



## Clinical trial results:

**A multicenter, randomised, double blind, placebo-controlled, incomplete block, 3-way cross-over study to evaluate the efficacy and safety of 4 doses of glycopyrronium bromide DPI in moderate to severe patients with chronic obstructive pulmonary disease (COPD)**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-000558-40   |
| Trial protocol           | DE HU CZ RO      |
| Global end of trial date | 06 February 2017 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 31 January 2018 |
| First version publication date | 31 January 2018 |

### Trial information

#### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CCD-06302AA1-01 |
|-----------------------|-----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02680197 |
| 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.,<br>ClinicalTrials_info@chiesi.com |
| Scientific contact           | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A.,<br>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                       | 28 August 2017   |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 06 February 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 February 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to identify the optimal dose of CHF 5259 glycopyrronium bromide (GB) to be further developed for the treatment of patients with COPD.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. There was no anticipated benefit for patients receiving placebo. However, patients were closely monitored and the risks for patients were minimised by measures such as training of patients in the early recognition of COPD exacerbations and on appropriate early actions to be taken, including contacting the investigator if their condition was worsening, and discontinuation in case of disease worsening. Moreover, patients received placebo only for a maximum of one out the three treatment periods and had access to rescue medication as needed throughout the study.

Background therapy:

If the patient was receiving treatment with inhaled corticosteroid (ICS) in combination with a bronchodilator (long-acting  $\beta_2$  agonist [LABA] or long-acting muscarinic agonist [LAMA]) at the time of informed consent signature, the combination was discontinued at screening and an equipotent daily dose of Flixotide® Accuhaler® DPI 250  $\mu$ g/actuation was prescribed according to the Global Initiative for asthma pocket guide for health professionals. This background treatment was maintained for the entire run-in period and the remainder of the study.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 29 February 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 | Romania: 31        |
| Country: Number of subjects enrolled | Czech Republic: 88 |
| Country: Number of subjects enrolled | Germany: 19        |
| Country: Number of subjects enrolled | Hungary: 64        |
| Worldwide total number of subjects   | 202                |
| EEA total number of subjects         | 202                |

Notes:

### Subjects enrolled per age group

|  |   |
|--|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|  |     |
|--|-----|
| wk                                       |     |
| 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)                     | 118 |
| From 65 to 84 years                      | 84  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Overall, 202 patients were randomised into one of the ten treatment sequences (Sequence A-C-D [n=20], Sequence E-D-B [n=20], Sequence C-B-E [n=20], Sequence D-E-C [n=20], Sequence B-C-A [n=20], Sequence B-A-D [n=20], Sequence A-D-E [n=20], Sequence D-B-C [n=21], Sequence E-A-B [n=20], Sequence C-E-A [n=21]) and 178 patients completed the study.

### Pre-assignment

Screening details:

This study comprised a pre-screening visit, occurring no more than seven days prior to a screening visit. A total of 262 patients were screened, 202 (77.1%) were randomised and 60 (22.9%) failed screening due to inclusion/exclusion criteria (51 patients), consent withdrawal (3 patients), adverse events (2 patients) and other reasons (4 patients)

### Period 1

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

Blinding implementation details:

At randomisation, patients in each centre were centrally assigned to one of the ten treatment sequences by the interactive response technology system using a list-based randomisation algorithm. The randomisation list was provided to the labelling facility but was not available to patients, investigators, monitors or employees of the centre involved in the management of the study before unblinding of the data, unless in case of emergency.

### Arms

|                              |                |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes            |
| <b>Arm title</b>             | Sequence A-C-D |

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment D = CHF 5259 DPI 100 µg.

|  |  |
|--|--|
| Arm type                               | Experimental - experimental - experimental |
| Investigational medicinal product name | Glycopyrronium Bromide                     |
| Investigational medicinal product code | CHF 5259                                   |
| Other name                             |  |
| Pharmaceutical forms                   | Inhalation powder                          |
| Routes of administration               | Inhalation use                             |

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence E-D-B |
|------------------|----------------|

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259

DPI 25 µg.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Placebo - experimental - experimental |
| Investigational medicinal product name | Glycopyrronium Bromide                |
| Investigational medicinal product code | CHF 5259                              |
| Other name                             |                                       |
| Pharmaceutical forms                   | Inhalation powder                     |
| Routes of administration               | Inhalation use                        |

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence C-B-E |
|------------------|----------------|

Arm description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment E = Placebo.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental - experimental - placebo |
| Investigational medicinal product name | Glycopyrronium Bromide                |
| Investigational medicinal product code | CHF 5259                              |
| Other name                             |                                       |
| Pharmaceutical forms                   | Inhalation powder                     |
| Routes of administration               | Inhalation use                        |

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily).

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence D-E-C |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo; Treatment C = CHF 5259 DPI 50 µg.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental - placebo - experimental |
| Investigational medicinal product name | Glycopyrronium Bromide                |
| Investigational medicinal product code | CHF 5259                              |
| Other name                             |                                       |
| Pharmaceutical forms                   | Inhalation powder                     |
| Routes of administration               | Inhalation use                        |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence B-C-A |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment A = CHF 5259 DPI 12.5 µg.

|  |  |
|--|--|
| Arm type                               | Experimental - experimental - experimental |
| Investigational medicinal product name | Glycopyrronium Bromide                     |
| Investigational medicinal product code | CHF 5259                                   |
| Other name                             |  |
| Pharmaceutical forms                   | Inhalation powder                          |
| Routes of administration               | Inhalation use                             |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence B-A-D |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg;

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

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Glycopyrronium Bromide |
| Investigational medicinal product code | CHF 5259               |
| Other name                             |                        |
| Pharmaceutical forms                   | Inhalation powder      |
| Routes of administration               | Inhalation use         |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence A-D-E |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental - experimental - placebo |
| Investigational medicinal product name | Glycopyrronium Bromide                |
| Investigational medicinal product code | CHF 5259                              |
| Other name                             |                                       |
| Pharmaceutical forms                   | Inhalation powder                     |
| Routes of administration               | Inhalation use                        |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence D-B-C |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg.

|  |  |
|--|--|
| Arm type                               | Experimental - experimental - experimental |
| Investigational medicinal product name | Glycopyrronium Bromide                     |
| Investigational medicinal product code | CHF 5259                                   |
| Other name                             |  |
| Pharmaceutical forms                   | Inhalation powder                          |
| Routes of administration               | Inhalation use                             |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily); Treatment D = CHF 5259 DPI 100 µg (2 inhalations of CHF 5259 DPI 25 µg twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence E-A-B |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg; Treatment B = CHF 5259 DPI 25 µg.

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

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Glycopyrronium Bromide |
| Investigational medicinal product code | CHF 5259               |
| Other name                             |                        |
| Pharmaceutical forms                   | Inhalation powder      |
| Routes of administration               | Inhalation use         |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment B = CHF 5259 DPI 25 µg (2 inhalations of CHF 5259 DPI 6.25 µg twice daily).

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Sequence C-E-A |
|------------------|----------------|

**Arm description:**

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental - placebo - experimental |
| Investigational medicinal product name | Glycopyrronium Bromide                |
| Investigational medicinal product code | CHF 5259                              |
| Other name                             |                                       |
| Pharmaceutical forms                   | Inhalation powder                     |
| Routes of administration               | Inhalation use                        |

**Dosage and administration details:**

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment A = CHF 5259 DPI 12.5 µg (1 inhalation of CHF 5259 DPI 6.25 µg and 1 inhalation of placebo twice daily); Treatment C = CHF 5259 DPI 50 µg (2 inhalations of CHF 5259 DPI 12.5 µg twice daily).



|  |                   |
|--|-------------------|
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

Dosage and administration details:

Study medication was administered using NEXThaler® technology (Dry Powder Inhaler, DPI). The study treatment kit for each period contained two inhalers. During each four-week treatment period, the study medication was administered twice daily by inhaling one puff from each inhaler every morning and one puff from each inhaler every evening, adding up to four puffs per day: Treatment E = Placebo (2 inhalations of placebo twice daily).

| Number of subjects in period 1 | Sequence A-C-D | Sequence E-D-B | Sequence C-B-E |
|--------------------------------|----------------|----------------|----------------|
| Started                        | 20             | 20             | 20             |
| Completed                      | 17             | 15             | 16             |
| Not completed                  | 3              | 5              | 4              |
| Consent withdrawn by subject   | 1              | 2              | 2              |
| Adverse event, non-fatal       | 2              | 3              | 2              |
| Other (family problems)        | -              | -              | -              |
| Lost to follow-up              | -              | -              | -              |

| Number of subjects in period 1 | Sequence D-E-C | Sequence B-C-A | Sequence B-A-D |
|--------------------------------|----------------|----------------|----------------|
| Started                        | 20             | 20             | 20             |
| Completed                      | 20             | 17             | 18             |
| Not completed                  | 0              | 3              | 2              |
| Consent withdrawn by subject   | -              | -              | -              |
| Adverse event, non-fatal       | -              | 2              | 2              |
| Other (family problems)        | -              | -              | -              |
| Lost to follow-up              | -              | 1              | -              |

| Number of subjects in period 1 | Sequence A-D-E | Sequence D-B-C | Sequence E-A-B |
|--------------------------------|----------------|----------------|----------------|
| Started                        | 20             | 21             | 20             |
| Completed                      | 17             | 20             | 17             |
| Not completed                  | 3              | 1              | 3              |
| Consent withdrawn by subject   | 1              | -              | 2              |
| Adverse event, non-fatal       | 2              | 1              | -              |
| Other (family problems)        | -              | -              | 1              |
| Lost to follow-up              | -              | -              | -              |

| Number of subjects in period 1 | Sequence C-E-A |
|--------------------------------|----------------|
| Started                        | 21             |
| Completed                      | 21             |
| Not completed                  | 0              |

|                              |   |
|------------------------------|---|
| Consent withdrawn by subject | - |
| Adverse event, non-fatal     | - |
| Other (family problems)      | - |
| Lost to follow-up            | - |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence A-C-D |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment D = CHF 5259 DPI 100 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence E-D-B |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence C-B-E |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment E = Placebo.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence D-E-C |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo; Treatment C = CHF 5259 DPI 50 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence B-C-A |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment A = CHF 5259 DPI 12.5 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence B-A-D |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg;

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence A-D-E |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence D-B-C |
|-----------------------|----------------|

#### Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence E-A-B |
|-----------------------|----------------|

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg; Treatment B = CHF 5259 DPI 25 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence C-E-A |
|-----------------------|----------------|

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg.

| Reporting group values                             | Sequence A-C-D | Sequence E-D-B | Sequence C-B-E |
|--|----------------|----------------|----------------|
| Number of subjects                                 | 20             | 20             | 20             |
| Age categorical                                    |                |                |                |
| Units: Subjects                                    |                |                |                |
| In utero   | 0              | 0              | 0              |
| Preterm newborn infants (gestational age < 37 wks) | 0              | 0              | 0              |
| Newborns (0-27 days)                               | 0              | 0              | 0              |
| Infants and toddlers (28 days-23 months)           | 0              | 0              | 0              |
| Children (2-11 years)                              | 0              | 0              | 0              |
| Adolescents (12-17 years)                          | 0              | 0              | 0              |
| Adults (18-64 years)                               | 8              | 12             | 14             |
| From 65-84 years                                   | 12             | 8              | 6              |
| 85 years and over                                  | 0              | 0              | 0              |
| Age continuous                                     |                |                |                |
| Units: years                                       |                |                |                |
| arithmetic mean                                    | 64.3           | 60.4           | 62             |
| standard deviation                                 | ± 7.5          | ± 7            | ± 6.6          |
| Gender categorical                                 |                |                |                |
| Units: Subjects                                    |                |                |                |
| Female   | 8              | 7              | 6              |
| Male   | 12             | 13             | 14             |

| Reporting group values                             | Sequence D-E-C | Sequence B-C-A | Sequence B-A-D |
|--|----------------|----------------|----------------|
| Number of subjects                                 | 20             | 20             | 20             |
| Age categorical                                    |                |                |                |
| Units: Subjects                                    |                |                |                |
| In utero   | 0              | 0              | 0              |
| Preterm newborn infants (gestational age < 37 wks) | 0              | 0              | 0              |
| Newborns (0-27 days)                               | 0              | 0              | 0              |
| Infants and toddlers (28 days-23 months)           | 0              | 0              | 0              |
| Children (2-11 years)                              | 0              | 0              | 0              |
| Adolescents (12-17 years)                          | 0              | 0              | 0              |
| Adults (18-64 years)                               | 12             | 12             | 10             |
| From 65-84 years                                   | 8              | 8              | 10             |
| 85 years and over                                  | 0              | 0              | 0              |

|   |               |             |               |
|---|---------------|-------------|---------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 59.5<br>± 9.3 | 64<br>± 8.8 | 64.7<br>± 7.8 |
| Gender categorical<br>Units: Subjects                                   |               |             |               |
| Female  | 10            | 9           | 8             |
| Male  | 10            | 11          | 12            |

| Reporting group values  | Sequence A-D-E | Sequence D-B-C | Sequence E-A-B |
|---|----------------|----------------|----------------|
| Number of subjects  | 20             | 21             | 20             |
| Age categorical<br>Units: Subjects                                      |                |                |                |
| In utero  | 0              | 0              | 0              |
| Preterm newborn infants<br>(gestational age < 37 wks)                   | 0              | 0              | 0              |
| Newborns (0-27 days)  | 0              | 0              | 0              |
| Infants and toddlers (28 days-23<br>months)                             | 0              | 0              | 0              |
| Children (2-11 years)   | 0              | 0              | 0              |
| Adolescents (12-17 years)   | 0              | 0              | 0              |
| Adults (18-64 years)  | 14             | 12             | 12             |
| From 65-84 years  | 6              | 9              | 8              |
| 85 years and over   | 0              | 0              | 0              |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 61.5<br>± 6.3  | 62.9<br>± 6.5  | 63.3<br>± 7.9  |
| Gender categorical<br>Units: Subjects                                   |                |                |                |
| Female  | 6              | 10             | 9              |
| Male  | 14             | 11             | 11             |

| Reporting group values  | Sequence C-E-A | Total |  |
|---|----------------|-------|--|
| Number of subjects  | 21             | 202   |  |
| Age categorical<br>Units: Subjects                                      |                |       |  |
| In utero  | 0              | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                   | 0              | 0     |  |
| Newborns (0-27 days)  | 0              | 0     |  |
| Infants and toddlers (28 days-23<br>months)                             | 0              | 0     |  |
| Children (2-11 years)   | 0              | 0     |  |
| Adolescents (12-17 years)   | 0              | 0     |  |
| Adults (18-64 years)  | 12             | 118   |  |
| From 65-84 years  | 9              | 84    |  |
| 85 years and over   | 0              | 0     |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 64<br>± 6.5    | -     |  |

|                    |    |     |  |
|--------------------|----|-----|--|
| Gender categorical |    |     |  |
| Units: Subjects    |    |     |  |
| Female             | 6  | 79  |  |
| Male               | 15 | 123 |  |

## End points

### End points reporting groups

|   |                |
|---|----------------|
| Reporting group title   | Sequence A-C-D |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment D = CHF 5259 DPI 100 µg. |                |
| Reporting group title   | Sequence E-D-B |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg.              |                |
| Reporting group title   | Sequence C-B-E |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment E = Placebo.               |                |
| Reporting group title   | Sequence D-E-C |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo; Treatment C = CHF 5259 DPI 50 µg.              |                |
| Reporting group title   | Sequence B-C-A |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg; Treatment A = CHF 5259 DPI 12.5 µg.  |                |
| Reporting group title   | Sequence B-A-D |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment B = CHF 5259 DPI 25 µg; Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; |                |
| Reporting group title   | Sequence A-D-E |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment A = CHF 5259 DPI 12.5 µg; Treatment D = CHF 5259 DPI 100 µg; Treatment E = Placebo.            |                |
| Reporting group title   | Sequence D-B-C |
| Reporting group description:<br>Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment D = CHF 5259 DPI 100 µg; Treatment B = CHF 5259 DPI 25 µg; Treatment C = CHF 5259 DPI 50 µg.   |                |

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence E-A-B |
|-----------------------|----------------|

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg; Treatment B = CHF 5259 DPI 25 µg.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Sequence C-E-A |
|-----------------------|----------------|

Reporting group description:

Patients were randomised to receive three out of five different possible treatments (total daily doses of 12.5 µg, 25 µg, 50 µg and 100 µg of CHF 5259 DPI or matched placebo given twice daily) during three treatment periods. Treatment periods lasted four weeks each and were separated by three-week wash-out periods. Treatment C = CHF 5259 DPI 50 µg; Treatment E = Placebo; Treatment A = CHF 5259 DPI 12.5 µg.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | A) CHF 5259 DPI 12.5 µg - ITT |
|----------------------------|-------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Treatment A = CHF 5259 DPI 12.5 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | B) CHF 5259 DPI 25 µg - ITT |
|----------------------------|-----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Treatment B = CHF 5259 DPI 25 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | C) CHF 5259 DPI 50 µg - ITT |
|----------------------------|-----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Treatment C = CHF 5259 DPI 50 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | D) CHF 5259 DPI 100 µg - ITT |
|----------------------------|------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Treatment D = CHF 5259 DPI 100 µg; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | E) Placebo - ITT |
|----------------------------|------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Treatment E = Placebo; The ITT population was defined as all randomised patients who received at least one dose of the study treatment and with available evaluation of efficacy (primary or secondary efficacy variables) in at least two treatment periods.

## Primary: FEV1 AUC0-12h on Day 28

|                 |                         |
|-----------------|-------------------------|
| End point title | FEV1 AUC0-12h on Day 28 |
|-----------------|-------------------------|

End point description:

Forced expiratory volume in the 1st second (FEV1) area under the curve between 0 and 12 hours (AUC0-12h) normalised by time was calculated based on the actual times using the linear trapezoidal rule. Results for FVC were comparable to those observed with FEV1

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

End point timeframe:

FEV1, assessed in each treatment period at 15 min, 30 min, 45 min and 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 11.5 h and 12 h post-morning dose, was used to calculate FEV1 area under the curve between 0-12 h (AUC0-12h) on Day 28.



| End point values                                | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|---|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                              | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed                     | 104 <sup>[1]</sup>                  | 106 <sup>[2]</sup>             | 112 <sup>[3]</sup>             | 108 <sup>[4]</sup>                 |
| Units: litre(s)                                 |                                     |                                |                                |                                    |
| least squares mean (confidence interval<br>95%) | 1.505 (1.483<br>to 1.528)           | 1.517 (1.495<br>to 1.539)      | 1.535 (1.513<br>to 1.556)      | 1.579 (1.557<br>to 1.601)          |

Notes:

[1] - ITT population, available for change from baseline (complete ITT population n=113)

[2] - ITT population, available for change from baseline (complete ITT population n=110)

[3] - ITT population, available for change from baseline (complete ITT population n=117)

[4] - ITT population, available for change from baseline (complete ITT population n=112)

| End point values                                | E) Placebo -<br>ITT       |  |  |  |
|---|---------------------------|--|--|--|
| Subject group type                              | Subject analysis set      |  |  |  |
| Number of subjects analysed                     | 103 <sup>[5]</sup>        |  |  |  |
| Units: litre(s)                                 |                           |  |  |  |
| least squares mean (confidence interval<br>95%) | 1.392 (1.369<br>to 1.414) |  |  |  |

Notes:

[5] - ITT population, available for change from baseline (complete ITT population n=108)

## Statistical analyses

| Statistical analysis title | CHF 5259 DPI 12.5 µg vs. placebo |
|----------------------------|----------------------------------|
|----------------------------|----------------------------------|

Statistical analysis description:

The value N=207, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |  |
|---|--|
| Comparison groups                       | A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 207  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                     |
| Point estimate                          | 0.114  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.074  |
| upper limit                             | 0.154  |

| Statistical analysis title | CHF 5259 DPI 25 µg vs. placebo |
|----------------------------|--------------------------------|
|----------------------------|--------------------------------|

Statistical analysis description:

The value N=209, shown below, is generated automatically and is due to innate error of the EudraCT

database system

|   |  |
|---|--|
| Comparison groups                       | B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 209  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                   |
| Point estimate                          | 0.125  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.085  |
| upper limit                             | 0.166  |

---

**Statistical analysis title**

CHF 5259 DPI 50 µg vs. placebo

Statistical analysis description:

The value N=215, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |  |
|---|--|
| Comparison groups                       | C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 215  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                   |
| Point estimate                          | 0.143  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.104  |
| upper limit                             | 0.183  |

---

**Statistical analysis title**

CHF 5259 DPI 100 µg vs. placebo

Statistical analysis description:

The value N=211, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |   |
|---|---|
| Comparison groups                       | D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 211   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | < 0.001   |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Least square mean difference                    |
| Point estimate                          | 0.187   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.147   |
| upper limit         | 0.228   |

### Secondary: Change from baseline in morning pre-dose FEV1 on Day 28

|   |   |
|---|---|
| End point title   | Change from baseline in morning pre-dose FEV1 on Day 28 |
| End point description:  |   |
| Morning pre-dose FEV1 was defined as the mean of 45 min and 10 min pre-dose measurements. Baseline was defined as the mean of 45 min and 10 min pre-dose measurements on Day 1. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| The change from baseline in morning pre-dose FEV1 was analysed on Day 28.   |   |

| End point values                             | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|--|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                           | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed                  | 111 <sup>[6]</sup>                  | 109 <sup>[7]</sup>             | 115 <sup>[8]</sup>             | 109 <sup>[9]</sup>                 |
| Units: litre(s)                              |                                     |                                |                                |                                    |
| least squares mean (confidence interval 95%) | 0.084 (0.059 to 0.109)              | 0.072 (0.047 to 0.097)         | 0.097 (0.073 to 0.122)         | 0.136 (0.111 to 0.162)             |

Notes:

[6] - ITT population, available for change from baseline

[7] - ITT population, available for change from baseline

[8] - ITT population, available for change from baseline

[9] - ITT population, available for change from baseline

| End point values                             | E) Placebo -<br>ITT      |  |  |  |
|--|--------------------------|--|--|--|
| Subject group type                           | Subject analysis set     |  |  |  |
| Number of subjects analysed                  | 107 <sup>[10]</sup>      |  |  |  |
| Units: litre(s)                              |                          |  |  |  |
| least squares mean (confidence interval 95%) | -0.023 (-0.048 to 0.003) |  |  |  |

Notes:

[10] - ITT population, available for change from baseline

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | CHF 5259 DPI 12.5 µg vs. placebo                 |
| Statistical analysis description:  |  |
| The value N=218, shown below, is generated automatically and is due to innate error of the EudraCT database system |  |
| Comparison groups  | A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 218                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001                      |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | Least square mean difference |
| Point estimate                          | 0.106                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.07                         |
| upper limit                             | 0.142                        |

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | CHF 5259 DPI 25 µg vs. placebo |
|-----------------------------------|--------------------------------|

Statistical analysis description:

The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |  |
|---|--|
| Comparison groups                       | B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 216  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                   |
| Point estimate                          | 0.095  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.058  |
| upper limit                             | 0.131  |

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | CHF 5259 DPI 50 µg vs. placebo |
|-----------------------------------|--------------------------------|

Statistical analysis description:

The value N=222, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |  |
|---|--|
| Comparison groups                       | C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 222  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                   |
| Point estimate                          | 0.12   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.084   |
| upper limit         | 0.155   |

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | CHF 5259 DPI 100 µg vs. placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |   |
|---|---|
| Comparison groups                       | D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 216   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | < 0.001   |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Least square mean difference                    |
| Point estimate                          | 0.159   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.123   |
| upper limit                             | 0.195   |

## Secondary: Change from baseline in trough FEV1 at 12 h on Day 28

|                 |   |
|-----------------|---|
| End point title | Change from baseline in trough FEV1 at 12 h on Day 28 |
|-----------------|---|

End point description:

Trough FEV1 was defined as the mean of 11.5 h and 12 h post-dose measurements. Baseline was defined as the mean of 45 min and 10 min pre-dose measurements on Day 1.

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

End point timeframe:

The change from baseline in trough FEV1 at 12 h was analysed on Day 28.

| End point values                             | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|--|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                           | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed                  | 104 <sup>[11]</sup>                 | 106 <sup>[12]</sup>            | 112 <sup>[13]</sup>            | 108 <sup>[14]</sup>                |
| Units: litre(s)                              |                                     |                                |                                |                                    |
| least squares mean (confidence interval 95%) | 0.052 (0.024 to 0.08)               | 0.07 (0.042 to 0.097)          | 0.092 (0.066 to 0.119)         | 0.132 (0.105 to 0.159)             |

Notes:

[11] - ITT population, available for change from baseline

[12] - ITT population, available for change from baseline

[13] - ITT population, available for change from baseline

[14] - ITT population, available for change from baseline

|  |                          |  |  |  |
|--|--------------------------|--|--|--|
| <b>End point values</b>                      | E) Placebo - ITT         |  |  |  |
| Subject group type                           | Subject analysis set     |  |  |  |
| Number of subjects analysed                  | 103 <sup>[15]</sup>      |  |  |  |
| Units: litre(s)                              |                          |  |  |  |
| least squares mean (confidence interval 95%) | -0.025 (-0.053 to 0.003) |  |  |  |

Notes:

[15] - ITT population, available for change from baseline

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | CHF 5259 DPI 12.5 µg vs. placebo                 |
| Statistical analysis description:<br>The value N=207, shown below, is generated automatically and is due to innate error of the EudraCT database system |  |
| Comparison groups   | A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis   | 207  |
| Analysis specification  | Pre-specified                                    |
| Analysis type   | superiority                                      |
| P-value   | < 0.001  |
| Method  | ANCOVA   |
| Parameter estimate  | Least square mean difference                     |
| Point estimate  | 0.077  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.037  |
| upper limit   | 0.116  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | CHF 5259 DPI 25 µg vs. placebo                 |
| Statistical analysis description:<br>The value N=209, shown below, is generated automatically and is due to innate error of the EudraCT database system |  |
| Comparison groups   | B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis   | 209  |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | < 0.001  |
| Method  | ANCOVA   |
| Parameter estimate  | Least square mean difference                   |
| Point estimate  | 0.094  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.055   |
| upper limit         | 0.134   |

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | CHF 5259 DPI 50 µg vs. placebo |
|-----------------------------------|--------------------------------|

Statistical analysis description:

The value N=215, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |  |
|---|--|
| Comparison groups                       | C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 215  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                   |
| Point estimate                          | 0.117  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.078  |
| upper limit                             | 0.156  |

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | CHF 5259 DPI 100 µg vs. placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

The value N=211, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |   |
|---|---|
| Comparison groups                       | D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 211   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | < 0.001   |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Least square mean difference                    |
| Point estimate                          | 0.157   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.117   |
| upper limit                             | 0.196   |

## Secondary: Change from baseline in peak0-4h FEV1 on Day 28

|                 |   |
|-----------------|---|
| End point title | Change from baseline in peak0-4h FEV1 on Day 28 |
|-----------------|---|

End point description:

Peak0-4h FEV1 was defined as the maximum FEV1 value from 15 min to 4 h post-dose. Baseline was defined as the mean of 45 min and 10 min pre-dose measurements on Day 1.

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

End point timeframe:

The change from baseline in peak0-4h FEV1 was analysed on Day 28.

| End point values                                | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|---|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                              | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed                     | 111 <sup>[16]</sup>                 | 109 <sup>[17]</sup>            | 115 <sup>[18]</sup>            | 109 <sup>[19]</sup>                |
| Units: litre(s)                                 |                                     |                                |                                |                                    |
| least squares mean (confidence interval<br>95%) | 0.24 (0.214 to<br>0.265)            | 0.25 (0.225 to<br>0.276)       | 0.269 (0.244<br>to 0.294)      | 0.31 (0.284 to<br>0.336)           |

Notes:

[16] - ITT population, available for change from baseline

[17] - ITT population, available for change from baseline

[18] - ITT population, available for change from baseline

[19] - ITT population, available for change from baseline

| End point values                                | E) Placebo -<br>ITT       |  |  |  |
|---|---------------------------|--|--|--|
| Subject group type                              | Subject analysis set      |  |  |  |
| Number of subjects analysed                     | 107 <sup>[20]</sup>       |  |  |  |
| Units: litre(s)                                 |                           |  |  |  |
| least squares mean (confidence interval<br>95%) | 0.105 (0.079<br>to 0.131) |  |  |  |

Notes:

[20] - ITT population, available for change from baseline

## Statistical analyses

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | CHF 5259 DPI 12.5 µg vs. placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The value N=218, shown below, is generated automatically and is due to innate error of the EudraCT database system

|   |  |
|---|--|
| Comparison groups                       | A) CHF 5259 DPI 12.5 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis | 218  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | < 0.001  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square mean difference                     |
| Point estimate                          | 0.135  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.098  |
| upper limit                             | 0.172  |



|   |  |
|---|--|
| <b>Statistical analysis title</b>   | CHF 5259 DPI 25 µg vs. placebo                 |
| Statistical analysis description:<br>The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system |  |
| Comparison groups   | B) CHF 5259 DPI 25 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis   | 216  |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | < 0.001  |
| Method  | ANCOVA   |
| Parameter estimate  | Least square mean difference                   |
| Point estimate  | 0.145  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.108  |
| upper limit   | 0.183  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | CHF 5259 DPI 50 µg vs. placebo                 |
| Statistical analysis description:<br>The value N=222, shown below, is generated automatically and is due to innate error of the EudraCT database system |  |
| Comparison groups   | C) CHF 5259 DPI 50 µg - ITT v E) Placebo - ITT |
| Number of subjects included in analysis   | 222  |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | < 0.001  |
| Method  | ANCOVA   |
| Parameter estimate  | Least square mean difference                   |
| Point estimate  | 0.163  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.127  |
| upper limit   | 0.2  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | CHF 5259 DPI 100 µg vs. placebo                 |
| Statistical analysis description:<br>The value N=216, shown below, is generated automatically and is due to innate error of the EudraCT database system |   |
| Comparison groups   | D) CHF 5259 DPI 100 µg - ITT v E) Placebo - ITT |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 216                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001                      |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | Least square mean difference |
| Point estimate                          | 0.204                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.167                        |
| upper limit                             | 0.242                        |

## Secondary: TDI focal score on Day 28

|   |                           |
|---|---------------------------|
| End point title   | TDI focal score on Day 28 |
| End point description:  |                           |
| Dyspnoea at baseline was assessed with the Baseline Dyspnoea Index (BDI) , which covers three domains: functional impairment, magnitude of task and magnitude of effort with the values added for a combined focal score. The BDI scores ranged from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12). The changes from baseline were measured by the Transition Dyspnoea Index (TDI) score which ranged from -3 (major deterioration) to +3 (major improvement) for each domain, with the TDI focal score consisting of the sum of each domain (-9 to +9). |                           |
| End point type  | Secondary                 |
| End point timeframe:  |                           |
| TDI was assessed in the morning of Day 28 of each treatment period or in case of ET visit. (BDI was assessed in the morning of Day 1 of each treatment period.)   |                           |

| End point values                          | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|---|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                        | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed               | 113 <sup>[21]</sup>                 | 110 <sup>[22]</sup>            | 117 <sup>[23]</sup>            | 111 <sup>[24]</sup>                |
| Units: unit(s)                            |                                     |                                |                                |                                    |
| arithmetic mean (confidence interval 95%) | 1.372 (0.878 to 1.865)              | 1.718 (1.264 to 2.173)         | 1.462 (1.000 to 1.923)         | 2.036 (1.559 to 2.513)             |

Notes:

[21] - ITT population, available for change from baseline

[22] - ITT population, available for change from baseline

[23] - ITT population, available for change from baseline

[24] - ITT population, available for change from baseline

| End point values                          | E) Placebo -<br>ITT    |  |  |  |
|---|------------------------|--|--|--|
| Subject group type                        | Subject analysis set   |  |  |  |
| Number of subjects analysed               | 108 <sup>[25]</sup>    |  |  |  |
| Units: unit(s)                            |                        |  |  |  |
| arithmetic mean (confidence interval 95%) | 0.750 (0.266 to 1.234) |  |  |  |

Notes:

[25] - ITT population, available for change from baseline

## Statistical analyses

No statistical analyses for this end point

## Secondary: TDI focal score responders on Day 28

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | TDI focal score responders on Day 28 |
|-----------------|--------------------------------------|

End point description:

Responders were patients with a TDI focal score  $\geq 1$  on Day 28. Real non-responders were patients with a TDI focal score  $< 1$  on Day 28. Non-responders due to missing values were patients with a missing TDI focal score on Day 28.

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

End point timeframe:

TDI focal score responders were analysed on Day 28.

| End point values                     | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|--------------------------------------|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                   | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed          | 113 <sup>[26]</sup>                 | 110 <sup>[27]</sup>            | 117 <sup>[28]</sup>            | 112 <sup>[29]</sup>                |
| Units: patients                      |                                     |                                |                                |                                    |
| Responders                           | 59                                  | 67                             | 65                             | 71                                 |
| Real non-responders                  | 54                                  | 43                             | 52                             | 40                                 |
| Non-responders due to missing values | 0                                   | 0                              | 0                              | 1                                  |

Notes:

[26] - ITT population

[27] - ITT population

[28] - ITT population

[29] - ITT population

| End point values                     | E) Placebo -<br>ITT  |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 108 <sup>[30]</sup>  |  |  |  |
| Units: patients                      |                      |  |  |  |
| Responders                           | 48                   |  |  |  |
| Real non-responders                  | 60                   |  |  |  |
| Non-responders due to missing values | 0                    |  |  |  |

Notes:

[30] - ITT population

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of patients using rescue medication**

|                 |  |
|-----------------|--|
| End point title | Number of patients using rescue medication |
|-----------------|--|

End point description:

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

End point timeframe:

Number of patients who used rescue medication at least once during the treatment period.

| End point values            | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|-----------------------------|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type          | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed | 113 <sup>[31]</sup>                 | 110 <sup>[32]</sup>            | 117 <sup>[33]</sup>            | 112 <sup>[34]</sup>                |
| Units: patients             | 81                                  | 80                             | 87                             | 77                                 |

Notes:

[31] - ITT population

[32] - ITT population

[33] - ITT population

[34] - ITT population

| End point values            | E) Placebo -<br>ITT  |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 108 <sup>[35]</sup>  |  |  |  |
| Units: patients             | 89                   |  |  |  |

Notes:

[35] - ITT population

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Days with rescue medication administration during the treatment period (%)**

|                 |  |
|-----------------|--|
| End point title | Days with rescue medication administration during the treatment period (%) |
|-----------------|--|

End point description:

The percentage of days with intake of rescue medication was calculated as: (number of days with rescue medication intake / number of days with available data) \* 100.

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

End point timeframe:

Treatment period.

| End point values                             | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|--|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                           | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed                  | 107 <sup>[36]</sup>                 | 104 <sup>[37]</sup>            | 113 <sup>[38]</sup>            | 110 <sup>[39]</sup>                |
| Units: days (%)                              |                                     |                                |                                |                                    |
| arithmetic mean (confidence interval<br>95%) | 46.332 (38.517<br>to 54.147)        | 48.844 (41.158<br>to 56.530)   | 49.006 (41.679<br>to 56.334)   | 36.572 (29.446<br>to 43.697)       |

Notes:

[36] - ITT population, available for change from baseline

[37] - ITT population, available for change from baseline

[38] - ITT population, available for change from baseline

[39] - ITT population, available for change from baseline

| End point values                             | E) Placebo -<br>ITT          |  |  |  |
|--|------------------------------|--|--|--|
| Subject group type                           | Subject analysis set         |  |  |  |
| Number of subjects analysed                  | 103 <sup>[40]</sup>          |  |  |  |
| Units: days (%)                              |                              |  |  |  |
| arithmetic mean (confidence interval<br>95%) | 59.452 (51.847<br>to 67.058) |  |  |  |

Notes:

[40] - ITT population, available for change from baseline

## Statistical analyses

No statistical analyses for this end point

## Secondary: Average use of rescue medication during the treatment period (puffs/day)

|  |  |
|--|--|
| End point title  | Average use of rescue medication during the treatment period (puffs/day) |
| End point description:<br>The average use of rescue medication was calculated as total number of puffs / number of days with available data. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Treatment period.  |  |

| End point values                             | A) CHF 5259<br>DPI 12.5 µg -<br>ITT | B) CHF 5259<br>DPI 25 µg - ITT | C) CHF 5259<br>DPI 50 µg - ITT | D) CHF 5259<br>DPI 100 µg -<br>ITT |
|--|-------------------------------------|--------------------------------|--------------------------------|------------------------------------|
| Subject group type                           | Subject analysis set                | Subject analysis set           | Subject analysis set           | Subject analysis set               |
| Number of subjects analysed                  | 107 <sup>[41]</sup>                 | 104 <sup>[42]</sup>            | 113 <sup>[43]</sup>            | 110 <sup>[44]</sup>                |
| Units: puffs/day                             |                                     |                                |                                |                                    |
| arithmetic mean (confidence interval<br>95%) | 1.358 (1.018<br>to 1.698)           | 1.331 (1.003<br>to 1.659)      | 1.130 (0.868<br>to 1.392)      | 1.085 (0.753<br>to 1.416)          |

Notes:

[41] - ITT population, available for change from baseline

[42] - ITT population, available for change from baseline

[43] - ITT population, available for change from baseline

[44] - ITT population, available for change from baseline

|   |                        |  |  |  |
|---|------------------------|--|--|--|
| <b>End point values</b>                   | E) Placebo - ITT       |  |  |  |
| Subject group type                        | Subject analysis set   |  |  |  |
| Number of subjects analysed               | 103 <sup>[45]</sup>    |  |  |  |
| Units: puffs/day                          |                        |  |  |  |
| arithmetic mean (confidence interval 95%) | 1.831 (1.448 to 2.214) |  |  |  |

Notes:

[45] - ITT population, available for change from baseline

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The reporting period for AEs was from the signature of the informed consent form until the patient's participation in the study ended (follow-up call included).

Adverse event reporting additional description:

All AEs starting on or after the time of first study treatment intake and before the last visit in Treatment Period 3 or the early termination visit (as applicable) were classified as treatment emergent AEs (TEAEs). TEAEs were assigned to the last study medication received.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | A) CHF 5259 DPI 12.5 µg - Safety |
|-----------------------|----------------------------------|

Reporting group description:

Treatment A = CHF 5259 DPI 12.5 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | B) CHF 5259 DPI 25 µg - Safety |
|-----------------------|--------------------------------|

Reporting group description:

Treatment B = CHF 5259 DPI 25 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | C) CHF 5259 DPI 50 µg - Safety |
|-----------------------|--------------------------------|

Reporting group description:

Treatment C = CHF 5259 DPI 50 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | D) CHF 5259 DPI 100 µg - Safety |
|-----------------------|---------------------------------|

Reporting group description:

Treatment D = CHF 5259 DPI 100 µg; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | E) Placebo - Safety |
|-----------------------|---------------------|

Reporting group description:

Treatment E = placebo; The Safety population was defined as all randomised patients who received at least one dose of the study medication.

| Serious adverse events  | A) CHF 5259 DPI 12.5 µg - Safety | B) CHF 5259 DPI 25 µg - Safety | C) CHF 5259 DPI 50 µg - Safety |
|---|----------------------------------|--------------------------------|--------------------------------|
| Total subjects affected by serious adverse events                   |                                  |                                |                                |
| subjects affected / exposed   | 1 / 116 (0.86%)                  | 1 / 111 (0.90%)                | 0 / 119 (0.00%)                |
| number of deaths (all causes)                                       | 0                                | 0                              | 0                              |
| number of deaths resulting from adverse events                      | 0                                | 0                              | 0                              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |                                |                                |
| Small cell lung cancer extensive stage                              |                                  |                                |                                |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 116 (0.86%) | 0 / 111 (0.00%) | 0 / 119 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Limb traumatic amputation                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 111 (0.00%) | 0 / 119 (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 |                 |                 |                 |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 111 (0.00%) | 0 / 119 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Psoriatic arthropathy                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 1 / 111 (0.90%) | 0 / 119 (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           |

| <b>Serious adverse events</b>                                       | D) CHF 5259 DPI<br>100 µg - Safety | E) Placebo - Safety |  |
|---|------------------------------------|---------------------|--|
| Total subjects affected by serious adverse events                   |                                    |                     |  |
| subjects affected / exposed   | 2 / 112 (1.79%)                    | 2 / 115 (1.74%)     |  |
| number of deaths (all causes)                                       | 0                                  | 0                   |  |
| number of deaths resulting from adverse events                      | 0                                  | 0                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                    |                     |  |
| Small cell lung cancer extensive stage                              |                                    |                     |  |
| subjects affected / exposed   | 0 / 112 (0.00%)                    | 0 / 115 (0.00%)     |  |
| occurrences causally related to treatment / all                     | 0 / 0                              | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 0                              | 0 / 0               |  |
| Injury, poisoning and procedural complications                      |                                    |                     |  |
| Limb traumatic amputation   |                                    |                     |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 112 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 2 / 112 (1.79%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Psoriatic arthropathy                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 112 (0.00%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | A) CHF 5259 DPI<br>12.5 µg - Safety | B) CHF 5259 DPI 25<br>µg - Safety | C) CHF 5259 DPI 50<br>µg - Safety |
|---|-------------------------------------|-----------------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events |                                     |                                   |                                   |
| subjects affected / exposed                           | 17 / 116 (14.66%)                   | 18 / 111 (16.22%)                 | 13 / 119 (10.92%)                 |
| Respiratory, thoracic and mediastinal disorders       |                                     |                                   |                                   |
| Chronic obstructive pulmonary disease                 |                                     |                                   |                                   |
| subjects affected / exposed                           | 4 / 116 (3.45%)                     | 1 / 111 (0.90%)                   | 1 / 119 (0.84%)                   |
| occurrences (all)                                     | 4                                   | 1                                 | 1                                 |
| Infections and infestations                           |                                     |                                   |                                   |
| Nasopharyngitis                                       |                                     |                                   |                                   |
| subjects affected / exposed                           | 5 / 116 (4.31%)                     | 7 / 111 (6.31%)                   | 3 / 119 (2.52%)                   |
| occurrences (all)                                     | 5                                   | 7                                 | 3                                 |

| <b>Non-serious adverse events</b>                     | D) CHF 5259 DPI<br>100 µg - Safety | E) Placebo - Safety |  |
|---|------------------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                                    |                     |  |
| subjects affected / exposed                           | 15 / 112 (13.39%)                  | 16 / 115 (13.91%)   |  |
| Respiratory, thoracic and mediastinal disorders       |                                    |                     |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences (all)          | 1 / 112 (0.89%)<br>1 | 3 / 115 (2.61%)<br>4 |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 112 (0.89%)<br>1 | 1 / 115 (0.87%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported