocardiogram parameter: QRS interval

Results represent changes from screening (Week -2), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

Due to the limitations of the EudraCT database, the number of subjects analysed in the Treatment B group cannot be correctly reported in the table below. The correct number is specified in a note to the table.

End point type	Secondary

End point timeframe:

Screening (Week -2) to Week 26, 52.

End point values	Treatment A: CHF 5993 pMDI (100/6/12.5µg)	Treatment B: Tiotropium (18µg)	Treatment C: CHF 1535 pMDI (100/6µg) + Tiotropium (18µg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1077[167]	1075[168]	537[169]	
Units: msec				
arithmetic mean (standard deviation)				
Week 26, pre-dose	0.69 (± 7.8)	0.24 (± 8.14)	0.51 (± 7.26)	
Week 26, 10 min post-dose	0.88 (± 7.18)	0.16 (± 7.49)	0.91 (± 7.55)	
Week 52, pre-dose	0.74 (± 8.14)	0.79 (± 8.57)	0.78 (± 8.67)	
Week 52, 10 min post-dose	1.07 (± 8.46)	0.63 (± 8.8)	0.8 (± 8.17)	

Notes:

[167] - Safety population
W 26 pre n=1015
W 26 post n=983
W 52 pre n=963
W 52 post n=958

[168] - Safety population actual N=1076
W 26 pre n=978
W 26 post n=911
W 52 pre n=902
W 52 post n=879

[169] - Safety population
W 26 pre n=504
W 26 post n=491
W 52 pre n=486
W 52 post n=485

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Treatment A: fixed combination CHF 5993 pMDI (400/24/50µg/d)
Reporting group description: -	
Reporting group title	Treatment B: Tiotropium (18µg/d)
Reporting group description: -	
Reporting group title	Treatment C: CHF 1535 pMDI (400/24µg/d) + Tiotropium (18µg/d)

Reporting group description: -

Serious adverse events	Treatment A: fixed combination CHF 5993 pMDI (400/24/50µg/d)	Treatment B: Tiotropium (18µg/d)	Treatment C: CHF 1535 pMDI (400/24µg/d) + Tiotropium (18µg/d)
Total subjects affected by serious adverse events			
subjects affected / exposed	140 / 1077 (13.00%)	164 / 1076 (15.24%)	68 / 537 (12.66%)
number of deaths (all causes)	20	29	8
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1077 (0.00%)	2 / 1076 (0.19%)	0 / 537 (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
Bladder cancer			
subjects affected / exposed	1 / 1077 (0.09%)	1 / 1076 (0.09%)	2 / 537 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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

Bronchial carcinoma			
subjects affected / exposed	1 / 1077 (0.09%)	2 / 1076 (0.19%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Craniopharyngioma			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Gallbladder neoplasm			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Hepatic cancer			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Lung neoplasm			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Lung neoplasm malignant			

subjects affected / exposed	2 / 1077 (0.19%)	2 / 1076 (0.19%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Metastatic gastric cancer			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nasal sinus cancer			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Prostate cancer			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage IV			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Small cell lung cancer			
subjects affected / exposed	2 / 1077 (0.19%)	0 / 1076 (0.00%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 1077 (0.00%)	2 / 1076 (0.19%)	0 / 537 (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
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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			
Aortic aneurysm			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial thrombosis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Arteriosclerosis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Embolism			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Hypertensive crisis			
subjects affected / exposed	2 / 1077 (0.19%)	0 / 1076 (0.00%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 1077 (0.19%)	0 / 1076 (0.00%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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			
Death			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Facial pain			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Multi-organ failure			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Non-cardiac chest pain			

subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Sudden death			
subjects affected / exposed	2 / 1077 (0.19%)	2 / 1076 (0.19%)	2 / 537 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 2
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	76 / 1077 (7.06%)	100 / 1076 (9.29%)	35 / 537 (6.52%)
occurrences causally related to treatment / all	0 / 90	0 / 124	0 / 40
deaths causally related to treatment / all	0 / 5	0 / 4	0 / 1
Epistaxis			
subjects affected / exposed	1 / 1077 (0.09%)	1 / 1076 (0.09%)	0 / 537 (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
Haemothorax			

subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Interstitial lung disease			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Mediastinal disorder			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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 / 1077 (0.09%)	1 / 1076 (0.09%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 1077 (0.09%)	1 / 1076 (0.09%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	3 / 1077 (0.28%)	1 / 1076 (0.09%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Abdominal injury			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Brain contusion			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Chest injury			
subjects affected / exposed	0 / 1077 (0.00%)	2 / 1076 (0.19%)	0 / 537 (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
Femur fracture			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Fibula fracture			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Hand fracture			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Hip fracture			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Humerus fracture			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Incisional hernia			

subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Tongue injury			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Toxicity to various agents			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Acute myocardial infarction			

subjects affected / exposed	2 / 1077 (0.19%)	2 / 1076 (0.19%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 1077 (0.09%)	2 / 1076 (0.19%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Atrial fibrillation			
subjects affected / exposed	2 / 1077 (0.19%)	2 / 1076 (0.19%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Cardiac arrest			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			

subjects affected / exposed	3 / 1077 (0.28%)	3 / 1076 (0.28%)	2 / 537 (0.37%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 1077 (0.00%)	4 / 1076 (0.37%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 1077 (0.09%)	1 / 1076 (0.09%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	1 / 1077 (0.09%)	2 / 1076 (0.19%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	1 / 1077 (0.09%)	3 / 1076 (0.28%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Cor pulmonale chronic			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Coronary artery disease			
subjects affected / exposed	2 / 1077 (0.19%)	4 / 1076 (0.37%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Myocardial infarction			

subjects affected / exposed	2 / 1077 (0.19%)	1 / 1076 (0.09%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	3 / 1077 (0.28%)	1 / 1076 (0.09%)	3 / 537 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Cerebellar ischaemia			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Cerebral infarction			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 1077 (0.09%)	1 / 1076 (0.09%)	0 / 537 (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
Embolic cerebral infarction			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Ischaemic stroke			
subjects affected / exposed	5 / 1077 (0.46%)	1 / 1076 (0.09%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Radial nerve palsy			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Radicular syndrome			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Spinal cord compression			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			

subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Polycythaemia			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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 upper			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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

Dyspepsia			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Faecal incontinence			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Gastritis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Gastritis haemorrhagic			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Inguinal hernia			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Intestinal polyp haemorrhage			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Nausea			

subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Oesophagitis haemorrhagic			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Cholecystitis chronic			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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			
Intervertebral disc degeneration			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Spinal osteoarthritis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 1077 (0.00%)	0 / 1076 (0.00%)	1 / 537 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Bronchitis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Erysipelas			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Liver abscess			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Lobar pneumonia			
subjects affected / exposed	2 / 1077 (0.19%)	0 / 1076 (0.00%)	0 / 537 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Mycobacterial infection			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Pneumonia			

subjects affected / exposed	19 / 1077 (1.76%)	13 / 1076 (1.21%)	9 / 537 (1.68%)
occurrences causally related to treatment / all	0 / 19	0 / 14	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 1
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Scrotal abscess			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Sepsis			
subjects affected / exposed	1 / 1077 (0.09%)	1 / 1076 (0.09%)	0 / 537 (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
Septic shock			
subjects affected / exposed	0 / 1077 (0.00%)	1 / 1076 (0.09%)	0 / 537 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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
Gout			
subjects affected / exposed	1 / 1077 (0.09%)	0 / 1076 (0.00%)	0 / 537 (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: 5 %

Non-serious adverse events	Treatment A: fixed combination CHF 5993 pMDI (400/24/50µg/d)	Treatment B: Tiotropium (18µg/d)	Treatment C: CHF 1535 pMDI (400/24µg/d) + Tiotropium (18µg/d)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	556 / 1077 (51.62%)	565 / 1076 (52.51%)	297 / 537 (55.31%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	296 / 1077 (27.48%)	315 / 1076 (29.28%)	146 / 537 (27.19%)
occurrences (all)	411	464	218
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	57 / 1077 (5.29%)	66 / 1076 (6.13%)	20 / 537 (3.72%)
occurrences (all)	64	85	22

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported