Clinical trial results:
A Multinational, Multicentre, Randomised, Open-Label, Active-Controlled, 26-Week, 2-Arm, Parallel Group Study to Evaluate the Non-Inferiority of Fixed Combination of Beclometasone Dipropionate Plus Formoterol Fumarate Plus Glycopyrronium Bromide Administered Via pMDI (CHF 5993) Versus Fixed Combination Of Fluticasone Furoate Plus Vilanterol Administered Via DPI (Relvar®) Plus Tiotropium Bromide (Spiriva®) for the Treatment of Patients With Chronic Obstructive Pulmonary Disease

Summary

EudraCT number	2014-001487-35
Trial protocol	SE GB LT NL HU DE BE PL
Global end of trial date	05 January 2017

Results information

Result version number	v1
This version publication date	07 January 2018
First version publication date	07 January 2018

Trial information

Trial identification

Sponsor protocol code	CCD-05993AA1-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02467452
WHO universal trial number (UTN)	-
Other trial identifiers	TRISTAR: Tristar

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Chiesi Farmaceutici S.p.A., Clinical Trial Transparency, ClinicalTrials_info@chiesi.com
Scientific contact	Chiesi Farmaceutici S.p.A., Clinical Trial Transparency, 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	07 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 January 2017
Global end of trial reached?	Yes
Global end of trial date	05 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of CHF 5993 pMDI versus fixed combination of fluticasone furoate/vilanterol plus tiotropium in terms of quality of life (change from baseline in the St. George's Respiratory Questionnaire [SGRQ] total score after 26 weeks of treatment).

Protection of trial subjects:

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

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 night-time impact of COPD, rescue medication use and compliance with treatment. 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 0 and Week 26 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	Romania: 274
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Hungary: 134
Country: Number of subjects enrolled	Lithuania: 65
Country: Number of subjects enrolled	Poland: 210
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Russian Federation: 388
Country: Number of subjects enrolled	South Africa: 33
Country: Number of subjects enrolled	Turkey: 13

Worldwide total number of subjects	1157
EEA total number of subjects	723

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)	619
From 65 to 84 years	536
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Overall, 1477 patients were screened according to inclusion and exclusion criteria; of these, 1157 patients were randomised.

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 (one 18 µg capsule inhaled, once daily [od]).

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

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

Arm title	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)

Arm description: -

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

Dosage and administration details:

Reference product: Tiotropium bromide (Spiriva®).
Dose: Tiotropium bromide 18 µg per capsule, 1 inhalation, od.
Total daily dose: Tiotropium bromide 18 µg.
Mode of administration: DPI, HandiHaler® inhaler.
Patients were trained with training kits containing placebo in the proper use of the HandiHaler® inhaler for the inhalation of DPI in capsule.

Investigational medicinal product name	Fluticasone/vilanterol (100/25 µg)
Investigational medicinal product code	
Other name	Relvar®
Pharmaceutical forms	Inhalation powder, pre-dispensed

Routes of administration	Inhalation use

Dosage and administration details:

Reference product: Fluticasone furoate/vilanterol trifenatate (Relvar®).
Dose: Fluticasone furoate 100 µg, vilanterol trifenatate 25 µg per pre-dispensed unit dose, 1 inhalation, od.
Total daily dose: Fluticasone furoate 100 µg, vilanterol trifenatate 25 µg.
Mode of administration: Dry powder inhaler (DPI), Ellipta® inhaler.

Number of subjects in period 1	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)
Started	578	579
Completed	545	549
Not completed	33	30
Adverse event, serious fatal	3	4
Consent withdrawn by subject	13	9
Adverse event, non-fatal	6	10
Other	4	1
Lost to follow-up	2	2
Lack of efficacy	2	3
Protocol deviation	3	1

Baseline characteristics

Reporting groups	
Reporting group title	CHF 5993 pMDI (100/6/12.5 µg)
Reporting group description: -	
Reporting group title	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)
Reporting group description: -	

Reporting group values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)	Total
Number of subjects	578	579	1157
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)	320	299	619
From 65-84 years	257	279	536
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	63.6	64.2	
standard deviation	± 7.7	± 7.7	-
Gender categorical Units: Subjects			
Female	133	150	283
Male	445	429	874

End points

End points reporting groups

Reporting group title	CHF 5993 pMDI (100/6/12.5 µg)
Reporting group description: -	
Reporting group title	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)
Reporting group description: -	

Primary: Change from baseline in the SGRQ total score at Week 26

End point title	Change from baseline in the SGRQ total score at Week 26
End point description:	
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 26 (95% Confidence Interval [CI]). Shown are the number of patients included in the model (Intention-to-Treat [ITT] population [N]; patients with available results [n]).	
End point type	Primary
End point timeframe:	
Baseline to Week 26	

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	553[1]	553[2]		
Units: SGRQ total score				
least squares mean (confidence interval 95%)	-6.77 (-7.91 to -5.64)	-7.82 (-8.95 to -6.68)		

Notes:

[1] - N=577; n=553

[2] - N=579; n=553

Statistical analyses

Statistical analysis title	LS mean diff in Δ from baseline in SGRQ at Week 26
Statistical analysis description:	
Least squares mean difference in change from baseline in SGRQ total score at Week 26. Primary efficacy analysis.	
Comparison groups	CHF 5993 pMDI (100/6/12.5 µg) v Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)
Number of subjects included in analysis	1106
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.204
Method	Mixed model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	2.65

Notes:

[3] - Analysis is based on a linear mixed model for repeated measures (MMRM) 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 fluticasone/vilanterol + tiotropium was demonstrated by an upper confidence limit below 4 units.

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)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[4]	579[5]		
Units: Subjects				
SGRQ responders	295	307		

Notes:

[4] - ITT population

[5] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the SGRQ total score at each visit

End point title	Change from baseline in the SGRQ total score at each visit

End point description:

SGRQ total score. Data are presented as arithmetic mean change from baseline at Week 4 and Week 12 (standard deviation; SD). Shown are the number of patients in the ITT population (N) and the number of patients with available results at each time point (n).

End point type	Secondary

End point timeframe:

Baseline to study visits (Week 4, Week 12)

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[6]	579[7]		
Units: SGRQ total score				
arithmetic mean (standard deviation)				
Week 4	-5.04 (± 13.62)	-6.62 (± 12.37)		
Week 12	-6.29 (± 14.11)	-7.32 (± 13.87)		

Notes:

[6] - N=577; Week 4 n=569; Week 12 n=565

[7] - N=579; Week 4 n=577; Week 12 n=566

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change from baseline in pre-dose morning FEV1 at Week 26. FEV1 is the volume of air that can be forced out in the first second after taking a deep breath. Data are presented as arithmetic mean change from baseline at Week 26 (SD). 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 26

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[8]	579[9]		
Units: Litres				
arithmetic mean (standard deviation)	0.059 (± 0.245)	0.109 (± 0.252)		

Notes:

[8] - N=577; n=553

[9] - N=579; n=548

Statistical analyses

No statistical analyses for this end point

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)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[10]	579[11]		
Units: Subjects				
FEV1 responders	211	248		

Notes:

[10] - ITT population

[11] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose morning FVC at Week 26

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

End point description:

Change from baseline in pre-dose morning FVC at Week 26. FVC is the volume of air that can be forced out after taking a deep breath. Data are presented as arithmetic mean change from baseline at Week 26 (SD). 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 26

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[12]	579[13]		
Units: Litres				
arithmetic mean (standard deviation)	0.03 (± 0.465)	0.096 (± 0.425)		

Notes:

[12] - N=577; n=553

[13] - N=579; n=548

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the impact of night-time COPD symptoms on sleep quality over the entire treatment period

End point title	Change from baseline in the impact of night-time COPD symptoms on sleep quality over the entire treatment period

End point description:

Change from baseline in the impact of night-time COPD symptoms on sleep quality over the entire treatment period. Impacts were evaluated daily on a 7 point Likert scale and averaged over the entire treatment period. Data are presented as arithmetic mean change from baseline over the entire treatment period (Week 1-26) (SD). 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 26 (entire treatment period)

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[14]	579[15]		
Units: Impact score				
arithmetic mean (standard deviation)	-0.200 (± 0.793)	-0.224 (± 0.754)		

Notes:

[14] - N=577; n=573

[15] - N=579; n=573

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, night 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 1-26) (SD). 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 26 (entire treatment period)

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[16]	579[17]		
Units: Percentage of days				
arithmetic mean (standard deviation)				
Days	12.94 (± 31.51)	13.94 (± 30.13)		
Nights	13.45 (± 28.50)	13.00 (± 30.61)		
Complete days	14.53 (± 30.51)	14.78 (± 29.67)		

Notes:

[16] - N=577; Days n=575; Nights n=573; Complete days n=571

[17] - N=579; Days n=573; Nights n=573; Complete days n=567

Statistical analyses

No statistical analyses for this end point

Secondary: COPD assessment test (CAT) score at baseline and Week 26

End point title	COPD assessment test (CAT) score at baseline and Week 26

End point description:

CAT score. CAT is a questionnaire developed to measure manifestations of COPD, lower scores correspond to better health. Data are presented as mean (SD). 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 Week 26

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[18]	579[19]		
Units: CAT score				
arithmetic mean (standard deviation)				
Baseline	21.8 (± 5.7)	21.8 (± 5.9)		
Week 26	19 (± 6.7)	18.4 (± 6.7)		

Notes:

[18] - N=577; Baseline n=577; Week 26 n=559

[19] - N=579; Baseline n=579; Week 26 n=560

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of moderate and severe COPD exacerbation over 26 weeks of

treatment

End point title	Rate of moderate and severe COPD exacerbation over 26 weeks of treatment

End point description:

Rate of moderate and severe COPD exacerbation evaluated over 26 weeks of treatment. 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. Data are presented as exacerbation rate per patient per year.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	577[20]	579[21]		
Units: Exacerbation/patient/year				
number (not applicable)	0.516	0.474		

Notes:

[20] - ITT population

[21] - ITT population

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	18.0

Reporting groups

Reporting group title	CHF 5993 pMDI (100/6/12.5 µg)
Reporting group description: -	
Reporting group title	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)

Reporting group description: -

Serious adverse events	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 578 (6.75%)	56 / 579 (9.67%)	
number of deaths (all causes)	3	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 578 (0.17%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
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	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant mediastinal neoplasm			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 578 (0.35%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	21 / 578 (3.63%)	31 / 579 (5.35%)	
occurrences causally related to treatment / all	0 / 26	0 / 39	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nasal disorder			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	1 / 578 (0.17%)	2 / 579 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 578 (0.17%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 578 (0.17%)	4 / 579 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vocal cord disorder			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Hepatic enzyme increased			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (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 left ventricular failure			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 578 (0.17%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Angina pectoris			
subjects affected / exposed	1 / 578 (0.17%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (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 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 578 (0.35%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid cyst			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Ileus			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
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			
Leukoplakia			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle tightness			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			

subjects affected / exposed	0 / 578 (0.00%)	2 / 579 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia	Additional description: Pneumonia includes the preferred terms of bronchopneumonia, lobar pneumonia, pneumonia and pneumonia staphylococcal.		
subjects affected / exposed	9 / 578 (1.56%)	11 / 579 (1.90%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis chronic			
subjects affected / exposed	1 / 578 (0.17%)	0 / 579 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 578 (0.00%)	1 / 579 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CHF 5993 pMDI (100/6/12.5 µg)	Fluticasone/vilanterol + tiotropium (100/25 + 18 µg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	241 / 578 (41.70%)	230 / 579 (39.72%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 578 (2.25%)	13 / 579 (2.25%)	
occurrences (all)	14	15	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	106 / 578 (18.34%)	87 / 579 (15.03%)	
occurrences (all)	127	103	
Dyspnoea			
subjects affected / exposed	10 / 578 (1.73%)	12 / 579 (2.07%)	
occurrences (all)	11	13	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	26 / 578 (4.50%)	17 / 579 (2.94%)	
occurrences (all)	28	17	
Oral candidiasis			
subjects affected / exposed	13 / 578 (2.25%)	5 / 579 (0.86%)	
occurrences (all)	14	5	
Respiratory tract infection viral			
subjects affected / exposed	13 / 578 (2.25%)	11 / 579 (1.90%)	
occurrences (all)	15	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2015	There was one substantial general amendment, which comprised the following main changes: change of Sponsor Medical Expert; a rationale for the non-inferiority margin was required by the Regulatory Authorities in Sweden (LAKEMEDELSVERKET Medical Product Agency), and was added to the protocol section on determination of sample size; and an update of the list of forbidden concomitant treatments was required by the Regulatory Authorities in Hungary (the National Institute of Pharmacy and Nutrition). Co-administration of potent inhibitors of CYP34A (e.g. ketoconazole, ritonavir, clarithromycin, chloramphenicol and indinavir) was to be avoided with the comparator used in the study: Relvar® Ellipta®, as based on the relevant summary of product characteristics.

Notes:

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: