Clinical trial results:
A 52-week, Double Blind, Double dummy, Randomized, Multinational, Multicentre, 2-arm Parallel Group, active Controlled Clinical Trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus Glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro®) via DPI in patients with Chronic Obstructive Pulmonary Disease

Summary

EudraCT number	2014-001704-22
Trial protocol	LV PT HU CZ RO DK DE AT NO PL FR BG HR IT
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	29 April 2018
First version publication date	29 April 2018

Trial information

Trial identification

Sponsor protocol code	CCD-05993AA1-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02579850
WHO universal trial number (UTN)	-
Other trial identifiers	TRIBUTE: Tribute

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	22 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2017
Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of CHF 5993 pMDI over Indacaterol/GB in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practice (GCP) guidelines in force during study conduct, and following all other requirements of local laws.

At all visits, from screening onwards, concomitant medication, adverse events (AEs) and vital signs were recorded, COPD exacerbations were assessed, pre-dose spirometry (including forced expiratory volume in the 1st second [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 COPD exacerbation-related outcomes (using the EXAcerbations of chronic pulmonary disease tool-patient reported outcome [EXACT-PRO] questionnaire). Furthermore, 12-lead electrocardiogram (ECG) parameters: heart rate (HR), Fridericia corrected QT interval (QTcF), PR interval (PR), and QRS interval (QRS) were collected at screening, Week 26 and Week 52 of treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 205
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Romania: 217
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Croatia: 30
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Bulgaria: 311
Country: Number of subjects enrolled	Czech Republic: 154
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Hungary: 86
Country: Number of subjects enrolled	Latvia: 177
Country: Number of subjects enrolled	Argentina: 64

Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Mexico: 100
Worldwide total number of subjects	1532
EEA total number of subjects	1343

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)	765
From 65 to 84 years	766
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Overall, 2103 patients were screened according to inclusion and exclusion criteria; of these, 1532 patients were randomised.

Pre-assignment

Screening details:

At the screening visit, inclusion/exclusion criteria were assessed. There were 571 screening failures. The screening visit was followed by a 2-week, open-label, run-in period during which patients self-administered indacaterol/glycopyrronium bromide (GB) (85/43 µg/day, one capsule, once daily [od]).

Period 1

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

Blinding implementation details:

An Interactive Response Technology (IRT) system was used to generate the randomisation list.

Arms

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

Arm description: -

Arm type	Experimental
Investigational medicinal product name	CHF 5993 pMDI (100/6/12.5 µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Test product: CHF 5993 pMDI, fixed-dose combination of beclometasone dipropionate (BDP) + formoterol fumarate (FF) + glycopyrronium bromide (GB).

Dose: BDP 100 µg, FF 6 µg, GB 12.5 µg per actuation, 2 puffs, twice daily (bid).

Total daily dose: BDP 400 µg, FF 24 µg, GB 50 µg.

Mode of administration: pMDI using a standard actuator.

Double-dummy design: patients in the CHF 5993 pMDI (100/6/12.5 µg) group received pMDI inhalers with CHF 5993 pMDI 100/6/12.5 µg and Breezhaler® inhalers with indacaterol/GB-matched placebo.

Patients were trained with training kits containing placebo in the proper use of pMDI.

Arm title	Indacaterol/GB (85/43 µg)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Indacaterol/GB (85/43 µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Reference product: Indacaterol/GB.

Dose: Indacaterol 85 µg, GB 43 µg, 1 inhalation, once daily (od).

Total daily dose: Indacaterol 85 µg, GB 43 µg.

Mode of administration: DPI, Breezhaler® inhaler.

Double-dummy design: patients in the Indacaterol/GB (85/43 µg) group received DPI inhalers (Breezhaler®) with indacaterol/GB 85/43 µg and pMDI inhalers with CHF 5993-matched placebo.

Patients were trained with training kits containing placebo in the proper use of the Breezhaler® inhaler for the inhalation of DPI in capsule.

Number of subjects in period 1	CHF 5993 pMDI (100/6/12.5 µg)	Indacaterol/GB (85/43 µg)
Started	764	768
Completed	666	648
Not completed	98	120
Adverse event, serious fatal	15	20
Consent withdrawn by subject	42	51
Adverse event, non-fatal	23	26
Other	1	3
Lost to follow-up	4	3
Lack of efficacy	7	12
Protocol deviation	6	5

Baseline characteristics

Reporting groups	
Reporting group title	CHF 5993 pMDI (100/6/12.5 µg)
Reporting group description: -	
Reporting group title	Indacaterol/GB (85/43 µg)
Reporting group description: -	

Reporting group values	CHF 5993 pMDI (100/6/12.5 µg)	Indacaterol/GB (85/43 µg)	Total
Number of subjects	764	768	1532
Age categorical Units: Subjects			
Adults (18-64 years)	389	376	765
From 65-84 years	374	392	766
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	64.4	64.5	
standard deviation	± 7.7	± 7.7	-
Gender categorical Units: Subjects			
Female	216	216	432
Male	548	552	1100

End points

End points reporting groups

Reporting group title	CHF 5993 pMDI (100/6/12.5 µg)
Reporting group description: -	
Reporting group title	Indacaterol/GB (85/43 µg)
Reporting group description: -	
Subject analysis set title	CHF 5993 pMDI (100/6/12.5 µg) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-to-Treat (ITT) population was defined as all randomised patients who received at least one dose of study treatment and with at least one available evaluation of efficacy after baseline.	
Subject analysis set title	Indacaterol/GB (85/43 µg) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-to-Treat (ITT) population was defined as all randomised patients who received at least one dose of study treatment and with at least one available evaluation of efficacy after baseline.	
Subject analysis set title	CHF 5993 pMDI (100/6/12.5 µg) - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per-Protocol (PP) population was defined as all patients from the ITT population without any major protocol violations (e.g. inclusion/exclusion criteria not respected, poor compliance, non-permitted medications).	
Subject analysis set title	Indacaterol/GB (85/43 µg) - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per-Protocol (PP) population was defined as all patients from the ITT population without any major protocol violations (e.g. inclusion/exclusion criteria not respected, poor compliance, non-permitted medications).	

Primary: Moderate and severe COPD exacerbation rate over 52 weeks of treatment

End point title	Moderate and severe COPD exacerbation rate over 52 weeks of treatment
End point description:	
Rate of moderate and severe COPD exacerbations evaluated over 52 weeks of treatment. The exacerbations were classified as moderate or severe as per EMA/Committee for Medicinal Products for Human Use (CHMP) guidelines definitions. A moderate COPD exacerbation was defined as a sustained worsening of the patient’s condition which required treatment with systemic corticosteroids and/or antibiotics, a severe exacerbation was one which led to hospitalisation or death. The recognition of exacerbations was facilitated by the daily recording of symptoms through the EXACT-PRO. Data are presented as adjusted exacerbation rate per patient per year.	
End point type	Primary
End point timeframe:	
Baseline to Week 52	

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT	CHF 5993 pMDI (100/6/12.5 µg) - PP	Indacaterol/GB (85/43 µg) - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	764	768	742	737
Units: Exacerbation/patient/year				
number (confidence interval 95%)	0.504 (0.447 to 0.569)	0.595 (0.530 to 0.668)	0.486 (0.430 to 0.551)	0.573 (0.508 to 0.645)

Statistical analyses

Statistical analysis title	Adjusted exacerbation rate ratio - ITT population

Statistical analysis description:

The number of moderate and severe COPD exacerbations was analysed using a negative binomial model including treatment, country, number of COPD exacerbations during the previous year (1, >1), severity of airflow limitation and smoking status as fixed effects and log-time on study in years as an offset. The adjusted exacerbation rate in each treatment group and the adjusted rate ratio (CHF 5993 pMDI / Indacaterol/GB) with associated 95% Wald confidence intervals (CIs) were estimated by the model.

Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - ITT v Indacaterol/GB (85/43 µg) - ITT
Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.043
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.848
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.723
upper limit	0.995

Notes:

[1] - Superiority of CHF 5993 pMDI over indacaterol/GB was demonstrated if the upper limit of the 95% CI for the adjusted exacerbation rate ratio was <1.

Statistical analysis title	Adjusted exacerbation rate ratio - PP population

Statistical analysis description:

The number of moderate and severe COPD exacerbations was analysed using a negative binomial model including treatment, country, number of COPD exacerbations during the previous year (1, >1), severity of airflow limitation and smoking status as fixed effects and log-time on study in years as an offset. The adjusted exacerbation rate in each treatment group and the adjusted rate ratio (CHF 5993 pMDI / Indacaterol/GB) with associated 95% Wald confidence intervals (CIs) were estimated by the model.

Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - PP v Indacaterol/GB (85/43 µg) - PP
Number of subjects included in analysis	1479
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.05
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.849

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.721
upper limit	1

Notes:

[2] - Superiority of CHF 5993 pMDI over indacaterol/GB was demonstrated if the upper limit of the 95% CI for the adjusted exacerbation rate ratio was <1.

Secondary: Severe COPD exacerbation rate over 52 weeks of treatment

End point title	Severe COPD exacerbation rate over 52 weeks of treatment

End point description:

Rate of severe COPD exacerbations evaluated over 52 weeks of treatment. The exacerbations were classified as moderate or severe as per EMA/CHMP guidelines definitions. A severe exacerbation was one which led to hospitalisation or death. The recognition of exacerbations was facilitated by the daily recording of symptoms through the EXACT-PRO.

Data are presented as adjusted exacerbation rate per patient per year.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: Exacerbation/patient/year				
number (confidence interval 95%)	0.074 (0.055 to 0.099)	0.094 (0.072 to 0.123)		

Statistical analyses

Statistical analysis title	Adjusted exacerbation rate ratio

Statistical analysis description:

The number of severe COPD exacerbations was analysed using a negative binomial model including treatment, country, number of COPD exacerbations during the previous year (1, >1), severity of airflow limitation and smoking status as fixed effects and log-time on study in years as an offset. The adjusted exacerbation rate in each treatment group and the adjusted rate ratio (CHF 5993 pMDI / Indacaterol/GB) with associated 95% Wald confidence intervals (CIs) were estimated by the model.

Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - ITT v Indacaterol/GB (85/43 µg) - ITT
Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.189
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.787

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.551
upper limit	1.125

Notes:

[3] - Superiority of CHF 5993 pMDI over indacaterol/GB was demonstrated if the upper limit of the 95% CI for the adjusted exacerbation rate ratio was <1.

Secondary: Moderate COPD exacerbation rate over 52 weeks of treatment

End point title	Moderate COPD exacerbation rate over 52 weeks of treatment

End point description:

Rate of moderate COPD exacerbations evaluated over 52 weeks of treatment. The exacerbations were classified as moderate or severe as per EMA/CHMP guidelines definitions. A moderate COPD exacerbation was defined as a sustained worsening of the patient's condition which required treatment with systemic corticosteroids and/or antibiotics. The recognition of exacerbations was facilitated by the daily recording of symptoms through the EXACT-PRO.

Data are presented as adjusted exacerbation rate per patient per year.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: Exacerbation/patient/year				
number (confidence interval 95%)	0.408 (0.356 to 0.468)	0.471 (0.413 to 0.537)		

Statistical analyses

Statistical analysis title	Adjusted exacerbation rate ratio

Statistical analysis description:

The number of moderate COPD exacerbations was analysed using a negative binomial model including treatment, country, number of COPD exacerbations during the previous year (1, >1), severity of airflow limitation and smoking status as fixed effects and log-time on study in years as an offset. The adjusted exacerbation rate in each treatment group and the adjusted rate ratio (CHF 5993 pMDI / Indacaterol/GB) with associated 95% Wald confidence intervals (CIs) were estimated by the model.

Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - ITT v Indacaterol/GB (85/43 µg) - ITT
Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.118
Method	Negative binomial model
Parameter estimate	Adjusted rate ratio
Point estimate	0.866

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.723
upper limit	1.037

Notes:

[4] - Superiority of CHF 5993 pMDI over indacaterol/GB was demonstrated if the upper limit of the 95% CI for the adjusted exacerbation rate ratio was <1.

Secondary: Time to first severe COPD exacerbation

End point title	Time to first severe COPD exacerbation

End point description:

The number of patients experiencing a severe exacerbation during the 52-week treatment period is presented.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: patients	62	69		

Statistical analyses

Statistical analysis title	Time to first exacerbation (hazard ratio)

Statistical analysis description:

Time to first severe COPD exacerbation was analysed using a regression model including treatment, country, number of COPD exacerbations during the previous year. Shown is the hazard ratio for CHF 5339 pMDI / Indacaterol/GB.

Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - ITT v Indacaterol/GB (85/43 µg) - ITT
Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.405
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.864
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.613
upper limit	1.219

Secondary: Time to first moderate or severe COPD exacerbation

End point title	Time to first moderate or severe COPD exacerbation
End point description:	
The number of patients experiencing a moderate or severe exacerbation during the 52-week treatment period is presented.	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: patients	273	288		

Statistical analyses

Statistical analysis title	Time to first exacerbation (hazard ratio)
Statistical analysis description:	
Time to first moderate or severe COPD exacerbation was analysed using a regression model including treatment, country, number of COPD exacerbations during the previous year. Shown is the hazard ratio for CHF 5339 pMDI / Indacaterol/GB.	
Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - ITT v Indacaterol/GB (85/43 µg) - ITT
Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.901
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	1.064

Secondary: Change from baseline in SGRQ total score at Week 52

End point title	Change from baseline in SGRQ total score at Week 52

End point description:

St. George's Respiratory Questionnaire (SGRQ) total score. SGRQ is a questionnaire developed to measure health in chronic airflow limitation. The total score for SGRQ was calculated, whereby lower scores correspond to better health. Data are presented as least squares mean change from baseline at Week 52. Shown are the number of patients in the ITT population (N) and the number of patients with available results (n).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	760[5]	763[6]		
Units: SGRQ total score				
least squares mean (confidence interval 95%)	-3.49 (-4.36 to -2.63)	-1.85 (-2.72 to -0.98)		

Notes:

[5] - N=764; n=760

[6] - N=768; n=763

Statistical analyses

Statistical analysis title	LS mean difference in change from baseline in SGRQ

Statistical analysis description:

Least squares mean difference in change from baseline in SGRQ total score at Week 52.

Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) - ITT v Indacaterol/GB (85/43 µg) - ITT
Number of subjects included in analysis	1523
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.009
Method	Mixed model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	-1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	-0.42

Notes:

[7] - Change from baseline in SGRQ total score at Week 52 analysed using a linear mixed model for repeated measures (MMRM) including treatment, country, visit, treatment by visit interaction, number of COPD exacerbations during the previous year (1, > 1), severity of airflow limitation and smoking status as fixed effects, and baseline and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed.

Secondary: SGRQ response at Week 26

End point title	SGRQ response at Week 26

End point description:

SGRQ response was 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 total score. Patients with missing data at Week 26 were considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: patients				
Responder	310	292		

Statistical analyses

No statistical analyses for this end point

Secondary: SGRQ response at Week 52

End point title	SGRQ response at Week 52

End point description:

SGRQ response was 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 total score. Patients with missing data at Week 52 were considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: patients				
Responders	311	279		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose morning FEV1 over 52 weeks of treatment

End point title	Change from baseline in pre-dose morning FEV1 over 52 weeks of treatment

End point description:

Change from baseline in pre-dose morning FEV1 over 52 weeks of treatment. FEV1 is the volume of air that can be forced out in the first second after taking a deep breath. Data are presented as LS mean change from baseline averaged over 52 weeks of treatment. Shown are the number of patients in the ITT population (N) and the number of patients with available results (n).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	757[8]	760[9]		
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.003 (-0.016 to 0.010)	-0.026 (-0.039 to -0.013)		

Notes:

[8] - N=764; n=757

[9] - N=768; n=760

Statistical analyses

Statistical analysis title	LS mean difference in change from baseline
Comparison groups	Indacaterol/GB (85/43 µg) - ITT v CHF 5993 pMDI (100/6/12.5 µg) - ITT
Number of subjects included in analysis	1517
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.018
Method	Mixed model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.04

Notes:

[10] - Changes from baseline in pre-dose morning FEV1 were analysed using a linear MMRM including treatment, country, visit, treatment by visit interaction, number of COPD exacerbations during the previous year (1, > 1), severity of airflow limitation and smoking status as fixed effects, and baseline and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed.

Secondary: FEV1 response at Week 26

End point title	FEV1 response at Week 26

End point description:

FEV1 response was 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. Patients with missing data at Week 26 were considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: patients				
Responders	176	156		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 response at Week 52

End point title	FEV1 response at Week 52

End point description:

FEV1 response was 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. Patients with missing data at Week 52 were considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	764	768		
Units: patients				
Responders	145	125		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose morning FVC over 52 weeks of treatment

End point title	Change from baseline in pre-dose morning FVC over 52 weeks of treatment

End point description:

Change from baseline in pre-dose morning FVC over 52 weeks of treatment. FVC is the volume of air that can be forced out after taking a deep breath. Data are presented as LS mean change from baseline over 52 weeks. Shown are the number of patients in the ITT population (N) and the number of patients with available results (n).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	757[11]	760[12]		
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.058 (-0.082 to -0.034)	-0.082 (-0.106 to -0.058)		

Notes:

[11] - N=764; n=757

[12] - N=768; n=760

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CAT score at Week 52

End point title	Change from baseline in CAT score at Week 52

End point description:

The COPD assessment test (CAT) is a questionnaire developed to measure manifestations of COPD, lower scores correspond to better health. Data are presented as arithmetic mean change from baseline. Shown are the number of patients included in the ITT population (N) and the number of patients with available results for each visit (n).

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Week 52)

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	700[13]	704[14]		
Units: CAT score				
arithmetic mean (standard deviation)	-0.8 (± 5.8)	-0.6 (± 6.2)		

Notes:

[13] - N=764; n=700

[14] - N=768; n=704

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in E-RS score over 52 weeks of treatment

End point title	Change from baseline in E-RS score over 52 weeks of treatment

End point description:

The Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (E-RS) is a derivative of the EXACT-PRO questionnaire, developed to evaluate the effect of treatment on respiratory symptom severity in patients with COPD, i.e. to test the extent to which treatments improve respiratory symptoms also when patients are stable/non exacerbating. Higher scores correspond to a more severe health status.

Data are presented as arithmetic mean change from baseline over the entire treatment period (Week 1-52). Shown are the number of patients in the ITT population (N) and the number of patients with available results (n).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	755[15]	761[16]		
Units: E-RS score				
arithmetic mean (standard deviation)	-0.72 (± 3.85)	-0.44 (± 4.02)		

Notes:

[15] - N=764; n=755

[16] - N=768; n=761

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of days, night and complete days (day + night) without rescue medication over the entire treatment period

End point title	Change from baseline in percentage of days, night and complete days (day + night) without rescue medication over the entire treatment period

End point description:

Change from baseline in percentage of days, nights and complete days (day + night) without rescue medication over the entire treatment period. Rescue medication use was recorded daily and averaged over the entire treatment period. Data are presented as arithmetic mean change from baseline over the entire treatment period (Week 1-52). Shown are the number of patients in the ITT population (N) and the number of patients with available results for each category (n).

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period)

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	752[17]	756[18]		
Units: Percentage				
arithmetic mean (standard deviation)				
Days	5.64 (± 29.30)	6.86 (± 31.10)		
Nights	8.66 (± 31.40)	6.79 (± 31.48)		
Complete days	8.39 (± 29.41)	9.42 (± 31.46)		

Notes:

[17] - N=764; Days n=755; Nights n=757; Complete days n=752

[18] - N=768; Days n=761; Nights n=761; Complete days n=756

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EXACT-PRO nocturnal symptoms score averaged over the treatment period

End point title	Change from baseline in EXACT-PRO nocturnal symptoms score averaged over the treatment period

End point description:

The EXACT-PRO is a validated, patient-reported outcome measure to evaluate exacerbation-related outcomes of COPD treatment using an electronic real-time-based technology. The patient's health status is correlated to the global score meaning higher score corresponds to more severe health status. The EXACT-PRO item 13, was completed to verify the status of patients' nocturnal symptoms.

Data are presented as arithmetic mean change from baseline over the entire treatment period (Week 1-52). Shown are the number of patients in the ITT population (N) and the number of patients with available results (n).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	CHF 5993 pMDI (100/6/12.5 µg) - ITT	Indacaterol/GB (85/43 µg) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	757[19]	761[20]		
Units: score				
arithmetic mean (standard deviation)	-0.05 (± 0.50)	-0.04 (± 0.48)		

Notes:

[19] - N=764, n=757

[20] - N=768, n=761

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	CHF 5993 pMDI (100/6/12.5 µg)
Reporting group description: -	
Reporting group title	Indacaterol/GB (85/43 µg)

Reporting group description: -

Serious adverse events	CHF 5993 pMDI (100/6/12.5 µg)	Indacaterol/GB (85/43 µg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	117 / 764 (15.31%)	130 / 768 (16.93%)	
number of deaths (all causes)	16	21	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			

subjects affected / exposed	2 / 764 (0.26%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 764 (0.13%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			

subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	4 / 764 (0.52%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Phyllodes tumour			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			

subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential hypertension			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: The PT "death" corresponds to cases where the cause of death was unknown.		
subjects affected / exposed	2 / 764 (0.26%)	3 / 768 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Facial pain			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 764 (0.00%)	3 / 768 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Sudden death			
subjects affected / exposed	1 / 764 (0.13%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Acute respiratory failure			
subjects affected / exposed	2 / 764 (0.26%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 764 (0.13%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	Additional description: COPD is the PT for the reported "COPD exacerbation".		
subjects affected / exposed	61 / 764 (7.98%)	69 / 768 (8.98%)	
occurrences causally related to treatment / all	0 / 75	0 / 94	
deaths causally related to treatment / all	0 / 2	0 / 2	
Chronic respiratory failure			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	2 / 764 (0.26%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory distress			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 764 (0.13%)	3 / 768 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			

subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Post procedural complication			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congenital, familial and genetic disorders			
Porphyria non-acute			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 764 (0.00%)	5 / 768 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 4	
Aortic valve stenosis			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Atrial fibrillation			
subjects affected / exposed	0 / 764 (0.00%)	5 / 768 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atrial flutter			
subjects affected / exposed	0 / 764 (0.00%)	3 / 768 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	2 / 764 (0.26%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 764 (0.13%)	3 / 768 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid sinus syndrome			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 764 (0.26%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Diabetic coma			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 764 (0.13%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Retinal detachment			
subjects affected / exposed	2 / 764 (0.26%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis chronic			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 764 (0.00%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periostitis			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 764 (0.00%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			

subjects affected / exposed	1 / 764 (0.13%)	2 / 768 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	16 / 764 (2.09%)	10 / 768 (1.30%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection bacterial			

subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	0 / 764 (0.00%)	1 / 768 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 764 (0.13%)	0 / 768 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CHF 5993 pMDI (100/6/12.5 µg)	Indacaterol/GB (85/43 µg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	453 / 764 (59.29%)	471 / 768 (61.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 764 (1.96%)	22 / 768 (2.86%)	
occurrences (all)	16	24	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 764 (5.76%)	35 / 768 (4.56%)	
occurrences (all)	50	39	
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease is the PT for the reported "COPD exacerbation"		
subjects affected / exposed	231 / 764 (30.24%)	239 / 768 (31.12%)	
occurrences (all)	369	407	
Cough			
subjects affected / exposed	13 / 764 (1.70%)	21 / 768 (2.73%)	
occurrences (all)	14	25	
Dyspnoea			
subjects affected / exposed	21 / 764 (2.75%)	21 / 768 (2.73%)	
occurrences (all)	25	23	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	21 / 764 (2.75%)	23 / 768 (2.99%)	
occurrences (all)	21	27	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	43 / 764 (5.63%)	37 / 768 (4.82%)	
occurrences (all)	56	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29429593