

**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 trifenate (Relvar®).

Dose: Fluticasone furoate 100 µg, vilanterol trifenate 25 µg per pre-dispensed unit dose, 1 inhalation, od.

Total daily dose: Fluticasone furoate 100 µg, vilanterol trifenate 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/vilantero I + 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/vilantero l + 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/vila nterol + 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/vila nterol + 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 \geq 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 μ g) | Fluticasone/vila nterol + tiotropium (100/25 + 18 μ g) | | |
| 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 μ g) | Fluticasone/vila nterol + tiotropium (100/25 + 18 μ g) | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 577 ^[12] | 579 ^[13] | | |
| Units: Litres | | | | |
| arithmetic mean (standard deviation) | 0.03 (\pm 0.465) | 0.096 (\pm 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/vila nterol + 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/vila nterol + 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/vila nterol + 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/vilantero l + 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/vilantero I + 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: