

**Clinical trial results:**

A 52-week, double-blind, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrrolate bromide administered via pMDI (CHF 5993) versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI in patients with chronic obstructive pulmonary disease

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2013-001057-27 |
| Trial protocol | GB BE HU DE IT CZ SK PL BG |
| Global end of trial date | 14 January 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 10 February 2017 |
| First version publication date | 10 February 2017 |

Trial information**Trial identification**

| | |
|-----------------------|------------------|
| Sponsor protocol code | CCD-1207-PR-0091 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01917331 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | TRILOGY: TRILOGY |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Chiesi Farmaceutici S.p.A. |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy, 43122 |
| Public contact | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.com |
| Scientific contact | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, 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 | 23 May 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- Demonstrate superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of lung function (change from baseline in pre-dose and 2-hour post-dose morning FEV1 at Week 26).
- Demonstrate superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of dyspnea (Transition Dyspnea Index focal score at Week 26).

CHF 5993 = Fixed combination of BDP and FF and GB

CHF 1535=Fixed combination of BDP and FF

BDP = Beclomethasone dipropionate

COPD=Chronic obstructive pulmonary disease

FF=Formoterol fumarate

GB=Glycopyrronium bromide

pMDI=Pressurised metered dose inhaler

Protection of trial subjects:

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

At all visits, from screening onward, concomitant medications, adverse events and vital signs were recorded, COPD exacerbations were assessed and 12-lead electrocardiogram (ECG) and physical examinations were performed. Treatment compliance was evaluated on the basis of the information recorded daily by the patient on the digital platform.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 21 March 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 53 |
| Country: Number of subjects enrolled | Mexico: 4 |
| Country: Number of subjects enrolled | Romania: 105 |
| Country: Number of subjects enrolled | Russian Federation: 320 |
| Country: Number of subjects enrolled | Ukraine: 224 |
| Country: Number of subjects enrolled | Poland: 113 |
| Country: Number of subjects enrolled | Slovakia: 33 |

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Bulgaria: 92 |
| Country: Number of subjects enrolled | Czech Republic: 208 |
| Country: Number of subjects enrolled | Germany: 63 |
| Country: Number of subjects enrolled | Hungary: 103 |
| Country: Number of subjects enrolled | Italy: 23 |
| Worldwide total number of subjects | 1368 |
| EEA total number of subjects | 767 |

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) | 739 |
| From 65 to 84 years | 627 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Overall, 1812 patients were screened according to inclusion and exclusion criteria; of these 1368 patients were randomized.

Pre-assignment

Screening details:

Pre-screening visit was at most 1 week before the screening visit when inclusion/exclusion criteria were assessed and the run-in period of 2 weeks started. During the run-in period patients stopped their current treatment and received an open-label CHF 1535 pMDI to take as 2 puffs bid for 2 weeks (BDP 400 µg/FF 24 µg daily).

Period 1

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

Blinding implementation details:

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

The canisters/actuators of CHF 5993 pMDI and CHF 1535 pMDI were of identical appearance.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment A - fixed combination CHF 5993 100/6/12.5µg |

Arm description:

Treatment A:

CHF 5993 pMDI: Patients followed a schedule of 2 puffs of CHF 5993 100/6/12.5 µg bid. Therefore, the total daily dose was BDP/FF/GB 400/24/50 µg;

BDP=Beclomethasone dipropionate

GB=Glycopyrronium bromide

FF=Formoterol fumarate

CHF 5993 pMDI=Fixed combination of BDP 50µg, FF 6 µg, GB 12.5µg per metered dose

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 5993 100/6/12.5 µg |
| Investigational medicinal product code | |
| Other name | BDP/FF/GB, Fixed combination of beclomethasone dipropionate, formoterol fumarate, Glycopyrronium bromide |
| Pharmaceutical forms | Pressurised inhalation, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

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

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

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

| | |
|------------------|--|
| Arm title | Treatment B - fixed combination CHF 1535 100/6µg |
|------------------|--|

Arm description:

Treatment B:

CHF 1535 pMDI: Patients followed a schedule of 2 puffs of CHF 1535 100/6 µg bid.

Therefore, the total daily dose was BDP/FF 400/24 µg.

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535 pMDI=Fixed combination of BDP 100µg, FF 6 µg,

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | CHF 1535 100/6 µg |
| Investigational medicinal product code | |
| Other name | BDP/FF, Fixed combination of beclomethasone dipropionate and formoterol fumarate |
| Pharmaceutical forms | Pressurised inhalation, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

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

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

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

| Number of subjects in period 1 | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg |
|---------------------------------------|--|---|
| Started | 687 | 681 |
| Completed | 602 | 579 |
| Not completed | 85 | 102 |
| Adverse event, serious fatal | 13 | 15 |
| Consent withdrawn by subject | 45 | 54 |
| Adverse event, non-fatal | 20 | 17 |
| Other | - | 2 |
| Lost to follow-up | 2 | 5 |
| Lack of efficacy | 3 | 6 |
| Protocol deviation | 2 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Treatment A - fixed combination CHF 5993 100/6/12.5µg |
|-----------------------|---|

Reporting group description:

Treatment A:

CHF 5993 pMDI: Patients followed a schedule of 2 puffs of CHF 5993 100/6/12.5 µg bid.

Therefore, the total daily dose was BDP/FF/GB 400/24/50 µg;

BDP=Beclomethasone dipropionate

GB=Glycopyrronium bromide

FF=Formoterol fumarate

CHF 5993 pMDI=Fixed combination of BDP 50µg, FF 6 µg, GB 12.5µg per metered dose

| | |
|-----------------------|--|
| Reporting group title | Treatment B - fixed combination CHF 1535 100/6µg |
|-----------------------|--|

Reporting group description:

Treatment B:

CHF 1535 pMDI: Patients followed a schedule of 2 puffs of CHF 1535 100/6 µg bid.

Therefore, the total daily dose was BDP/FF 400/24 µg.

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535 pMDI=Fixed combination of BDP 100µg, FF 6 µg,

| Reporting group values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | Total |
|------------------------|---|--|-------|
| Number of subjects | 687 | 681 | 1368 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 391 | 348 | 739 |
| From 65-84 years | 295 | 332 | 627 |
| 85 years and over | 1 | 1 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.3 | 63.8 | |
| standard deviation | ± 7.9 | ± 8.2 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 178 | 154 | 332 |
| Male | 509 | 527 | 1036 |
| Race | | | |
| Units: Subjects | | | |
| Other | 3 | 1 | 4 |
| White | 684 | 680 | 1364 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Treatment A - fixed combination CHF 5993 100/6/12.5µg |
| Reporting group description: | |
| Treatment A: CHF 5993 pMDI: Patients followed a schedule of 2 puffs of CHF 5993 100/6/12.5 µg bid. Therefore, the total daily dose was BDP/FF/GB 400/24/50 µg; | |
| BDP=Beclomethasone dipropionate GB=Glycopyrronium bromide FF=Formoterol fumarate CHF 5993 pMDI=Fixed combination of BDP 50µg, FF 6 µg, GB 12.5µg per metered dose | |
| Reporting group title | Treatment B - fixed combination CHF 1535 100/6µg |
| Reporting group description: | |
| Treatment B: CHF 1535 pMDI: Patients followed a schedule of 2 puffs of CHF 1535 100/6 µg bid. Therefore, the total daily dose was BDP/FF 400/24 µg. | |
| BDP=Beclomethasone dipropionate FF=Formoterol fumarate CHF 1535 pMDI=Fixed combination of BDP 100µg, FF 6 µg, | |

Primary: 1_Change from baseline in pre-dose morning FEV1 at week 26

| | |
|---|--|
| End point title | 1_Change from baseline in pre-dose morning FEV1 at week 26 |
| End point description: | |
| FEV1=Forced expiratory volume in the 1st second. It is the volume of air that can be forced out in one second after taking a deep breath. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to Week 26. | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 642 ^[1] | 616 ^[2] | | |
| Units: litre(s) | | | | |
| least squares mean (confidence interval 95%) | 0.082 (0.062 to 0.102) | 0.001 (-0.019 to 0.021) | | |

Notes:

[1] - ITT population; Change from baseline available;

[2] - ITT population; Change from baseline available;

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Adjusted mean difference between treatment groups |
| Comparison groups | Treatment B - fixed combination CHF 1535 100/6µg v Treatment A - fixed combination CHF 5993 100/6/12.5µg |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.081 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.052 |
| upper limit | 0.109 |

Notes:

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

Treatment A (CHF 5993 pMDI) - Treatment B (CHF 1535 pMDI)

Primary: 2_Change from baseline to 2-hour post-dose value of FEV1 at Week 26

| | |
|------------------------|---|
| End point title | 2_Change from baseline to 2-hour post-dose value of FEV1 at Week 26 |
| End point description: | Change from baseline to 2-hour post-dose value of FEV1 at Week 26. |
| End point type | Primary |
| End point timeframe: | Baseline to 2-hour post-dose at Week 26. |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 631 ^[4] | 609 ^[5] | | |
| Units: litre(s) | | | | |
| least squares mean (confidence interval 95%) | 0.261 (0.24 to 0.283) | 0.145 (0.123 to 0.166) | | |

Notes:

[4] - ITT population; Change from baseline available;

[5] - ITT population; Change from baseline available;

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Adjusted mean difference between treatment groups |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1240 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.117 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.086 |
| upper limit | 0.147 |

Notes:

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

Treatment A (CHF 5993 pMDI) - Treatment B (CHF 1535 pMDI)

Primary: 3_TDI focal score at Week 26

| | |
|-----------------|------------------------------|
| End point title | 3_TDI focal score at Week 26 |
|-----------------|------------------------------|

End point description:

TDI focal score is a symptom-based variable, used to assess breathlessness and the impact of intervention. The BDI/TDI is a clinical rating method based on a validated instrument, developed to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task, and magnitude of effort.

The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (i.e. from 0 to 12). Change from baseline in dyspnoea severity was measured using the TDI. TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (i.e. from -9 to +9).

BDI and TDI are based on validated questionnaires. BDI focal score is the baseline value from which TDI focal score is assessed.

BDI=Baseline Dyspnoea Index

TDI=Transition Dyspnoea Index

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to Week 26.

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 642 ^[7] | 619 ^[8] | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | 1.71 (1.5 to 1.92) | 1.5 (1.29 to 1.71) | | |

Notes:

[7] - ITT population; Change from baseline available;

[8] - ITT population; Change from baseline available;

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Adjusted mean difference between treatment groups |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1261 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | = 0.16 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.08 |
| upper limit | 0.51 |

Notes:

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

Treatment A (CHF 5993 pMDI) - Treatment B (CHF 1535 pMDI)

Secondary: 4_Change from baseline in pre-dose morning FEV1 at all study visits

| | |
|-----------------|---|
| End point title | 4_Change from baseline in pre-dose morning FEV1 at all study visits |
|-----------------|---|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| | | | | |
|--|---|--|--|--|
| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 681 ^[10] | 670 ^[11] | | |
| Units: litre(s) | | | | |
| least squares mean (confidence interval 95%) | | | | |

| | | | | |
|---------|------------------------|-------------------------|--|--|
| Week 4 | 0.093 (0.076 to 0.109) | 0.022 (0.005 to 0.039) | | |
| Week 12 | 0.078 (0.06 to 0.096) | 0.01 (-0.008 to 0.028) | | |
| Week 26 | 0.082 (0.062 to 0.102) | 0.001 (-0.019 to 0.021) | | |
| Week 40 | 0.095 (0.073 to 0.116) | 0.018 (-0.004 to 0.04) | | |
| Week 52 | 0.071 (0.05 to 0.093) | 0.008 (-0.014 to 0.03) | | |

Notes:

[10] - ITT population (analysed)

Wk 04 n=679

Wk 12 n=660

Wk 26 n=642

Wk 40 n=622

Wk 52 n=606

[11] - ITT population (analysed)

Wk 04 n=669

Wk 12 n=654

Wk 26 n=616

Wk 40 n=597

Wk 52 n=578

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1348:

n (CHF 5993 pMDI)=679

n (CHF 1535 pMDI)=669

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1351 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.071 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.047 |
| upper limit | 0.094 |

Notes:

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

CHF 5993 pMDI - CHF 1535 pMDI

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1314:

n (CHF 5993 pMDI)=660

n (CHF 1535 pMDI)=654

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1351 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.068 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.042 |
| upper limit | 0.094 |

Notes:

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

CHF 5993 pMDI - CHF 1535 pMDI

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1258:

n (CHF 5993 pMDI)=642

n (CHF 1535 pMDI)=616

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1351 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.081 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.052 |
| upper limit | 0.109 |

Notes:

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

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|--|---|
| Statistical analysis description: | |
| Adjusted mean difference between treatment groups at Week 40. | |
| The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below. | |
| The total number of subjects in this analysis with available data is 1219: | |
| n (CHF 5993 pMDI)=622 | |
| n (CHF 1535 pMDI)=597 | |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1351 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.077 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.046 |
| upper limit | 0.108 |

Notes:

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

CHF 5993 pMDI - CHF 1535 pMDI

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|--|---|
| Statistical analysis description: | |
| Adjusted mean difference between treatment groups at Week 52. | |
| The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below. | |
| The total number of subjects in this analysis with available data is 1184: | |
| n (CHF 5993 pMDI)=606 | |
| n (CHF 1535 pMDI)=578 | |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1351 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.063 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.032 |
| upper limit | 0.094 |

Notes:

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

CHF 5993 pMDI - CHF 1535 pMDI

Secondary: 5_Change from baseline to the average over the treatment period in pre-dose morning FEV1

| | |
|-----------------|--|
| End point title | 5_Change from baseline to the average over the treatment period in pre-dose morning FEV1 |
|-----------------|--|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 681 ^[17] | 670 ^[18] | | |
| Units: litre(s) | | | | |
| least squares mean (confidence interval 95%) | 0.084 (0.067 to 0.1) | 0.012 (-0.005 to 0.029) | | |

Notes:

[17] - ITT population; Change from baseline available;

[18] - ITT population; Change from baseline available;

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Adjusted mean difference between treatment groups. |
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups.

| | |
|---|--|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1351 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.072 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.048 |
| upper limit | 0.096 |

Notes:

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

CHF 5993 pMDI - CHF 1535 pMDI

Secondary: 6_FEV1 response (change from baseline in pre-dose morning FEV1 ≥100 mL) at Week 26 and Week 52

| | |
|-----------------|--|
| End point title | 6_FEV1 response (change from baseline in pre-dose morning FEV1 ≥100 mL) at Week 26 and Week 52 |
|-----------------|--|

End point description:

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

Results are shown as the number of responders for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to study visit at Week 26, Week 52.

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[20] | 680 ^[21] | | |
| Units: subject | | | | |
| Week 26 | 287 | 165 | | |
| Week 52 | 259 | 158 | | |

Notes:

[20] - ITT population

[21] - ITT population

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Btw grp analysis, change in FEV1 ≥100 mL, Wk 26 |
|----------------------------|---|

Statistical analysis description:

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

CHF 5993 pMDI / CHF 1535 pMDI

| | |
|-------------------|--|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[22] |
| P-value | < 0.001 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.299 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.817 |
| upper limit | 2.91 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Btw grp analysis, change in FEV1 ≥100 mL, Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

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

CHF 5993 pMDI / CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | < 0.001 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.061 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.621 |
| upper limit | 2.62 |

Notes:

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

Secondary: 7_Change from baseline to 2-hour post-dose value of FEV1 at all study visits

| | |
|-----------------|--|
| End point title | 7_Change from baseline to 2-hour post-dose value of FEV1 at all study visits |
|-----------------|--|

End point description:

Change from baseline to 2-hour post-dose value of FEV1 at all study visits.

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to 2-hour post-dose at each study visit (Week 0, 4, 12, 26, 40, 52).

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 686 ^[24] | 679 ^[25] | | |
| Units: litre(s) | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 0 | 0.215 (0.203 to 0.228) | 0.138 (0.126 to 0.15) | | |
| Week 4 | 0.268 (0.25 to 0.286) | 0.153 (0.135 to 0.171) | | |
| Week 12 | 0.261 (0.241 to 0.281) | 0.146 (0.125 to 0.166) | | |
| Week 26 | 0.261 (0.24 to 0.283) | 0.145 (0.123 to 0.166) | | |
| Week 40 | 0.253 (0.23 to 0.275) | 0.15 (0.127 to 0.174) | | |
| Week 52 | 0.249 (0.226 to 0.273) | 0.146 (0.122 to 0.17) | | |

Notes:

[24] - ITT population (analysed)

W 0 n=683

W 4 n=675

W 12 n=657

W 26 n=631

W 40 n=615

W 52 n=598

[25] - ITT population (analysed)

W 0 n=674

W 4 n=660

W 12 n=648

W 26 n=609

W 40 n=590

W 52 n=575

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 0 |
|--|---|
| Statistical analysis description: | |
| Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 0. CHF 5993 pMDI vs CHF 1535 pMDI | |
| The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below. | |
| The total number of subjects with available data in this analysis is 1357: n (CHF 5993 p65) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below. | |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[26] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.077 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 0.095 |

Notes:

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

| | |
|-----------------------------------|--|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|-----------------------------------|--|

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1335:

n (CHF 5993 pMDI)=675

n (CHF 1535 pMDI)=660

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[27] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.116 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.09 |
| upper limit | 0.141 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1305:

n (CHF 5993 pMDI)=657
n (CHF 1535 pMDI)=648

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[28] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.116 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.087 |
| upper limit | 0.144 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1240:

n (CHF 5993 pMDI)=631
n (CHF 1535 pMDI)=609

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[29] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.117 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.086 |
| upper limit | 0.147 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1205:

n (CHF 5993 pMDI)=615

n (CHF 1535 pMDI)=590

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[30] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.102 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.07 |
| upper limit | 0.135 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 52.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1173:

n (CHF 5993 pMDI)=598

n (CHF 1535 pMDI)=575

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[31] |
| P-value | < 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.103 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.069 |
| upper limit | 0.137 |

Notes:

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

Secondary: 8_Change from pre-dose to 2-hour post-dose value of FEV1 at all study

visits

| | |
|-----------------|--|
| End point title | 8_Change from pre-dose to 2-hour post-dose value of FEV1 at all study visits |
|-----------------|--|

End point description:

Change from pre-dose to 2-hour post-dose value of FEV1 at all study visits.

The number of patients shown represents the ITT population; change from baseline for available patients at the specified week (Wk) for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose to 2-hour post-dose at each study visit (Week 4, 12, 26, 40, 52).

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[32] | 680 ^[33] | | |
| Units: litre(s) | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 4 | 0.177 (0.165 to 0.189) | 0.13 (0.118 to 0.143) | | |
| Week 12 | 0.183 (0.171 to 0.194) | 0.138 (0.126 to 0.149) | | |
| Week 26 | 0.18 (0.169 to 0.192) | 0.149 (0.138 to 0.161) | | |
| Week 40 | 0.159 (0.147 to 0.171) | 0.138 (0.125 to 0.15) | | |
| Week 52 | 0.18 (0.167 to 0.193) | 0.146 (0.133 to 0.159) | | |

Notes:

[32] - ITT population

Wk 04 n=674

Wk 12 n=658

Wk 26 n=632

Wk 40 n=616

Wk 52 n=599

[33] - ITT population

Wk 04 n=661

Wk 12 n=648

Wk 26 n=610

Wk 40 n=591

Wk 52 n=575

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1355.

n (CHF 5993 pMDI)=674

n (CHF 1535 pMDI)=661

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[34] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.046 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.029 |
| upper limit | 0.064 |

Notes:

[34] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1306.

n (CHF 5993 pMDI)=658

n (CHF 1535 pMDI)=648

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[35] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.045 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.029 |
| upper limit | 0.062 |

Notes:

[35] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1242.

n (CHF 5993 pMDI)=632

n (CHF 1535 pMDI)=610

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[36] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.031 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.015 |
| upper limit | 0.047 |

Notes:

[36] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1207.

n (CHF 5993 pMDI)=616

n (CHF 1535 pMDI)=591

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[37] |
| P-value | = 0.013 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.022 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.005 |
| upper limit | 0.039 |

Notes:

[37] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1174.

n (CHF 5993 pMDI)=599

n (CHF 1535 pMDI)=575

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[38] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.034 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.016 |
| upper limit | 0.052 |

Notes:

[38] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

Secondary: 9_TDI focal score at all study visits

| | |
|-----------------|---------------------------------------|
| End point title | 9_TDI focal score at all study visits |
|-----------------|---------------------------------------|

End point description:

TDI focal score is a symptom-based variable, used to assess breathlessness and the impact of intervention. The BDI/TDI is a clinical rating method based on a validated instrument, developed to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task, and magnitude of effort.

The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (i.e. from 0 to 12). Change from baseline in dyspnoea severity was measured using the TDI. TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (i.e. from -9 to +9).

BDI and TDI are based on validated questionnaires. BDI focal score is the baseline value from which TDI focal score is assessed.

BDI=Baseline Dyspnoea Index

TDI=Transition Dyspnoea Index

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[39] | 680 ^[40] | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 4 | 1.54 (1.35 to 1.72) | 1.12 (0.94 to 1.31) | | |
| Week 12 | 1.77 (1.58 to 1.97) | 1.39 (1.19 to 1.58) | | |
| Week 26 | 1.71 (1.5 to 1.92) | 1.5 (1.29 to 1.71) | | |
| Week 40 | 1.8 (1.58 to 2.01) | 1.65 (1.43 to 1.86) | | |
| Week 52 | 2.03 (1.81 to 2.25) | 1.81 (1.59 to 2.04) | | |

Notes:

[39] - ITT population (analysed)

Wk 04 n=680

Wk 12 n=661

Wk 26 n=642

Wk 40 n=622

Wk 52 n=608

[40] - ITT population (analysed)

Wk 04 n=672

Wk 12 n=651

Wk 26 n=619

Wk 40 n=596

Wk 52 n=579

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 4.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1352:

n (CHF 5993 pMDI)=680

n (CHF 1535 pMDI)=672

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[41] |
| P-value | = 0.002 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.15 |
| upper limit | 0.68 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1312:

n (CHF 5993 pMDI)=661

n (CHF 1535 pMDI)=651

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[42] |
| P-value | = 0.007 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.11 |
| upper limit | 0.66 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1261:

n (CHF 5993 pMDI)=642

n (CHF 1535 pMDI)=619

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[43] |
| P-value | = 0.16 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.21 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.08 |
| upper limit | 0.51 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1218:

n (CHF 5993 pMDI)=622

n (CHF 1535 pMDI)=596

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[44] |
| P-value | = 0.343 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.16 |
| upper limit | 0.45 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1187:

n (CHF 5993 pMDI)=608

n (CHF 1535 pMDI)=579

| | |
|-------------------|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
|-------------------|---|

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[45] |
| P-value | = 0.186 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.53 |

Notes:

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

Secondary: 10_TDI response (focal score ≥ 1) at Week 26 and Week 52

| | |
|-----------------|--|
| End point title | 10_TDI response (focal score ≥ 1) at Week 26 and Week 52 |
|-----------------|--|

End point description:

TDI response is defined as a TDI focal score ≥ 1 . If the TDI focal score was <1 , the patient was classified as a non-responder in terms of TDI. Patients with missing TDI focal score at the relevant time points were also classed as non-responders.

Results are shown as the number of responders for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

TDI=Transition Dyspnoea Index

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 26, Week 52. | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[46] | 680 ^[47] | | |
| Units: subjects | | | | |
| Week 26 | 394 | 352 | | |
| Week 52 | 370 | 354 | | |

Notes:

[46] - ITT population

[47] - ITT population

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Between group analysis (TDI score ≥ 1 , Week 26) |
|----------------------------|---|

Statistical analysis description:

Between treatment group analysis for subjects with a TDI focal score ≥ 1 at Week 26.

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[48] |
| P-value | = 0.027 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.029 |
| upper limit | 1.594 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Between group analysis (TDI score ≥ 1 , Week 52) |
|-----------------------------------|---|

Statistical analysis description:

Between treatment group analysis for subjects with a TDI focal score ≥ 1 at Week 52.

CHF 5993 pMDI vs CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[49] |
| P-value | = 0.43 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.093 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.877 |
| upper limit | 1.362 |

Notes:

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

Secondary: 11_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Total Score

| | |
|-----------------|---|
| End point title | 11_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Total Score |
|-----------------|---|

End point description:

SGRQ Total Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.

SGRQ questionnaire was completed by the patient at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).

In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on

daily life.

Change from baseline in SGRQ Total Score was calculated and presented for this end point.

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

SGRQ=Saint George's respiratory questionnaire

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and each study visit (Week 4, 12, 26, 40, 52). | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 658 ^[50] | 644 ^[51] | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 4 | -3.66 (-4.41 to -2.91) | -2.19 (-2.96 to -1.43) | | |
| Week 12 | -4.7 (-5.58 to -3.81) | -2.66 (-3.55 to -1.77) | | |
| Week 26 | -4.76 (-5.69 to -3.83) | -3.43 (-4.38 to -2.47) | | |
| Week 40 | -5.48 (-6.49 to -4.47) | -4.08 (-5.11 to -3.05) | | |
| Week 52 | -5.12 (-6.18 to -4.06) | -3.43 (-4.51 to -2.35) | | |

Notes:

[50] - ITT population (analysed)

Wk 04 n=628

Wk 12 n=601

Wk 26 n=594

Wk 40 n=572

Wk 52 n=559

[51] - ITT population (analysed)

Wk 04 n=607

Wk 12 n=597

Wk 26 n=558

Wk 40 n=545

Wk 52 n=532

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1235:

n (CHF 5993 pMDI)=628

n (CHF 1535 pMDI)=607

| | |
|-------------------|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v |
|-------------------|---|

| | |
|---|--|
| | Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[52] |
| P-value | = 0.007 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.54 |
| upper limit | -0.39 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1198:

n (CHF 5993 pMDI)=601

n (CHF 1535 pMDI)=597

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[53] |
| P-value | = 0.002 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | -0.78 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1152:

n (CHF 5993 pMDI)=594

n (CHF 1535 pMDI)=558

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[54] |
| P-value | = 0.051 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.66 |
| upper limit | 0.01 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1117:

n (CHF 5993 pMDI)=572

n (CHF 1535 pMDI)=545

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[55] |
| P-value | = 0.057 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.85 |
| upper limit | 0.04 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1091:

n (CHF 5993 pMDI)=559

n (CHF 1535 pMDI)=532

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[56] |
| P-value | = 0.029 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | -0.17 |

Notes:

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

Secondary: 12_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Symptoms Score

| | |
|-----------------|--|
| End point title | 12_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Symptoms Score |
|-----------------|--|

End point description:

SGRQ Symptoms Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.

SGRQ questionnaire was completed by the patient at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).

In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on daily life.

Change from baseline in SGRQ Symptoms Score was calculated and presented for this end point.

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

SGRQ=Saint George's respiratory questionnaire

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and each study visit (Week 4, 12, 26, 40, 52). | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 674 ^[57] | 664 ^[58] | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 4 | -5.02 (-6.1 to -3.95) | -3.83 (-4.92 to -2.75) | | |
| Week 12 | -5.09 (-6.29 to -3.89) | -4.56 (-5.77 to -3.34) | | |
| Week 26 | -6.8 (-8.06 to -5.53) | -5.17 (-6.46 to -3.88) | | |
| Week 40 | -8.35 (-9.73 to -6.96) | -7.12 (-8.53 to -5.71) | | |
| Week 52 | -8.22 (-9.67 to -6.77) | -7.26 (-8.74 to -5.78) | | |

Notes:

[57] - ITT population (analysed)

Wk 04 n=652

Wk 12 n=636

Wk 26 n=620

Wk 40 n=601

Wk 52 n=584

[58] - ITT population (analysed)

Wk 04 n=637

Wk 12 n=629

Wk 26 n=589

Wk 40 n=576

Wk 52 n=558

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1289:

n (CHF 5993 pMDI)=652

n (CHF 1535 pMDI)=637

| | |
|---|---|
| Comparison groups | Treatment B - fixed combination CHF 1535 100/6µg v Treatment A - fixed combination CHF 5993 100/6/12.5µg |
| Number of subjects included in analysis | 1338 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[59] |
| P-value | = 0.126 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.72 |
| upper limit | 0.34 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1265:

n (CHF 5993 pMDI)=636

n (CHF 1535 pMDI)=629

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1338 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[60] |
| P-value | = 0.54 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.24 |
| upper limit | 1.17 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1209:

n (CHF 5993 pMDI)=620

n (CHF 1535 pMDI)=589

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1338 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[61] |
| P-value | = 0.077 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.63 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.44 |
| upper limit | 0.17 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1177:

n (CHF 5993 pMDI)=601

n (CHF 1535 pMDI)=576

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1338 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[62] |
| P-value | = 0.224 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.21 |
| upper limit | 0.75 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1142:

n (CHF 5993 pMDI)=584

n (CHF 1535 pMDI)=558

| | |
|-------------------|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
|-------------------|---|

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1338 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[63] |
| P-value | = 0.364 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.03 |
| upper limit | 1.11 |

Notes:

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

Secondary: 13_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Impacts Score

| | |
|-----------------|---|
| End point title | 13_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Impacts Score |
|-----------------|---|

End point description:

SGRQ Impacts Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.

SGRQ questionnaire was completed by the patients at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).

In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on daily life.

Change from baseline in SGRQ Impacts Score was calculated and presented for this end point.

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

SGRQ=Saint George's respiratory questionnaire

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 678 ^[64] | 668 ^[65] | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 4 | -3.44 (-4.34 to -2.54) | -2.29 (-3.2 to -1.38) | | |
| Week 12 | -4.65 (-5.69 to -3.62) | -2.72 (-3.76 to -1.68) | | |

| | | | | |
|---------|------------------------|-----------------------|--|--|
| Week 26 | -4.88 (-5.96 to -3.8) | -3.5 (-4.6 to -2.39) | | |
| Week 40 | -5.33 (-6.45 to -4.2) | -3.75 (-4.89 to -2.6) | | |
| Week 52 | -4.68 (-5.85 to -3.51) | -2.59 (-3.79 to -1.4) | | |

Notes:

[64] - ITT population (analysed)

Wk 04 n=668

Wk 12 n=641

Wk 26 n=627

Wk 40 n=608

Wk 52 n=590

[65] - ITT population (analysed)

Wk 04 n=654

Wk 12 n=636

Wk 26 n=594

Wk 40 n=576

Wk 52 n=559

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1322:

n (CHF 5993 pMDI)=668

n (CHF 1535 pMDI)=654

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[66] |
| P-value | = 0.077 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.43 |
| upper limit | 0.13 |

Notes:

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

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1277:

n (CHF 5993 pMDI)=641

n (CHF 1535 pMDI)=636

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[67] |
| P-value | = 0.01 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | -0.46 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1221:

n (CHF 5993 pMDI)=627

n (CHF 1535 pMDI)=594

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[68] |
| P-value | = 0.079 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.93 |
| upper limit | 0.16 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1284:

n (CHF 5993 pMDI)=608

n (CHF 1535 pMDI)=576

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[69] |
| P-value | = 0.054 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.19 |
| upper limit | 0.03 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1149:

n (CHF 5993 pMDI)=590

n (CHF 1535 pMDI)=559

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[70] |
| P-value | = 0.015 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.76 |
| upper limit | -0.41 |

Notes:

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

Secondary: 14_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Activity Score

| | |
|-----------------|--|
| End point title | 14_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Activity Score |
|-----------------|--|

End point description:

SGRQ Activity Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.

SGRQ questionnaire was completed by the patients at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).

In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on daily life.

Change from baseline in SGRQ Activity Score was calculated and presented for this end point.

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

SGRQ=Saint George's respiratory questionnaire

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 672 ^[71] | 661 ^[72] | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 4 | -2.69 (-3.65 to -1.73) | -1.21 (-2.18 to -0.24) | | |
| Week 12 | -3.93 (-5.03 to -2.83) | -1.35 (-2.46 to -0.24) | | |
| Week 26 | -3.88 (-5.01 to -2.75) | -2.17 (-3.33 to -1.02) | | |
| Week 40 | -4.35 (-5.54 to -3.15) | -2.74 (-3.96 to -1.51) | | |
| Week 52 | -4.26 (-5.49 to -3.02) | -2.95 (-4.21 to -1.68) | | |

Notes:

[71] - ITT population (analysed)

Wk 04 n=659

Wk 12 n=626

Wk 26 n=616

Wk 40 n=596

Wk 52 n=583

[72] - ITT population (analysed)

Wk 4 n=639
Wk 12 n=621
Wk 26 n=585
Wk 40 n=562
Wk 52 n=554

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 4 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1298:

n (CHF 5993 pMDI)=659

n (CHF 1535 pMDI)=639

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[73] |
| P-value | = 0.034 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.84 |
| upper limit | -0.11 |

Notes:

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

| Statistical analysis title | Adjusted mean difference btw treat groups Wk 12 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1247:

n (CHF 5993 pMDI)=626

n (CHF 1535 pMDI)=621

| | |
|-------------------|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
|-------------------|---|

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[74] |
| P-value | = 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.14 |
| upper limit | -1.01 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1201:

n (CHF 5993 pMDI)=616

n (CHF 1535 pMDI)=585

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[75] |
| P-value | = 0.039 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.33 |
| upper limit | -0.09 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1158:

n (CHF 5993 pMDI)=596
n (CHF 1535 pMDI)=562

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[76] |
| P-value | = 0.065 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.32 |
| upper limit | -0.1 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups Wk 52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1158:

n (CHF 5993 pMDI)=596
n (CHF 1535 pMDI)=562

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[77] |
| P-value | = 0.145 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.08 |
| upper limit | 0.45 |

Notes:

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

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

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

End point description:

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

Results are shown as the number of responders for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

SGRQ=Saint George's respiratory questionnaire

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 26, Week 52. | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[78] | 680 ^[79] | | |
| Units: subject | | | | |
| Week 26 | 321 | 246 | | |
| Week 52 | 297 | 244 | | |

Notes:

[78] - ITT population

[79] - ITT population

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Btw grp analysis, change in SGRQ score ≤ -4 , Wk 26 |
|----------------------------|--|

Statistical analysis description:

SGRQ response = Subjects with a change from baseline in Total Score ≤ -4 , at week 26.
Between group analysis (change from baseline in SGRQ Total score ≤ -4 , Week 26).

CHF 5993 pMDI / CHF 1535 pMDI

| | |
|---|--|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[80] |
| P-value | < 0.001 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.521 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.211 |
| upper limit | 1.911 |

Notes:

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

| | |
|--|---|
| Statistical analysis title | Btw grp analysis, change in SGRQ score ≤ -4 , Wk 52 |
| Statistical analysis description: SGRQ response = Subjects with a change from baseline in Total Score ≤ -4 , at week 52. Between group analysis (change from baseline in SGRQ Total score ≤ -4 , Week 52). | |
| CHF 5993 pMDI / CHF 1535 pMDI | |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5 μ g v Treatment B - fixed combination CHF 1535 100/6 μ g |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[81] |
| P-value | = 0.014 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.327 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.661 |

Notes:

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

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

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

End point description:

Days without intake of rescue medication.

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

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

| | |
|-------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 4, 12, 26, 40, 52. | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5 μ g | Treatment B - fixed combination CHF 1535 100/6 μ g | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 653 ^[82] | 645 ^[83] | | |
| Units: days | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 1-4 | 6.67 (4.89 to 8.44) | 2.46 (0.67 to 4.25) | | |
| Week 5-12 | 6.23 (4.19 to 8.27) | 3.18 (1.12 to 5.24) | | |

| | | | | |
|------------|---------------------|----------------------|--|--|
| Week 13-26 | 5.49 (3.3 to 7.67) | 2.4 (0.19 to 4.6) | | |
| Week 27-40 | 4.39 (2.07 to 6.72) | 2.79 (0.43 to 5.15) | | |
| Week 41-52 | 3.82 (1.45 to 6.19) | 1.24 (-1.17 to 3.65) | | |
| Week 1-52 | 5.01 (3.05 to 6.98) | 2.36 (0.37 to 4.35) | | |

Notes:

[82] - ITT population

W 1-4 n=645

W 5-12 n=642

W 13-26 n=627

W 27-40 n=601

W 41-52 n=578

W 1-52 n=650

[83] - ITT population

W 1-4 n=637

W 5-12 n=629

W 13-26 n=610

W 27-40 n=572

W 41-52 n=552

W 1-52 n=640

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups W 1-4 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-4.

CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1282:

n (CHF 5993 pMDI)=645

n (CHF 1535 pMDI)=637

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[84] |
| P-value | = 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 4.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.69 |
| upper limit | 6.73 |

Notes:

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

| Statistical analysis title | Adjusted mean difference btw treat groups W 5-12 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 5-12.

CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1271:

n (CHF 5993 pMDI)=642

n (CHF 1535 pMDI)=629

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[85] |
| P-value | = 0.039 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 3.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.15 |
| upper limit | 5.95 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups W 13-26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 13-26.

CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1237:

n (CHF 5993 pMDI)=627

n (CHF 1535 pMDI)=610

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[86] |
| P-value | = 0.051 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 3.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 6.2 |

Notes:

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

| | |
|--|---|
| Statistical analysis title | Adjusted mean difference btw treat groups W 27-40 |
| Statistical analysis description: | |
| Adjusted mean difference between treatment groups during Week 27-40. CHF 5993 pMDI - CHF 1535 pMDI | |
| The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below. | |
| The total number of subjects with available data in this analysis is 1173: n (CHF 5993 pMDI)=601 n (CHF 1535 pMDI)=572 | |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[87] |
| P-value | = 0.342 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.71 |
| upper limit | 4.91 |

Notes:

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

| | |
|--|---|
| Statistical analysis title | Adjusted mean difference btw treat groups W 41-52 |
| Statistical analysis description: | |
| Adjusted mean difference between treatment groups during Week 41-52. CHF 5993 pMDI - CHF 1535 pMDI | |
| The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below. | |
| The total number of subjects with available data in this analysis is 1130: n (CHF 5993 pMDI)=578 n (CHF 1535 pMDI)=552 | |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[88] |
| P-value | = 0.134 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 5.97 |

Notes:

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

| | |
|-----------------------------------|--|
| Statistical analysis title | Adjusted mean difference btw treat groups W 1-52 |
|-----------------------------------|--|

Statistical analysis description:

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

CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1290:

n (CHF 5993 pMDI)=650

n (CHF 1535 pMDI)=640

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[89] |
| P-value | = 0.063 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.14 |
| upper limit | 5.45 |

Notes:

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

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

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

End point description:

Average use of rescue medication.

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 653 ^[90] | 645 ^[91] | | |
| Units: puffs/day | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 1-4 | -0.29 (-0.38 to -0.2) | -0.07 (-0.17 to 0.02) | | |
| Week 5-12 | -0.25 (-0.36 to -0.14) | -0.06 (-0.17 to 0.05) | | |
| Week 13-26 | -0.21 (-0.32 to -0.09) | -0.02 (-0.14 to 0.1) | | |
| Week 27-40 | -0.09 (-0.22 to 0.04) | 0.02 (-0.11 to 0.15) | | |
| Week 41-52 | -0.04 (-0.17 to 0.09) | 0.07 (-0.07 to 0.21) | | |
| Week 1-52 | -0.15 (-0.26 to -0.04) | 0 (-0.11 to 0.12) | | |

Notes:

[90] - ITT population

W 1-4 n=645

W 5-12 n=642

W 13-26 n=627

W 27-40 n=601

W 41-52 n=578

W 1-52 n=650

[91] - ITT population

W 1-4 n=637

W 5-12 n=629

W 13-26 n=610

W 27-40 n=572

W 41-52 n=552

W 1-52 n=640

Statistical analyses

| Statistical analysis title | Adjusted mean difference btw treat groups W 1-4 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-4.

CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1282:

n (CHF 5993 pMDI)=645

n (CHF 1535 pMDI)=637

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[92] |
| P-value | = 0.001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.21 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | -0.08 |

Notes:

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

| | |
|-----------------------------------|--|
| Statistical analysis title | Adjusted mean difference btw treat groups W 5-12 |
|-----------------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 5-12.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1271:

n (CHF 5993 pMDI)=642

n (CHF 1535 pMDI)=629

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[93] |
| P-value | = 0.016 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | -0.04 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups W 13-26 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 13-26.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1237:

n (CHF 5993 pMDI)=627

n (CHF 1535 pMDI)=610

| | |
|-------------------|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
|-------------------|---|

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[94] |
| P-value | = 0.029 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | -0.02 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups W 27-40 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 27-40.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1173:

n (CHF 5993 pMDI)=601

n (CHF 1535 pMDI)=572

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[95] |
| P-value | = 0.225 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | 0.07 |

Notes:

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted mean difference btw treat groups W 41-52 |
|-----------------------------------|---|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 41-52.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1130:

n (CHF 5993 pMDI)=578
n (CHF 1535 pMDI)=552

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[96] |
| P-value | = 0.262 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.08 |

Notes:

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

| | |
|-----------------------------------|--|
| Statistical analysis title | Adjusted mean difference btw treat groups W 1-52 |
|-----------------------------------|--|

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1290:

n (CHF 5993 pMDI)=650
n (CHF 1535 pMDI)=640

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1298 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[97] |
| P-value | = 0.062 |
| Method | Mixed model for repeated measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 0.01 |

Notes:

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

Secondary: 18_Moderate and severe COPD exacerbation rate over 52 weeks of treatment

| | |
|-----------------|--|
| End point title | 18_Moderate and severe COPD exacerbation rate over 52 weeks of treatment |
|-----------------|--|

End point description:

Rate of moderate or severe COPD exacerbation.

Evaluate the rate of moderate or severe COPD exacerbation over 52 weeks of treatment.

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

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

COPD=Chronic obstructive pulmonary disease

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 52 (entire treatment period). | |

| | | | | |
|----------------------------------|---|--|--|--|
| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[98] | 680 ^[99] | | |
| Units: exacerbation/patient/year | | | | |
| number (confidence interval 95%) | 0.41 (0.358 to 0.469) | 0.53 (0.468 to 0.6) | | |

Notes:

[98] - ITT population

[99] - ITT population

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted rate ratio for mod and sev exacerbations |
|-----------------------------------|---|

Statistical analysis description:

Adjusted rate ratio for moderate and severe exacerbations.

CHF 5993 pMDI / CHF 1535 pMDI

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[100] |
| P-value | = 0.005 |
| Method | Negative binomial model |
| Parameter estimate | Adjusted Rate Ratio |
| Point estimate | 0.773 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.647 |
| upper limit | 0.924 |

Notes:

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

Secondary: 19_Time to first moderate or severe COPD exacerbation

| | |
|---|---|
| End point title | 19_Time to first moderate or severe COPD exacerbation |
| End point description: Time to first moderate or severe COPD exacerbation. | |
| Shown are the number of subjects included in the model and the number of subjects with available results. | |
| COPD=Chronic obstructive pulmonary disease | |
| End point type | Secondary |
| End point timeframe: Baseline to Week 52 (entire treatment period). | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 678 ^[101] | 680 ^[102] | | |
| Units: Subjects, at least 1 mod or sev exacerbt | 214 | 240 | | |

Notes:

[101] - ITT population

[102] - ITT population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to first moderate or severe COPD exacerbation |
| Comparison groups | Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg |
| Number of subjects included in analysis | 1358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[103] |
| P-value | = 0.02 |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.803 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.668 |
| upper limit | 0.967 |

Notes:

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

CHF 5993 pMDI / CHF 1535 pMDI

Secondary: 20_Vital signs: Systolic blood pressure

| | |
|--|---|
| End point title | 20_Vital signs: Systolic blood pressure |
| End point description: Systolic Blood Pressure. | |

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[104] | 680 ^[105] | | |
| Units: mmHg | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Week 0, 10 min post-dose | -0.8 (-1.4 to -0.3) | -0.7 (-1.2 to -0.1) | | |
| Week 26, pre-dose | 0.3 (-0.6 to 1.2) | -0.5 (-1.4 to 0.4) | | |
| Week 26, 10 min post-dose | -1 (-1.9 to -0.1) | -1.9 (-2.8 to -1.1) | | |
| Week 52, pre-dose | -0.2 (-1.2 to 0.7) | -1.3 (-2.3 to -0.2) | | |
| Week 52, 10 min post-dose | -1.2 (-2.2 to -0.3) | -2 (-3 to -1) | | |

Notes:

[104] - Safety pop

W 0 post n=683

W 26 pre n=643

W 26 post n=633

W 52 pre n=608

W 52 post n=603

[105] - Safety pop

W 0 post n=679

W 26 pre n=619

W 26 post n=612

W 52 pre n=579

W 52 post n=576

Statistical analyses

No statistical analyses for this end point

Secondary: 21_Vital signs: Diastolic blood pressure

| | |
|-----------------|--|
| End point title | 21_Vital signs: Diastolic blood pressure |
|-----------------|--|

End point description:

Diastolic Blood Pressure.

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

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

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52). | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[106] | 680 ^[107] | | |
| Units: mmHg | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Week 0, 10 min post-dose | -0.5 (-0.9 to 0) | -0.3 (-0.7 to 0.1) | | |
| Week 26, pre-dose | -0.3 (-1 to 0.4) | 0.4 (-0.2 to 1) | | |
| Week 26, 10 min post-dose | -1 (-1.6 to -0.3) | -0.5 (-1.2 to 0.1) | | |
| Week 52, pre-dose | -0.5 (-1.2 to 0.2) | -0.1 (-0.7 to 0.6) | | |
| Week 52, 10 min post-dose | -1.4 (-2.1 to -0.7) | -0.6 (-1.2 to 0.1) | | |

Notes:

[106] - Safety pop

W 0 post n=683

W 26 pre n=643

W 26 post n=633

W 52 pre n=608

W 52 post n=603

[107] - Safety pop

W 0 post n=679

W 26 pre n=619

W 26 post n=612

W 52 pre n=579

W 52 post n=576

Statistical analyses

No statistical analyses for this end point

Secondary: 22_Vital signs: Body mass index

| | |
|---|---------------------------------|
| End point title | 22_Vital signs: Body mass index |
| End point description: | |
| Body Mass Index. | |
| Results represent changes from baseline (Week 0), on Week 26 and Week 52. | |
| Shown are the number of subjects included in the safety population and the number of subjects with available results. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52). | |

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[108] | 680 ^[109] | | |
| Units: kg/m2 | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Week 26 | 0.17 (0.09 to 0.25) | -0.02 (-0.09 to 0.06) | | |
| Week 52 | 0.12 (0 to 0.23) | -0.05 (-0.15 to 0.05) | | |

Notes:

[108] - Safety population

Wk 26 n=643

Wk 52 n=608

[109] - Safety population

Wk 26 n=620

Wk 52 n=579

Statistical analyses

No statistical analyses for this end point

Secondary: 23_Electrocardiogram parameters: Heart rate

| | |
|-----------------|---|
| End point title | 23_Electrocardiogram parameters: Heart rate |
|-----------------|---|

End point description:

Heart Rate.

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[110] | 680 ^[111] | | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0, 10 min post-dose | -2.68 (± 5.71) | -3.03 (± 5.43) | | |

| | | | | |
|---------------------------|-----------------|-----------------|--|--|
| Week 26, pre-dose | -0.28 (± 10.56) | -0.24 (± 11.52) | | |
| Week 26, 10 min post-dose | -2.01 (± 10.92) | -1.99 (± 11.42) | | |
| Week 52, pre-dose | 0.56 (± 11.05) | 0.56 (± 11.22) | | |
| Week 52, 10 min post-dose | -0.71 (± 10.93) | -0.66 (± 11.63) | | |

Notes:

[110] - Safety pop

W 0 post n=658

W 26 pre n=618

W 26 post n=611

W 52 pre n=588

W 52 post n=583

[111] - Safety pop

W 0 post n=656

W 26 pre n=597

W 26 post n=592

W 52 pre n=557

W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 24_Electrocardiogram parameters: QTcF interval

| | |
|-----------------|--|
| End point title | 24_Electrocardiogram parameters: QTcF interval |
|-----------------|--|

End point description:

QTcF (Fridericia's Corrected QT Interval).

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[112] | 680 ^[113] | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0, 10 min post-dose | -0.55 (± 10.68) | -0.27 (± 11.11) | | |
| Week 26, pre-dose | 0.38 (± 14.08) | 0.76 (± 15.76) | | |
| Week 26, 10 min post-dose | -0.09 (± 14.41) | -0.38 (± 15.97) | | |
| Week 52, pre-dose | -0.08 (± 14.43) | -0.96 (± 16.31) | | |
| Week 52, 10 min post-dose | 0.07 (± 14.26) | -1.1 (± 16.36) | | |

Notes:

[112] - Safety pop
W 0 post n=657
W 26 pre n=618
W 26 post n=611
W 52 pre n=589
W 52 post n=583
[113] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 25_Electrocardiogram parameters: PR interval

| | |
|-----------------|--|
| End point title | 25_Electrocardiogram parameters: PR interval |
|-----------------|--|

End point description:

PR Interval.

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[114] | 680 ^[115] | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0, 10 min post-dose | -0.65 (± 8.1) | -0.67 (± 7.74) | | |
| Week 26, pre-dose | -1.14 (± 12.82) | -0.23 (± 11.18) | | |
| Week 26, 10 min post-dose | -1.17 (± 12.49) | -0.98 (± 11.08) | | |
| Week 52, pre-dose | -0.35 (± 12.68) | -1.52 (± 12.89) | | |
| Week 52, 10 min post-dose | -1.28 (± 13.31) | -2.08 (± 12.22) | | |

Notes:

[114] - Safety pop
W 0 post n=658
W 26 pre n=618
W 26 post n=611
W 52 pre n=589
W 52 post n=583

[115] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 26_Electrocardiogram parameters: QRS interval

| | |
|-----------------|---|
| End point title | 26_Electrocardiogram parameters: QRS interval |
|-----------------|---|

End point description:

QRS interval.

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 687 ^[116] | 680 ^[117] | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0, 10 min post-dose | 0.1 (± 4.72) | 0.38 (± 4.57) | | |
| Week 26, pre-dose | -0.71 (± 6.91) | -0.17 (± 6.46) | | |
| Week 26, 10 min post-dose | -0.19 (± 6.74) | -0.39 (± 6.71) | | |
| Week 52, pre-dose | -0.58 (± 7.76) | -0.33 (± 7.69) | | |
| Week 52, 10 min post-dose | -0.24 (± 7.48) | -0.06 (± 7.67) | | |

Notes:

[116] - Safety pop
W 0 post n=658
W 26 pre n=618
W 26 post n=611
W 52 pre n=589
W 52 post n=583

[117] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 27_Holter electrocardiogram parameter: 24-h Average heart rate

| | |
|-----------------|--|
| End point title | 27_Holter electrocardiogram parameter: 24-h Average heart rate |
|-----------------|--|

End point description:

Holter electrocardiogram parameter: 24-h Average heart rate values.

Results represent change from baseline (Week 0, pre-dose), to Week 26 and Week 52.

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26, Week 52.

| End point values | Treatment A - fixed combination CHF 5993 100/6/12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 ^[118] | 71 ^[119] | | |
| Units: bmp | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 | 0.3 (± 7.27) | -0.68 (± 10.77) | | |
| Week 52 | 0.45 (± 6.87) | -0.3 (± 9.09) | | |

Notes:

[118] - Holter subset population

Wk 26 n=60

Wk 52 n=58

[119] - Holter subset population

Wk 26 n=62

Wk 52 n=56

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.

Adverse event reporting additional description:

Data represent treatment-emergent adverse events (i.e. events that occurred after the first randomised study drug intake).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Treatment A - fixed combination CHF 5993 100/6 /12.5µg |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Treatment B - fixed combination CHF 1535 100/6µg |
|-----------------------|--|

Reporting group description: -

| Serious adverse events | Treatment A - fixed combination CHF 5993 100/6 /12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 106 / 687 (15.43%) | 123 / 680 (18.09%) | |
| number of deaths (all causes) | 15 | 16 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal tract adenoma | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal cancer stage III | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 2 / 680 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung neoplasm | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 3 / 687 (0.44%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm of conjunctiva | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic gastric cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic thrombosis | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (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 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral artery aneurysm | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leriche syndrome | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 | 1 / 687 (0.15%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 2 / 680 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 66 / 687 (9.61%) | 75 / 680 (11.03%) | |
| occurrences causally related to treatment / all | 0 / 87 | 0 / 86 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 4 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung cyst | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (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 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 687 (0.29%) | 2 / 680 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Vocal cord leukoplakia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (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 | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cranio-cerebral injury | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Poisoning | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural fistula | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (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 myocardial infarction | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 3 / 680 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 687 (0.44%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 2 / 680 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 687 (0.58%) | 3 / 680 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 2 / 687 (0.29%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cor pulmonale | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 3 / 680 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 4 / 680 (0.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sick sinus syndrome | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| 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 | 0 / 687 (0.00%) | 2 / 680 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (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 | | | |
| Haemorrhagic disorder | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic erosive gastritis | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hernial eventration | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 2 / 680 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 2 / 687 (0.29%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 2 / 687 (0.29%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary colic | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Urinary retention | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 687 (0.00%) | 1 / 680 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 14 / 687 (2.04%) | 6 / 680 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 687 (0.15%) | 0 / 680 (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: 5 %

| Non-serious adverse events | Treatment A - fixed combination CHF 5993 100/6 /12.5µg | Treatment B - fixed combination CHF 1535 100/6µg | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 330 / 687 (48.03%) | 341 / 680 (50.15%) | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 159 / 687 (23.14%) | 184 / 680 (27.06%) | |
| occurrences (all) | 212 | 274 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 39 / 687 (5.68%) | 38 / 680 (5.59%) | |
| occurrences (all) | 50 | 45 | |

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. |
|-------|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27598678>