# Clinical trial results:
# A 24-WEEK, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO AND ACTIVE CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 4 DOSES OF CHF 6001 DPI IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) ON A BACKGROUND THERAPY.

## Summary

| | |
|---|---|
| EudraCT number | 2015-005548-32 |
| Trial protocol | GB DE HU PL BG |
| Global end of trial date | 09 January 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 January 2019 |
| First version publication date | 25 January 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CCD-06001AA1-01 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02986321 |
| WHO universal trial number (UTN) | - |

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 | 22 October 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 January 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 January 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this trial was to investigate the dose-response relationship of 4 doses of CHF 6001 dry powder inhaler (DPI) with respect to pre-dose forced expiratory volume in the 1st second (FEV1) after 12 weeks of treatment and to identify the optimal dose of CHF 6001 for further development in patients with moderate to severe COPD already treated with background therapy.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, and following all other requirements of local laws.
At all visits from screening onwards, concomitant medications and adverse events were recorded and physical examination of subjects was carried out. Vital signs were recorded pre-dose and pre-dose spirometry (including inspiratory capacity [IC], FEV1 and forced vital capacity [FVC]) was performed at screening, randomisation and all post-randomisation visits until the last treatment visit. Baseline Dyspnoea Index (BDI) was recorded at randomisation and Transition Dyspnoea Index (TDI) was recorded at all post-randomisation visits until the last treatment visit. COPD exacerbations were assessed at all post-randomisation visits.
Subjects were provided with salbutamol as rescue medication.
From screening, the electronic diary (eDiary) was completed by patients from home on a daily basis to record rescue medication use, compliance with background medication and study treatment, and COPD exacerbation-related outcomes (using the EXAcerbations of Chronic pulmonary disease Tool - Patient Reported Outcome [EXACT-PRO]/Respiratory Symptoms [E-RS] questionnaire). Health related quality of life was assessed at all visits over the randomised treatment period using the St. George's Respiratory Questionnaire (SGRQ).
Blood collection for routine haematology and blood chemistry was performed at screening, randomisation, Week 12 and last treatment visits; thyroid functions were tested at screening. From screening, 12-lead electrocardiogram (ECG) parameters (heart rate [HR], Fridericia-corrected QT interval [QTcF], PR interval [PR] and QRS interval [QRS]) were recorded.

Background therapy:

Patients received formoterol fumarate 12 µg (one inhalation twice daily, total daily dose 24 µg) as background medication during the two-week run-in period, which was continued at the same dose throughout the study. Patients also received salbutamol as rescue medication (dose of 100 µg pressured metered dose inhaler [pMDI] as needed [PRN], maximum of 8 puffs/day), to be used throughout the study.

Evidence for comparator:

Budesonide (ICS)

| | |
|---|---|
| Actual start date of recruitment | 15 December 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 210 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Bulgaria: 126 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Hungary: 87 |
| Country: Number of subjects enrolled | Russian Federation: 263 |
| Country: Number of subjects enrolled | Ukraine: 425 |
| Worldwide total number of subjects | 1130 |
| EEA total number of subjects | 442 |

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) | 554 |
| From 65 to 84 years | 573 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details:

Overall, 1593 patients were screened according to inclusion and exclusion criteria; of these, 1130 patients were randomised.

### Pre-assignment

Screening details:

At screening, not more than 7 days after a pre-screening visit, inclusion/exclusion criteria were assessed. There were 463 screening failures (failure to meet randomisation criteria [418 patients], consent withdrawal [31 patients] , other reasons [5 patients], AEs [4 patients], protocol deviations [3 patients], lost to follow-up [2 patients]).

### Period 1

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

Blinding implementation details:

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CHF 6001 800 µg |

Arm description:

Patients were randomised to receive CHF 6001 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, pre-dispensed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®100 µg/actuation.
Double-blind double-dummy design: During study visits patients in the CHF 6001 800 µg group received two boxes, each with two NEXThaler®s with CHF 6001 100 µg/actuation and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.
Dose: 2 inhalations of CHF 6001 100 µg/actuation plus 2 inhalations of CHF 6001 100 µg/actuation plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).
Total daily dose: CHF 6001 800 µg.
Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®). Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

| | |
|---|---|
| **Arm title** | CHF 6001 1600 µg |

Arm description:

Patients were randomised to receive CHF 6001 1600 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, pre-dispensed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®400 µg/actuation.
Double-blind double-dummy design: During study visits patients in the CHF 6001 1600 µg group received two boxes, each with a NEXThaler® with CHF 6001 400 µg/actuation, a NEXThaler® with CHF 6001 matched Placebo and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other box to be used for evening administration of study medication.
Dose: 2 inhalations of CHF 6001 400 µg/actuation plus 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).
Total daily dose: CHF 6001 1600 µg.
Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).
Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

| | |
|---|---|
| **Arm title** | CHF 6001 2400 µg |

Arm description:

Patients were randomised to receive CHF 6001 2400 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, pre-dispensed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®300 µg/actuation.
Double-blind double-dummy design: During study visits patients in the CHF 6001 2400 µg group received two boxes, each with two NEXThaler®s with CHF 6001 300 µg/actuation and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.
Dose: 2 inhalations of CHF 6001 300 µg/actuation plus 2 inhalations of CHF 6001 300 µg/actuation plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).
Total daily dose: CHF 6001 2400 µg.
Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).
Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

| | |
|---|---|
| **Arm title** | CHF 6001 3200 µg |

Arm description:

Patients were randomised to receive CHF 6001 3200 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 6001 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, pre-dispensed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: CHF 6001 DPI NEXThaler®400 µg/actuation.
Double-blind double-dummy design: During study visits patients in the CHF 6001 3200 µg group received two boxes, each with two NEXThaler®s with CHF 6001 400 µg/actuation and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.

Dose: 2 inhalations of CHF 6001 400 µg/actuation plus 2 inhalations of CHF 6001 400 µg/actuation plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).
Total daily dose: CHF 6001 3200 µg.
Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).
Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

| **Arm title** | Budesonide 800 µg |
|---|---|

Arm description:

Patients were randomised to receive Budesonide 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Budesonide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, pre-dispensed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: Budesonide DPI Pulmicort® Turbohaler® 200 µg/actuation.
Double-blind double-dummy design: During study visits, patients in the Budesonide 800 µg group received two boxes, each with two NEXThaler®s with CHF 6001 matched Placebo and a Budesonide DPI (Pulmicort® Turbohaler®) 200 µg/actuation, one box to be used for morning administration and the other to be used for evening administration of study medication.
Dose: 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of Budesonide DPI 200 µg/actuation, all twice daily (BID).
Total daily dose: Budesonide 800 µg.
Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).
Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

| **Arm title** | Placebo |
|---|---|

Arm description:

Patients were randomised to receive Placebo for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, pre-dispensed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: Matched Placebo.
Double-blind double-dummy design: During study visits patients in the Placebo group received two boxes, each with two CHF 6001 DPI NEXThaler® matched Placebos and a Budesonide DPI (Pulmicort® Turbohaler®) matched Placebo, one box to be used for morning administration and the other to be used for evening administration of study medication.
Dose: 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of CHF 6001 matched Placebo plus 2 inhalations of Budesonide DPI matched Placebo, all twice daily (BID).
Total daily dose: Not applicable.
Mode of administration: Dry powder inhalation using DPIs (NEXThaler®, Pulmicort® Turbohaler®).
Patients were trained in the use of DPIs with training kits containing a NEXThaler® and a Pulmicort® Turbohaler®, both with Placebo.

| **Number of subjects in period 1** | CHF 6001 800 µg | CHF 6001 1600 µg | CHF 6001 2400 µg |
|---|---|---|---|
| Started | 190 | 179 | 188 |
| Completed | 175 | 162 | 176 |
| Not completed | 15 | 17 | 12 |
| Adverse event, serious fatal | 1 | 1 | 1 |
| Consent withdrawn by subject | 7 | 10 | 5 |
| No reason specified | 2 | 1 | 1 |
| Adverse event, non-fatal | 3 | 2 | 3 |
| Lost to follow-up | - | - | - |
| Lack of efficacy | 2 | 1 | 2 |
| Protocol deviation | - | 2 | - |

| **Number of subjects in period 1** | CHF 6001 3200 µg | Budesonide 800 µg | Placebo |
|---|---|---|---|
| Started | 193 | 187 | 193 |
| Completed | 173 | 175 | 177 |
| Not completed | 20 | 12 | 16 |
| Adverse event, serious fatal | 2 | - | - |
| Consent withdrawn by subject | 5 | 4 | 7 |
| No reason specified | 4 | 1 | 3 |
| Adverse event, non-fatal | 6 | 2 | 5 |
| Lost to follow-up | - | 1 | - |
| Lack of efficacy | 3 | 4 | 1 |
| Protocol deviation | - | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | CHF 6001 800 µg |
| Reporting group description: | |
| Patients were randomised to receive CHF 6001 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period. | |
| Reporting group title | CHF 6001 1600 µg |
| Reporting group description: | |
| Patients were randomised to receive CHF 6001 1600 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period | |
| Reporting group title | CHF 6001 2400 µg |
| Reporting group description: | |
| Patients were randomised to receive CHF 6001 2400 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period | |
| Reporting group title | CHF 6001 3200 µg |
| Reporting group description: | |
| Patients were randomised to receive CHF 6001 3200 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period | |
| Reporting group title | Budesonide 800 µg |
| Reporting group description: | |
| Patients were randomised to receive Budesonide 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients were randomised to receive Placebo for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period | |

| Reporting group values | CHF 6001 800 µg | CHF 6001 1600 µg | CHF 6001 2400 µg |
|---|---|---|---|
| Number of subjects | 190 | 179 | 188 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 94 | 80 | 90 |
| From 65-84 years | 96 | 98 | 98 |
| 85 years and over | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 57 | 50 | 57 |
| Male | 133 | 129 | 131 |

| **Reporting group values** | CHF 6001 3200 µg | Budesonide 800 µg | Placebo |
|---|---|---|---|
| Number of subjects | 193 | 187 | 193 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 104 | 91 | 95 |
| From 65-84 years | 89 | 95 | 97 |
| 85 years and over | 0 | 1 | 1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 58 | 55 | 60 |
| Male | 135 | 132 | 133 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 1130 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 554 | | |
| From 65-84 years | 573 | | |
| 85 years and over | 3 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 337 | | |
| Male | 793 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CHF 6001 800 µg |

Reporting group description:

Patients were randomised to receive CHF 6001 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period.

| | |
|---|---|
| Reporting group title | CHF 6001 1600 µg |

Reporting group description:

Patients were randomised to receive CHF 6001 1600 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Reporting group title | CHF 6001 2400 µg |

Reporting group description:

Patients were randomised to receive CHF 6001 2400 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Reporting group title | CHF 6001 3200 µg |

Reporting group description:

Patients were randomised to receive CHF 6001 3200 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Reporting group title | Budesonide 800 µg |

Reporting group description:

Patients were randomised to receive Budesonide 800 µg for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Patients were randomised to receive Placebo for 24 weeks, following the 2-week run-in period during which they received background medication (formoterol fumarate 24 µg/day) and rescue medication (salbutamol, as required). Patients continued to receive the background and rescue medications throughout the treatment period

| | |
|---|---|
| Subject analysis set title | CHF 6001 800 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

| | |
|---|---|
| Subject analysis set title | CHF 6001 1600 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

| | |
|---|---|
| Subject analysis set title | CHF 6001 2400 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

| | |
|---|---|
| Subject analysis set title | CHF 6001 3200 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

| Subject analysis set title | Budesonide 800 µg - ITT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

| Subject analysis set title | Placebo - ITT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after the baseline.

## Primary: Change from baseline in morning pre-dose FEV1 at Week 12

| End point title | Change from baseline in morning pre-dose FEV1 at Week 12 |
|---|---|

End point description:

Morning pre-dose forced expiratory volume in the first second (FEV1).

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

End point timeframe:

Baseline (pre-dose at the randomisation visit, Week 0) to Week 12.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 177[1] | 166[2] | 178[3] | 178[4] |
| Units: Litres | | | | |
| least squares mean (confidence interval 95%) | -0.004 (-0.037 to 0.028) | 0.011 (-0.022 to 0.044) | 0.004 (-0.029 to 0.036) | -0.024 (-0.057 to 0.008) |

Notes:

[1] - Number of patients in the ITT population = 190, number of patients with available data = 177

[2] - Number of patients in the ITT population = 179, number of patients with available data = 166

[3] - Number of patients in the ITT population = 188, number of patients with available data = 178

[4] - Number of patients in the ITT population = 193, number of patients with available data = 178

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 178[5] | 176[6] | | |
| Units: Litres | | | | |
| least squares mean (confidence interval 95%) | -0.002 (-0.035 to 0.030) | -0.006 (-0.039 to 0.026) | | |

Notes:

[5] - Number of patients in the ITT population = 187, number of patients with available data = 178

[6] - Number of patients in the ITT population = 193, number of patients with available data = 176

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB FEV1 at Week 12 |
|---|---|

Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects

and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 353 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.932 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.002 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.044 |
| upper limit | 0.048 |

| **Statistical analysis title** | Adjusted mean difference in CFB FEV1 at Week 12 |
|---|---|

Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 342 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.47 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.017 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.029 |
| upper limit | 0.064 |

| **Statistical analysis title** | Adjusted mean difference in CFB FEV1 at Week 12 |
|---|---|

Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 354 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.673 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.036 |
| upper limit | 0.056 |

| **Statistical analysis title** | Adjusted mean difference in CFB FEV1 at Week 12 |
|---|---|

Statistical analysis description:

The CFB in pre-dose morning FEV1 was analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction and sites pooled by country as effects and baseline FEV1 value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo were estimated by the model. Comparisons with Budesonide were also provided.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 354 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.433 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.018 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.064 |
| upper limit | 0.027 |

## Secondary: TDI score at Week 3

| End point title | TDI score at Week 3 |
|---|---|

End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

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

End point timeframe:

Week 3

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 181[7] | 172[8] | 183[9] | 185[10] |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 0.84 (0.51 to 1.17) | 0.74 (0.39 to 1.08) | 0.65 (0.32 to 0.98) | 0.58 (0.25 to 0.91) |

Notes:

[7] - Number of patients in the ITT population = 190, number of patients with available data = 181

[8] - Number of patients in the ITT population = 179, number of patients with available data = 172

[9] - Number of patients in the ITT population = 188, number of patients with available data = 183

[10] - Number of patients in the ITT population = 193, number of patients with available data = 185

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 181[11] | 187[12] | | |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 0.89 (0.56 to 1.22) | 0.73 (0.40 to 1.06) | | |

Notes:

[11] - Number of patients in the ITT population = 187, number of patients with available data = 181

[12] - Number of patients in the ITT population = 193, number of patients with available data = 187

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 368 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.645 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.36 |
| upper limit | 0.57 |

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are

presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 359 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.968 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | 0.48 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 370 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.753 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 0.39 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.537 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.62 |
| upper limit | 0.32 |

## Secondary: TDI score at Week 6

| | |
|---|---|
| End point title | TDI score at Week 6 |

End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

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

End point timeframe:

Week 6

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 183[13] | 168[14] | 181[15] | 184[16] |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.28 (0.96 to 1.61) | 1.14 (0.79 to 1.48) | 1.17 (0.83 to 1.50) | 1.09 (0.75 to 1.42) |

Notes:

[13] - Number of patients in the ITT population = 190, number of patients with available data = 183

[14] - Number of patients in the ITT population = 179, number of patients with available data = 168

[15] - Number of patients in the ITT population = 188, number of patients with available data = 181

[16] - Number of patients in the ITT population = 193, number of patients with available data = 184

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179[17] | 186[18] | | |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.44 (1.11 to 1.77) | 1.15 (0.82 to 1.48) | | |

Notes:

[17] - Number of patients in the ITT population = 187, number of patients with available data = 179

[18] - Number of patients in the ITT population = 193, number of patients with available data = 186

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 369 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.574 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 0.6 |

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 354 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.957 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 0.46 |

| Statistical analysis title | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are

presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 367 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.945 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | 0.49 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 370 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.793 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.41 |

## Secondary: TDI score at Week 12

| End point title | TDI score at Week 12 |
|---|---|

End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

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

End point timeframe:

Week 12

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 179[19] | 164[20] | 178[21] | 182[22] |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.23 (0.88 to 1.57) | 1.21 (0.84 to 1.57) | 1.15 (0.80 to 1.50) | 0.99 (0.64 to 1.34) |

Notes:

[19] - Number of patients in the ITT population = 190, number of patients with available data = 179

[20] - Number of patients in the ITT population = 179, number of patients with available data = 164

[21] - Number of patients in the ITT population = 188, number of patients with available data = 178

[22] - Number of patients in the ITT population = 193, number of patients with available data = 182

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 180[23] | 178[24] | | |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.03 (0.68 to 1.37) | 1.21 (0.86 to 1.56) | | |

Notes:

[23] - Number of patients in the ITT population = 187, number of patients with available data = 180

[24] - Number of patients in the ITT population = 193, number of patients with available data = 178

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.948 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 0.51 |

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 342 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.988 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 0.5 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.82 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.44 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 360 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.387 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.72 |
| upper limit | 0.28 |

## Secondary: TDI score at Week 18

| | |
|---|---|
| End point title | TDI score at Week 18 |

End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

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

End point timeframe:

Week 18

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 178[25] | 164[26] | 178[27] | 172[28] |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.09 (0.74 to 1.45) | 1.14 (0.76 to 1.52) | 1.07 (0.71 to 1.43) | 1.11 (0.73 to 1.48) |

Notes:

[25] - Number of patients in the ITT population = 190, number of patients with available data = 178

[26] - Number of patients in the ITT population = 179, number of patients with available data = 164

[27] - Number of patients in the ITT population = 188, number of patients with available data = 178

[28] - Number of patients in the ITT population = 193, number of patients with available data = 172

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 177[29] | 178[30] | | |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.19 (0.83 to 1.55) | 0.96 (0.60 to 1.32) | | |

Notes:

[29] - Number of patients in the ITT population = 187, number of patients with available data = 177

[30] - Number of patients in the ITT population = 193, number of patients with available data = 178

## Statistical analyses

| **Statistical analysis title** | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.606 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.37 |
| upper limit | 0.64 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 342 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.496 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 0.7 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are

presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.678 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.62 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal score |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 350 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.582 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.37 |
| upper limit | 0.66 |

## Secondary: TDI score at Week 24

| End point title | TDI score at Week 24 |
|---|---|

End point description:

The Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI) is a clinical rating used to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. The BDI focal scores were recorded at the randomisation visit (Week 0) and TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). A TDI focal score ≥ 1 is considered the minimal clinically important difference (MCID) for this instrument.

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

End point timeframe:

Week 24

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 175[31] | 159[32] | 175[33] | 172[34] |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.54 (1.19 to 1.90) | 1.28 (0.90 to 1.65) | 1.49 (1.13 to 1.85) | 1.44 (1.08 to 1.81) |

Notes:

[31] - Number of patients in the ITT population = 190, number of patients with available data = 175

[32] - Number of patients in the ITT population = 179, number of patients with available data = 159

[33] - Number of patients in the ITT population = 188, number of patients with available data = 175

[34] - Number of patients in the ITT population = 193, number of patients with available data = 172

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 174[35] | 177[36] | | |
| Units: TDI focal scores | | | | |
| least squares mean (confidence interval 95%) | 1.49 (1.13 to 1.84) | 1.46 (1.11 to 1.82) | | |

Notes:

[35] - Number of patients in the ITT population = 187, number of patients with available data = 174

[36] - Number of patients in the ITT population = 193, number of patients with available data = 177

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.758 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | 0.58 |

| Statistical analysis title | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 336 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.484 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.33 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.922 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 0.53 |

| **Statistical analysis title** | Adjusted mean difference in TDI focal scores |
|---|---|

Statistical analysis description:

The TDI focal scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, BDI score at randomisation (Week 0) and BDI score by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 349 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.939 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.49 |

## Secondary: TDI response

| | |
|---|---|
| End point title | TDI response |

End point description:

TDI focal scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24) . A TDI response is defined as TDI focal score ≥ 1 unit. TDI response was assessed at each post-randomisation visit. Patients with TDI focal score < 1 unit or with missing data at any visit were classed as non-responders.

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

End point timeframe:

Week 3, Week 6, Week 12, Week 18, Week 24.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 190[37] | 179[38] | 188[39] | 193[40] |
| Units: Patients | | | | |
| number (not applicable) | | | | |
| Week 3 | 85 | 74 | 70 | 84 |
| Week 6 | 94 | 83 | 83 | 94 |
| Week 12 | 90 | 78 | 84 | 80 |
| Week 18 | 83 | 81 | 81 | 80 |
| Week 24 | 96 | 77 | 90 | 88 |

Notes:

[37] - ITT population

[38] - ITT population

[39] - ITT population

[40] - ITT population

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 187[41] | 193[42] | | |
| Units: Patients | | | | |
| number (not applicable) | | | | |
| Week 3 | 85 | 80 | | |

| | | | | |
|---|---|---|---|---|
| Week 6 | 95 | 88 | | |
| Week 12 | 86 | 93 | | |
| Week 18 | 85 | 86 | | |
| Week 24 | 95 | 100 | | |

Notes:

[41] - ITT population

[42] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline to Week 3 in SGRQ total score

| End point title | Change from baseline to Week 3 in SGRQ total score |
|---|---|

End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

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

End point timeframe:

Baseline to Week 3.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 184[43] | 173[44] | 185[45] | 186[46] |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -1.49 (-3.08 to 0.10) | -2.90 (-4.53 to -1.26) | -2.37 (-3.95 to -0.79) | -2.87 (-4.44 to -1.30) |

Notes:

[43] - Number of patients in the ITT population = 190, number of patients with available data = 184

[44] - Number of patients in the ITT population = 179, number of patients with available data = 173

[45] - Number of patients in the ITT population = 188, number of patients with available data = 185

[46] - Number of patients in the ITT population = 193, number of patients with available data = 186

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 183[47] | 189[48] | | |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -3.46 (-5.05 to -1.87) | -3.51 (-5.07 to -1.94) | | |

Notes:

[47] - Number of patients in the ITT population = 187, number of patients with available data = 183

[48] - Number of patients in the ITT population = 193, number of patients with available data = 189

### Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 373 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.075 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 2.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 4.25 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.594 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.65 |
| upper limit | 2.88 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 374 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.314 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.08 |
| upper limit | 3.37 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 375 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.572 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.58 |
| upper limit | 2.86 |

## Secondary: Change from baseline to Week 6 in SGRQ total score

| End point title | Change from baseline to Week 6 in SGRQ total score |
|---|---|

End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

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

End point timeframe:

Baseline to Week 6

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 181[49] | 170[50] | 184[51] | 182[52] |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -2.21 (-3.92 to -0.50) | -5.21 (-6.96 to -3.45) | -4.12 (-5.82 to -2.43) | -4.82 (-6.52 to -3.12) |

Notes:

[49] - Number of patients in the ITT population = 190, number of patients with available data = 181

[50] - Number of patients in the ITT population = 179, number of patients with available data = 170

[51] - Number of patients in the ITT population = 188, number of patients with available data = 184

[52] - Number of patients in the ITT population = 193, number of patients with available data = 182

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 182[53] | 184[54] | | |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -5.32 (-7.03 to -3.62) | -5.42 (-7.11 to -3.73) | | |

Notes:

[53] - Number of patients in the ITT population = 187, number of patients with available data = 182

[54] - Number of patients in the ITT population = 193, number of patients with available data = 184

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 3.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 5.61 |

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo

estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 354 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.865 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.23 |
| upper limit | 2.65 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 368 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.289 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 3.69 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The changes from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 366 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.624 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 2.99 |

## Secondary: Change from baseline to Week 12 in SGRQ total score

| | |
|---|---|
| End point title | Change from baseline to Week 12 in SGRQ total score |

End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

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

End point timeframe:

Baseline to Week 12

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 176[55] | 167[56] | 179[57] | 180[58] |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -4.53 (-6.43 to -2.62) | -6.62 (-8.57 to -4.66) | -4.58 (-6.47 to -2.69) | -6.38 (-8.26 to -4.50) |

Notes:

[55] - Number of patients in the ITT population = 190, number of patients with available data = 176

[56] - Number of patients in the ITT population = 179, number of patients with available data = 167

[57] - Number of patients in the ITT population = 188, number of patients with available data = 179

[58] - Number of patients in the ITT population = 193, number of patients with available data = 180

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 180[59] | 179[60] | | |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -5.56 (-7.45 to -3.67) | -6.17 (-8.06 to -4.29) | | |

Notes:

[59] - Number of patients in the ITT population = 187, number of patients with available data = 180

[60] - Number of patients in the ITT population = 193, number of patients with available data = 179

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.227 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.03 |
| upper limit | 4.33 |

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.75 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.15 |
| upper limit | 2.27 |

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo

estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.241 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.07 |
| upper limit | 4.26 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 359 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.879 |
| Method | Linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.87 |
| upper limit | 2.46 |

## Secondary: Change from baseline to Week 18 in SGRQ total score

| End point title | Change from baseline to Week 18 in SGRQ total score |
|---|---|

End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

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

End point timeframe:

Baseline to Week 18

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 176[61] | 163[62] | 179[63] | 176[64] |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -6.04 (-7.98 to -4.09) | -7.93 (-9.94 to -5.92) | -5.18 (-7.11 to -3.25) | -6.09 (-8.02 to -4.15) |

Notes:

[61] - Number of patients in the ITT population = 190, number of patients with available data = 176

[62] - Number of patients in the ITT population = 179, number of patients with available data = 163

[63] - Number of patients in the ITT population = 188, number of patients with available data = 179

[64] - Number of patients in the ITT population = 193, number of patients with available data = 176

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 176[65] | 178[66] | | |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -5.91 (-7.85 to -3.97) | -6.50 (-8.42 to -4.57) | | |

Notes:

[65] - Number of patients in the ITT population = 187, number of patients with available data = 176

[66] - Number of patients in the ITT population = 193, number of patients with available data = 178

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 354 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.742 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.28 |
| upper limit | 3.2 |

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.313 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -1.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.22 |
| upper limit | 1.35 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.344 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.41 |
| upper limit | 4.05 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 354 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.769 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.32 |
| upper limit | 3.14 |

## Secondary: Change from baseline to Week 24 in SGRQ total score

| | |
|---|---|
| End point title | Change from baseline to Week 24 in SGRQ total score |

End point description:

The St. George's Respiratory Questionnaire (SGRQ) is used to measure health-related quality of life. Decrease in SGRQ total scores indicates improvement. Baseline SGRQ total score was recorded at the randomisation visit (Week 0) and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). The minimal clinically important difference (MCID) for this instrument is a decrease from baseline of ≥ 4 units.

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

End point timeframe:

Baseline to Week 24

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 172[67] | 162[68] | 175[69] | 173[70] |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -5.54 (-7.64 to -3.43) | -8.06 (-10.24 to -5.89) | -5.95 (-8.04 to -3.86) | -6.96 (-9.06 to -4.87) |

Notes:

[67] - Number of patients in the ITT population = 190, number of patients with available data = 172

[68] - Number of patients in the ITT population = 179, number of patients with available data = 162

[69] - Number of patients in the ITT population = 188, number of patients with available data = 175

[70] - Number of patients in the ITT population = 193, number of patients with available data = 173

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 176[71] | 177[72] | | |
| Units: SGRQ total scores | | | | |
| least squares mean (confidence interval 95%) | -7.11 (-9.20 to -5.02) | -7.48 (-9.57 to -5.40) | | |

Notes:

[71] - Number of patients in the ITT population = 187, number of patients with available data = 176

[72] - Number of patients in the ITT population = 193, number of patients with available data = 177

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 349 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.198 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.02 |
| upper limit | 4.91 |

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 339 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.705 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.59 |
| upper limit | 2.43 |

| Statistical analysis title | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo

estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.307 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 1.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.42 |
| upper limit | 4.49 |

| **Statistical analysis title** | Adjusted mean difference in CFB, SGRQ total score |
|---|---|

Statistical analysis description:

The change from baseline (CFB) in SGRQ total scores were analysed using a linear MMRM including treatment, visit, treatment by visit interaction and sites pooled by country as effects, baseline (pre-dose at Week 0) and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 350 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.73 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.43 |
| upper limit | 3.47 |

## Secondary: SGRQ response

| End point title | SGRQ response |
|---|---|

End point description:

SGRQ response is defined as a decrease from baseline in SGRQ total score ≥ 4 units. Baseline SGRQ total scores were recorded at the randomisation visit (Week 0), and SGRQ total scores were recorded at all post-randomisation visits (Week 3, Week 6, Week 12, Week 18 and Week 24). Patients with decrease from baseline in SGRQ score ≥ 4 units at any visit were classed as responders. Patients with a decrease from baseline in SGRQ total score < 4 units or with missing data at any visit, were classed as non-responders.

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

End point timeframe:

Week 3, Week 6, Week 12, Week 18 and Week 24.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 190[73] | 179[74] | 188[75] | 193[76] |
| Units: Patients | | | | |
| number (not applicable) | | | | |
| Week 3 | 83 | 71 | 81 | 74 |
| Week 6 | 80 | 90 | 90 | 92 |
| Week 12 | 93 | 96 | 87 | 97 |
| Week 18 | 98 | 95 | 101 | 102 |
| Week 24 | 91 | 98 | 94 | 90 |

Notes:

[73] - ITT population

[74] - ITT population

[75] - ITT population

[76] - ITT population

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 187[77] | 193[78] | | |
| Units: Patients | | | | |
| number (not applicable) | | | | |
| Week 3 | 92 | 88 | | |
| Week 6 | 93 | 95 | | |
| Week 12 | 95 | 90 | | |
| Week 18 | 92 | 97 | | |
| Week 24 | 93 | 92 | | |

Notes:

[77] - ITT population

[78] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: CFB to the entire treatment period in average E-RS total score

| End point title | CFB to the entire treatment period in average E-RS total score |
|---|---|

End point description:

The EXAcerbations of Chronic pulmonary disease Tool (EXACT) collects patient-reported outcomes (PRO) data in order to capture frequency, severity and time course of COPD exacerbations. Digital platform technology was used for data collection in this study. Average EXACT-Respiratory Symptoms (E-RS) scores were recorded during the 2-week run-in period (baseline) and over the entire treatment period of 24 weeks. Change from baseline (CFB) over the entire treatment period was analysed. A decrease from baseline in average E-RS scores ≥ 2.0 is the minimal clinically important difference (MCID) for this instrument.

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

End point timeframe:

Baseline (run-in period) to 24 weeks treatment period.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 187[79] | 176[80] | 186[81] | 187[82] |
| Units: Average E-RS total scores | | | | |
| least squares mean (confidence interval 95%) | -1.53 (-2.21 to -0.94) | -2.41 (-3.01 to -1.80) | -1.89 (-2.48 to -1.31) | -2.07 (-2.66 to -1.48) |

Notes:

[79] - Number of patients in the ITT population = 190, number of patients with available data = 187

[80] - Number of patients in the ITT population = 179, number of patients with available data = 176

[81] - Number of patients in the ITT population = 188, number of patients with available data = 186

[82] - Number of patients in the ITT population = 193, number of patients with available data = 187

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 184[83] | 193[84] | | |
| Units: Average E-RS total scores | | | | |
| least squares mean (confidence interval 95%) | -2.35 (-2.94 to -1.76) | -2.12 (-2.79 to -1.63) | | |

Notes:

[83] - Number of patients in the ITT population = 187, number of patients with available data = 184

[84] - Number of patients in the ITT population = 193, number of patients with available data = 193

## Statistical analyses

| Statistical analysis title | Adjusted mean difference in CFB, E-RS total score |
|---|---|

Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 380 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.105 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.14 |
| upper limit | 1.5 |

| Statistical analysis title | Adjusted mean difference in CFB, E-RS total score |
|---|---|

Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 369 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.647 |
| Method | lnear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.03 |
| upper limit | 0.64 |

| **Statistical analysis title** | Adjusted mean difference in CFB, E-RS total score |
|---|---|

Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 379 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.451 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 1.14 |

| **Statistical analysis title** | Adjusted mean difference in CFB, E-RS total score |
|---|---|

Statistical analysis description:

Analysis of change from baseline (CFB) to the entire treatment period in average E-RS total scores was based on a linear mixed model for repeated measures (MMRM) including treatment, inter-Visit period, treatment by inter-Visit period interaction and Pooled Country as fixed effects, and baseline value and baseline by inter-Visit period interaction as covariates. Adjusted mean differences (95% CIs) between the CHF 6001 treatments and Placebo are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 380 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.737 |
| Method | linear MMRM |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 0.97 |

## Secondary: E-RS response

| | |
|---|---|
| End point title | E-RS response |

End point description:

Average E-RS total scores were recorded during the run-in period (baseline) and for each inter-visit period over the treatment period of 24 weeks. The proportion of patients with a decrease from baseline in average E-RS total score ≥ 2.0 were classed as responders; patients with a decrease from baseline in average E-RS total score < 2.0 units or with missing data for any inter-visit period were classed as non-responders.

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

End point timeframe:

Baseline (two-week run-in period) and inter-visit periods Week 1 to Week 3, Week 4 to Week 6, Week 7 to Week 12, Week 13 to Week 18 and Week 19 to Week 24.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 190[85] | 179[86] | 188[87] | 193[88] |
| Units: Patients | | | | |
| number (not applicable) | | | | |
| Week 1 to Week 3 | 58 | 65 | 54 | 58 |
| Week 4 to Week 6 | 73 | 82 | 62 | 82 |
| Week 7 to Week 12 | 78 | 86 | 72 | 87 |
| Week 13 to Week 18 | 74 | 84 | 83 | 77 |
| Week 19 to Week 24 | 79 | 94 | 80 | 82 |

Notes:

[85] - ITT population

[86] - ITT population

[87] - ITT population

[88] - ITT population

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 187[89] | 193[90] | | |
| Units: Patients | | | | |

| number (not applicable) | | | | |
|---|---|---|---|---|
| Week 1 to Week 3 | 60 | 62 | | |
| Week 4 to Week 6 | 76 | 73 | | |
| Week 7 to Week 12 | 89 | 81 | | |
| Week 13 to Week 18 | 90 | 93 | | |
| Week 19 to Week 24 | 86 | 89 | | |

Notes:

[89] - ITT population

[90] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Moderate and severe COPD exacerbation rate over 24 weeks of treatment

| End point title | Moderate and severe COPD exacerbation rate over 24 weeks of treatment |
|---|---|

End point description:

The rate of moderate or severe COPD exacerbations was evaluated over 24 weeks of treatment. Exacerbations were classified as moderate or severe as per European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) guideline definitions. A moderate exacerbation was defined as a sustained worsening of the patient's condition that required treatment with systemic (oral/IV/IM) corticosteroids and/or antibiotics. A severe exacerbation was defined as one that required hospitalisation or resulted in death. The recognition of potential COPD exacerbations was optimised by the daily reporting of worsened symptoms through the EXAcerbations of Chronic pulmonary disease Tool - Patient Reported Outcome (EXACT-PRO) questionnaire.

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

End point timeframe:

Baseline to 24 weeks.

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 190[91] | 179[92] | 188[93] | 193[94] |
| Units: Adjusted exacerbation rate/patient/year | | | | |
| number (confidence interval 95%) | 0.563 (0.414 to 0.764) | 0.585 (0.428 to 0.799) | 0.593 (0.440 to 0.801) | 0.487 (0.351 to 0.675) |

Notes:

[91] - ITT population

[92] - ITT population

[93] - ITT population

[94] - ITT population

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 187[95] | 193[96] | | |
| Units: Adjusted exacerbation rate/patient/year | | | | |
| number (confidence interval 95%) | 0.415 (0.292 to 0.589) | 0.681 (0.514 to 0.902) | | |

Notes:
[95] - ITT population
[96] - ITT population

## Statistical analyses

| **Statistical analysis title** | Adjusted exacerbation rate ratio |
|---|---|

Statistical analysis description:

The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 383 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.367 |
| Method | Negative binomial model |
| Parameter estimate | Adjusted rate ratio |
| Point estimate | 0.826 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.546 |
| upper limit | 1.251 |

| **Statistical analysis title** | Adjusted exacerbation rate ratio |
|---|---|

Statistical analysis description:

The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.479 |
| Method | Negative binomial model |
| Parameter estimate | Adjusted rate ratio |
| Point estimate | 0.859 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.565 |
| upper limit | 1.307 |

| Statistical analysis title | Adjusted exacerbation rate ratio |
|---|---|

Statistical analysis description:

The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 381 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51 |
| Method | Negative binomial model |
| Parameter estimate | Adjusted rate ratio |
| Point estimate | 0.871 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.578 |
| upper limit | 1.313 |

| Statistical analysis title | Adjusted exacerbation rate ratio |
|---|---|

Statistical analysis description:

The rate of moderate and severe COPD exacerbations over 24 weeks of treatment was analysed using a negative binomial model including treatment and sites pooled by country as factors and logarithm of time into the study as an offset. Adjusted rate ratios (95% CIs) for CHF 6001 treatments over Placebo estimated by the model are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 386 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.127 |
| Method | Negative binomial model |
| Parameter estimate | Adjusted rate ratio |
| Point estimate | 0.715 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.465 |
| upper limit | 1.1 |

## Secondary: Time to first moderate or severe COPD exacerbation

| End point title | Time to first moderate or severe COPD exacerbation |
|---|---|

End point description:

The number of patients at risk of a moderate or severe COPD exacerbation is presented.

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

End point timeframe:

Baseline to 24 weeks

| End point values | CHF 6001 800 µg - ITT | CHF 6001 1600 µg - ITT | CHF 6001 2400 µg - ITT | CHF 6001 3200 µg - ITT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 190[97] | 179[98] | 188[99] | 193[100] |
| Units: Patients | | | | |
| number (not applicable) | 37 | 36 | 42 | 35 |

Notes:

[97] - ITT population

[98] - ITT population

[99] - ITT population

[100] - ITT population

| End point values | Budesonide 800 µg - ITT | Placebo - ITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 187[101] | 193[102] | | |
| Units: Patients | | | | |
| number (not applicable) | 32 | 49 | | |

Notes:

[101] - ITT population

[102] - ITT population

### Statistical analyses

| Statistical analysis title | Hazard ratio - time to first exacerbation |
|---|---|

Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 800 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 383 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Cox proportional hazard regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.731 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.477 |
| upper limit | 1.12 |

| Statistical analysis title | Hazard ratio - time to first exacerbation |
|---|---|

Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 1600 µg - ITT v Placebo - ITT |

| | |
|---|---|
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Cox proportional hazard regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.768 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.499 |
| upper limit | 1.181 |

| **Statistical analysis title** | Hazard ratio - time to first exacerbation |
|---|---|

Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 2400 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 381 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Cox proportional hazard regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.829 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.549 |
| upper limit | 1.252 |

| **Statistical analysis title** | Hazard ratio - time to first exacerbation |
|---|---|

Statistical analysis description:

The time to first moderate or severe COPD exacerbation was analysed using Cox proportional hazard regression model including treatment and sites pooled by country as factors. The hazard ratios (95% CIs) for the CHF 6001 treatment groups (versus Placebo) are presented.

| | |
|---|---|
| Comparison groups | CHF 6001 3200 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 386 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Cox proportional hazard regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.693 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.449 |
| upper limit | 1.07 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Adverse events (AEs) were reported from the time of patient informed consent to study completion or discontinuation. | |
| Adverse event reporting additional description: | |
| Treatment-emergent adverse events (TEAEs) were defined as AEs starting on or after the first randomised study medication intake. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19 |

| Reporting groups | |
|---|---|
| Reporting group title | CHF 6001 800 µg - Safety |
| Reporting group description: | |
| The Safety population was defined as all randomised patients who received at least one dose of study medication. | |
| Reporting group title | CHF 6001 1600 µg - Safety |
| Reporting group description: | |
| The Safety population was defined as all randomised patients who received at least one dose of the study medication. | |
| Reporting group title | CHF 6001 2400 µg - Safety |
| Reporting group description: | |
| The Safety population was defined as all randomised patients who received at least one dose of the study medication. | |
| Reporting group title | CHF 6001 3200 µg - Safety |
| Reporting group description: | |
| The Safety population was defined as all randomised patients who received at least one dose of the study medication. | |
| Reporting group title | Budesonide 800 µg - Safety |
| Reporting group description: | |
| The Safety population was defined as all randomised patients who received at least one dose of the study medication. | |
| Reporting group title | Placebo - Safety |
| Reporting group description: | |
| The Safety population was defined as all randomised patients who received at least one dose of the study medication. | |

| Serious adverse events | CHF 6001 800 µg - Safety | CHF 6001 1600 µg - Safety | CHF 6001 2400 µg - Safety |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 190 (5.79%) | 13 / 179 (7.26%) | 12 / 188 (6.38%) |
| number of deaths (all causes) | 1 | 1 | 1 |
| number of deaths resulting from adverse events | 1 | 1 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Angina unstable | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|---|---|---|
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Duodenal stenosis | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 179 (0.56%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 7 / 179 (3.91%) | 7 / 188 (3.72%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 7 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 179 (0.56%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia escherichia | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 179 (0.00%) | 0 / 188 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | CHF 6001 3200 µg - Safety | Budesonide 800 µg - Safety | Placebo - Safety |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 193 (3.63%) | 10 / 187 (5.35%) | 7 / 193 (3.63%) |
| number of deaths (all causes) | 2 | 0 | 0 |
| number of deaths resulting from adverse events | 2 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 193 (0.00%) | 1 / 187 (0.53%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 193 (0.52%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 193 (0.52%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 1 / 187 (0.53%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 1 / 193 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 193 (0.52%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 193 (0.52%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 193 (0.52%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Duodenal stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 1 / 187 (0.53%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 193 (1.04%) | 5 / 187 (2.67%) | 5 / 193 (2.59%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 1 / 187 (0.53%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 193 (0.00%) | 1 / 187 (0.53%) | 1 / 193 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia escherichia | | | |
| subjects affected / exposed | 0 / 193 (0.00%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 193 (0.52%) | 0 / 187 (0.00%) | 0 / 193 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3.5 %

| **Non-serious adverse events** | CHF 6001 800 µg - Safety | CHF 6001 1600 µg - Safety | CHF 6001 2400 µg - Safety |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 86 / 190 (45.26%) | 90 / 179 (50.28%) | 91 / 188 (48.40%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 10 / 190 (5.26%) | 7 / 179 (3.91%) | 7 / 188 (3.72%) |
| occurrences (all) | 14 | 8 | 8 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 42 / 190 (22.11%) | 41 / 179 (22.91%) | 54 / 188 (28.72%) |
| occurrences (all) | 68 | 58 | 66 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 190 (3.68%) | 14 / 179 (7.82%) | 11 / 188 (5.85%) |
| occurrences (all) | 10 | 16 | 11 |

| **Non-serious adverse events** | CHF 6001 3200 µg - Safety | Budesonide 800 µg - Safety | Placebo - Safety |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 83 / 193 (43.01%) | 89 / 187 (47.59%) | 101 / 193 (52.33%) |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 11 / 193 (5.70%) | 10 / 187 (5.35%) | 8 / 193 (4.15%) |
| occurrences (all) | 15 | 12 | 10 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 43 / 193 (22.28%) | 39 / 187 (20.86%) | 58 / 193 (30.05%) |
| occurrences (all) | 60 | 56 | 75 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 12 / 193 (6.22%) | 9 / 187 (4.81%) | 13 / 193 (6.74%) |
| occurrences (all) | 15 | 10 | 13 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 October 2016 | There were three versions of the clinical study protocol. Version 1.0 was never used, and initial submissions were done with Version 2.0. Based on the Medicines and Healthcare products Regulatory Agency (MHRA) comments, there was one substantial protocol amendment, with the following main changes implemented further to the initial protocol version:<br>- The thyroid function tests were added at the screening visit to confirm the exclusion of the uncontrolled thyroid disease as per exclusion criterion #16;<br>- Monitoring of psychiatric adverse events was specified (including update of the physical examination section).<br>The first Competent Authority approval of Version 3.0 was received on 27 October 2016. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported