



## Clinical trial results:

**Open label, prospective study to evaluate the effect of step-up from non-extrafine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2020-002356-20  |
| Trial protocol           | BE HU           |
| Global end of trial date | 03 January 2022 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 25 February 2023 |
| First version publication date | 25 February 2023 |

### Trial information

#### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CLI-05993BA1-08 |
|-----------------------|-----------------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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                       | 27 January 2023 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 03 January 2022 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effect of stepping-up from fluticasone dipropionate (FP)/salmeterol (SLM) dry-powder inhaler (DPI) (SERETIDE™ DISKUS™) to extrafine beclometasone dipropionate (BDP)/formoterol fumarate (FF)/glycopyrronium bromide (GB) DPI (CHF5993) on airway geometry and lung ventilation.

The primary and secondary endpoints are shown in the database.

Protection of trial subjects:

The clinical study was performed in accordance with the principles that have their origin in the declaration of Helsinki, and with local regulations. The study was carried out in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH/CPMP/135/95).

All patients were to be well trained in the inhalation technique with In-Check Dial at screening to familiarise with the inhalation technique, in the attempt to yield repeatable inhalations.

During V1 (screening), all patients were to be trained on the proper use of SERETIDE™ DISKUS™ and CHF5993 NEXThaler® by using In-Check Dial.

During the training, two different assessments were to be performed: one set for DISKUS™ resistance, and the second set for NEXThaler®.

The study consisted of a screening visit (V1), followed by a 6 week run-in period. At the end of the run-in period (V2), patients were switched to the treatment period for 6 weeks (until V3). A follow-up call was planned after 2 weeks  $\pm$  2 days from V3 for males and women of non childbearing potential. The total study duration was approximately 14 weeks per patient.

Background therapy:

In the run-in period, patients were administered SERETIDE™ DISKUS™ 500/50 µg one inhalation b.i.d. (batch number: V66D), giving a total daily dose of 1 mg FP (Fluticasone dipropionate) and 100 µg SLM (Salmeterol).

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 11 June 2021 |
| 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 | Belgium: 8  |
| Country: Number of subjects enrolled | Hungary: 17 |
| Worldwide total number of subjects   | 25          |
| EEA total number of subjects         | 25          |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 12 |
| From 65 to 84 years                       | 13 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

In total, 45 patients were screened of whom 20 were screening failures. The other 25 patients were enrolled and received two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg. All enrolled and treated patients completed the study, and 23 patients were included in the PP analysis set.

### Pre-assignment

Screening details:

Screening visit was performed 6 weeks ± 2 days before Visit 2. The eligibility (inclusion/exclusion criteria) such as BMI, medical and smoking history, history of alcohol and drug abuse, vital signs, ECG test, pregnancy test, serology test, documented COVID-19 diagnosis, blood analysis, urine test, intake of concomitant medications were assessed.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 45 <sup>[1]</sup> |
| Number of subjects completed | 25                |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Adverse event, non-fatal: 1     |
| Reason: Number of subjects | Consent withdrawn by subject: 5 |
| Reason: Number of subjects | In-/exclusion criteria: 14      |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In total, 45 patients were screened of whom 20 were screening failures. The other 25 patients were enrolled and treated.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | CHF5993 DPI 100/6/12.5 µg (overall period) |
| Is this the baseline period? | Yes  |
| Allocation method            | Non-randomised - controlled                |
| Blinding used                | Not blinded                                |

### Arms

|           |                           |
|-----------|---------------------------|
| Arm title | CHF5993 DPI 100/6/12.5 µg |
|-----------|---------------------------|

Arm description:

All patients (25 subjects) received CHF5993 as follows:

- Treatment period (6 weeks): two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg.

After the screening visit (V1) that was to be performed 6 weeks ± 2 days before Visit 2 (V2), eligible patients were to undergo a 6-week run-in period with FP/SLM DPI 500/50 µg (SERETIDE™ DISKUS™). At the end of the run-in period (V2), patients were to be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks until Visit 3 (V3).

|  |                           |
|--|---------------------------|
| Arm type                               | Experimental              |
| Investigational medicinal product name | CHF5993 DPI 100/6/12.5 µg |
| Investigational medicinal product code |                           |
| Other name                             |                           |
| Pharmaceutical forms                   | Inhalation powder         |
| Routes of administration               | Respiratory use           |

Dosage and administration details:

Carried out treatment included two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg.

| <b>Number of subjects in period 1</b> | CHF5993 DPI<br>100/6/12.5 µg |
|---------------------------------------|------------------------------|
| Started                               | 25                           |
| Completed                             | 25                           |

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | CHF5993 DPI 100/6/12.5 µg |
|-----------------------|---------------------------|

Reporting group description:

After the screening visit (V1) that was to be performed 6 weeks  $\pm$  2 days before Visit 2 (V2), eligible patients were to undergo a 6-week run-in period with FP/SLM DPI 500/50 µg (SERETIDE™ DISKUS™). At the end of the run-in period (V2), patients were to be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks until Visit 3 (V3). During the treatment period all patients, (25 subjects) received two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg. All enrolled and treated patients completed the study.

| Reporting group values   | CHF5993 DPI<br>100/6/12.5 µg | Total |  |
|--------------------------|------------------------------|-------|--|
| Number of subjects       | 25                           | 25    |  |
| Age categorical          |                              |       |  |
| Units: Subjects          |                              |       |  |
| Adults (45-79 years)     | 25                           | 25    |  |
| Age continuous           |                              |       |  |
| Units: years             |                              |       |  |
| arithmetic mean          | 65.0                         |       |  |
| standard deviation       | $\pm$ 7.7                    | -     |  |
| Gender categorical       |                              |       |  |
| Units: Subjects          |                              |       |  |
| Female                   | 9                            | 9     |  |
| Male                     | 16                           | 16    |  |
| Race                     |                              |       |  |
| Units: Subjects          |                              |       |  |
| White                    | 25                           | 25    |  |
| BMI                      |                              |       |  |
| Units: kg/m <sup>2</sup> |                              |       |  |
| arithmetic mean          | 27.71                        |       |  |
| standard deviation       | $\pm$ 5.05                   | -     |  |

## End points

### End points reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | CHF5993 DPI 100/6/12.5 µg |
|-----------------------|---------------------------|

Reporting group description:

All patients (25 subjects) received CHF5993 as follows:

- Treatment period (6 weeks): two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg.

After the screening visit (V1) that was to be performed 6 weeks ± 2 days before Visit 2 (V2), eligible patients were to undergo a 6-week run-in period with FP/SLM DPI 500/50 µg (SERETIDE™ DISKUS™). At the end of the run-in period (V2), patients were to be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks until Visit 3 (V3).

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Baseline / V2 pre-dose, TLC |
|----------------------------|-----------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Baseline / Visit 2 pre-dose; distal lung region at Total Lung Capacity, TLC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | V2 post-dose, TLC |
|----------------------------|-------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Visit 2 post-dose; distal lung region at Total Lung Capacity, TLC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | V3 pre-dose, TLC |
|----------------------------|------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Visit 3 pre-dose; distal lung region at Total Lung Capacity, TLC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | V3 post-dose, TLC |
|----------------------------|-------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Visit 3 post-dose; distal lung region at Total Lung Capacity, TLC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Baseline / V2 pre-dose, FRC |
|----------------------------|-----------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Baseline / Visit 2 pre-dose; distal lung region at Functional Residual Capacity, FRC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | V2 post-dose, FRC |
|----------------------------|-------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Visit 2 post-dose; distal lung region at Functional Residual Capacity, FRC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | V3 pre-dose, FRC |
|----------------------------|------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects evaluated at Visit 3 pre-dose; distal lung region at Functional Residual Capacity, FRC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | V3 post-dose, FRC |
| Subject analysis set type  | Per protocol      |

Subject analysis set description:

Subjects evaluated at Visit 3 post-dose; distal lung region at Functional Residual Capacity, FRC. The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

### **Primary: Untrimmed siVaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose**

|                 |   |
|-----------------|---|
| End point title | Untrimmed siVaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose |
|-----------------|---|

End point description:

siVaw is Specific Image-Based Airway Volume (at Total Lung Capacity, TLC). Primary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD). The data were summarized by the descriptive statistics for actual values at each timepoint.

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

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be scanned at TLC, pre-dose.

| <b>End point values</b>              | Baseline / V2 pre-dose, TLC | V3 pre-dose, TLC       |  |  |
|--------------------------------------|-----------------------------|------------------------|--|--|
| Subject group type                   | Subject analysis set        | Subject analysis set   |  |  |
| Number of subjects analysed          | 23                          | 23                     |  |  |
| Units: percentage                    |                             |                        |  |  |
| arithmetic mean (standard deviation) | 1.4088 ( $\pm$ 0.6647)      | 1.3550 ( $\pm$ 0.6014) |  |  |

### **Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Percent change from Baseline to V3 pre-dose; TLC |
|-----------------------------------|--|

Statistical analysis description:

Overall, distal region value for primary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study. The correct value for subjects in the analysis is N=23.

|                   |  |
|-------------------|--|
| Comparison groups | V3 pre-dose, TLC v Baseline / V2 pre-dose, TLC |
|-------------------|--|



|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 46                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[1]</sup>  |
| P-value                                 | = 0.4521              |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Adjusted Mean Change  |
| Point estimate                          | -3.81                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -13.44                |
| upper limit                             | 6.89                  |

Notes:

[1] - The model included the logarithm of baseline (V2 pre-dose, but not for trimmed parameters) at TLC and visit (V2 post-dose, V3 pre-dose, V3 post-dose) as covariates, and the interaction between visit and logarithm of baseline (for untrimmed parameters).

The model parameters were estimated using the restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

### Primary: Trimmed siRaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose

|                 |   |
|-----------------|---|
| End point title | Trimmed siRaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose |
|-----------------|---|

End point description:

siRaw is the Specific Image-Based Airway Resistance (at Total Lung Capacity, TLC).

Primary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD).

The data were summarized by the descriptive statistics for actual values at each timepoint.

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

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be scanned at TLC, pre-dose.

| End point values                     | Baseline / V2 pre-dose, TLC | V3 pre-dose, TLC     |  |  |
|--------------------------------------|-----------------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set        | Subject analysis set |  |  |
| Number of subjects analysed          | 22 <sup>[2]</sup>           | 22 <sup>[3]</sup>    |  |  |
| Units: percentage                    |                             |                      |  |  |
| arithmetic mean (standard deviation) |                             |                      |  |  |
| TLC                                  | 0.7160 (± 0.4034)           | 0.8492 (± 0.5947)    |  |  |

Notes:

[2] - PP population

number of patients/number of patients with data: 23/22

[3] - PP population

number of patients/number of patients with data: 23/22

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Percent change from Baseline to V3 pre-dose; TLC |
|----------------------------|--|

Statistical analysis description:

Overall, distal region value for primary endpoints was log-transformed and analysed using a Mixed

Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=22.

|   |  |
|---|--|
| Comparison groups                       | V3 pre-dose, TLC v Baseline / V2 pre-dose, TLC |
| Number of subjects included in analysis | 44   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | other <sup>[4]</sup>                           |
| P-value                                 | = 0.4871                                       |
| Method                                  | Mixed models analysis                          |
| Parameter estimate                      | Adjusted Mean Change                           |
| Point estimate                          | 11.95  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -19.67   |
| upper limit                             | 56.02  |

Notes:

[4] - The model included the logarithm of baseline (V2 pre-dose, but not for trimmed parameters) at TLC and visit (V2 post-dose, V3 pre-dose, V3 post-dose) as covariates, and the interaction between visit and logarithm of baseline (for untrimmed parameters).

The model parameters were estimated using the restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

### **Secondary: Untrimmed siVaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose**

|                 |   |
|-----------------|---|
| End point title | Untrimmed siVaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose |
|-----------------|---|

End point description:

siVaw is Specific Image-Based Airway Volume (at Total Lung Capacity, TLC and Functional Residual Capacity, FRC).

Secondary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD). The data were summarized by the descriptive statistics for actual values at each timepoint.

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

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be scanned at TLC, pre-dose.

| End point values                     | Baseline / V2 pre-dose, TLC | V2 post-dose, TLC    | V3 pre-dose, TLC     | V3 post-dose, TLC    |
|--------------------------------------|-----------------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set        | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 23                          | 23                   | 23                   | 23                   |
| Units: percentage                    |                             |                      |                      |                      |
| arithmetic mean (standard deviation) | 1.4088 (± 0.6647)           | 1.8706 (± 0.4954)    | 1.3550 (± 0.6014)    | 1.9805 (± 0.6390)    |

| End point values                     | Baseline / V2 pre-dose, FRC | V2 post-dose, FRC      | V3 pre-dose, FRC       | V3 post-dose, FRC      |
|--------------------------------------|-----------------------------|------------------------|------------------------|------------------------|
| Subject group type                   | Subject analysis set        | Subject analysis set   | Subject analysis set   | Subject analysis set   |
| Number of subjects analysed          | 23                          | 23                     | 23                     | 23                     |
| Units: percentage                    |                             |                        |                        |                        |
| arithmetic mean (standard deviation) | 0.6321 ( $\pm$ 0.3164)      | 1.0204 ( $\pm$ 0.3404) | 0.6982 ( $\pm$ 0.3198) | 1.0442 ( $\pm$ 0.3825) |

## Statistical analyses

| Statistical analysis title  | Percent change from Baseline to V2 post-dose; TLC |
|---|---|
| Statistical analysis description:   |   |
| Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value. The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study. The correct value for subjects in the analysis is N=23. |   |
| Comparison groups   | V2 post-dose, TLC v Baseline / V2 pre-dose, TLC   |
| Number of subjects included in analysis   | 46  |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| P-value   | < 0.0001  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | Adjusted Mean Change                              |
| Point estimate  | 39.76   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 28.9  |
| upper limit   | 51.53   |

| Statistical analysis title  | Percent change from V3 post to V3 pre-dose; TLC |
|---|---|
| Statistical analysis description:   |   |
| Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value. The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study. The correct value for subjects in the analysis is N=23. |   |
| Comparison groups   | V3 post-dose, TLC v V3 pre-dose, TLC            |
| Number of subjects included in analysis   | 46  |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| P-value   | < 0.0001  |
| Method  | Mixed models analysis                           |
| Parameter estimate  | Adjusted Mean Change                            |
| Point estimate  | 62.63   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 41.78   |
| upper limit         | 86.56   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Percent change from Baseline to V3 pre-dose; FRC |
|-----------------------------------|--|

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=23.

|   |  |
|---|--|
| Comparison groups                       | V3 pre-dose, FRC v Baseline / V2 pre-dose, FRC |
| Number of subjects included in analysis | 46   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | other  |
| P-value                                 | = 0.0636                                       |
| Method                                  | Mixed models analysis                          |
| Parameter estimate                      | Adjusted Mean Change                           |
| Point estimate                          | 16.26  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.93  |
| upper limit                             | 36.44  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Percent change from Baseline to V2 post-dose; FRC |
|-----------------------------------|---|

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=23.

|   |   |
|---|---|
| Comparison groups                       | V2 post-dose, FRC v Baseline / V2 pre-dose, FRC |
| Number of subjects included in analysis | 46  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| P-value                                 | < 0.0001  |
| Method                                  | Mixed models analysis                           |
| Parameter estimate                      | Adjusted Mean Change                            |
| Point estimate                          | 77.87   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 60.28   |
| upper limit         | 97.39   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Percent change from V3 post to V3 pre-dose; FRC |
|-----------------------------------|---|

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=23.

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | V3 post-dose, FRC v V3 pre-dose, FRC |
| Number of subjects included in analysis | 46                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other                                |
| P-value                                 | = 0.0011                             |
| Method                                  | Mixed models analysis                |
| Parameter estimate                      | Adjusted Mean Change                 |
| Point estimate                          | 39.49                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 16.21                                |
| upper limit                             | 67.43                                |

### **Secondary: Trimmed siRaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose**

|                 |   |
|-----------------|---|
| End point title | Trimmed siRaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose |
|-----------------|---|

End point description:

siRaw is the Specific Image-Based Airway Resistance (at Total Lung Capacity, TLC and Functional Residual Capacity, FRC).

Secondary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD). The data were summarized by the descriptive statistics for actual values at each timepoint.

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

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be scanned at TLC, pre-dose.

| End point values                     | Baseline / V2 pre-dose, TLC | V2 post-dose, TLC    | V3 pre-dose, TLC     | V3 post-dose, TLC    |
|--------------------------------------|-----------------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set        | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 22 <sup>[5]</sup>           | 23                   | 22 <sup>[6]</sup>    | 23                   |
| Units: percentage                    |                             |                      |                      |                      |
| arithmetic mean (standard deviation) | 0.7160 (± 0.4034)           | 0.3685 (± 0.1594)    | 0.8492 (± 0.5947)    | 0.3121 (± 0.1416)    |

Notes:

[5] - PP population

number of patients/number of patients with data: 23/22.

[6] - PP population

number of patients/number of patients with data: 23/22.

| End point values                     | Baseline / V2 pre-dose, FRC | V2 post-dose, FRC    | V3 pre-dose, FRC     | V3 post-dose, FRC    |
|--------------------------------------|-----------------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set        | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 22 <sup>[7]</sup>           | 22 <sup>[8]</sup>    | 22 <sup>[9]</sup>    | 22 <sup>[10]</sup>   |
| Units: percentage                    |                             |                      |                      |                      |
| arithmetic mean (standard deviation) | 0.4981 (± 0.3383)           | 0.2200 (± 0.1664)    | 0.3625 (± 0.4733)    | 0.1889 (± 0.1453)    |

Notes:

[7] - PP population

number of patients/number of patients with data: 23/22.

[8] - PP population

number of patients/number of patients with data: 23/22.

[9] - PP population

number of patients/number of patients with data: 23/22.

[10] - PP population

number of patients/number of patients with data: 23/22.

## Statistical analyses

| Statistical analysis title | Percent change from Baseline to V2 post-dose; TLC |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=22.

|   |   |
|---|---|
| Comparison groups                       | V2 post-dose, TLC v Baseline / V2 pre-dose, TLC |
| Number of subjects included in analysis | 45  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| P-value                                 | = 0.0002  |
| Method                                  | Mixed models analysis                           |
| Parameter estimate                      | Adjusted Mean Change                            |
| Point estimate                          | -51.07  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -64.56  |
| upper limit                             | -32.44  |

| Statistical analysis title | Percent change from V3 post to V3 pre-dose; TLC |
|----------------------------|---|
|----------------------------|---|

**Statistical analysis description:**

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=22.

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | V3 post-dose, TLC v V3 pre-dose, TLC |
| Number of subjects included in analysis | 45                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other                                |
| P-value                                 | = 0.0009                             |
| Method                                  | Mixed models analysis                |
| Parameter estimate                      | Adjusted Mean Change                 |
| Point estimate                          | -57.22                               |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -72.88                               |
| upper limit                             | -32.52                               |

**Statistical analysis title**

Percent change from Baseline to V3 pre-dose; FRC

**Statistical analysis description:**

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.

The correct value for subjects in the analysis is N=22.

|   |  |
|---|--|
| Comparison groups                       | Baseline / V2 pre-dose, FRC v V3 pre-dose, FRC |
| Number of subjects included in analysis | 44   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | other  |
| P-value                                 | = 0.0261                                       |
| Method                                  | Mixed models analysis                          |
| Parameter estimate                      | Adjusted Mean Change                           |
| Point estimate                          | -63.57   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -84.85   |
| upper limit                             | -12.42   |

**Statistical analysis title**

Percent change from Baseline to V2 post-dose; FRC

**Statistical analysis description:**

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT

database system and to the cross-over nature of the study.  
The correct value for subjects in the analysis is N=22.

|   |   |
|---|---|
| Comparison groups                       | V2 post-dose, FRC v Baseline / V2 pre-dose, FRC |
| Number of subjects included in analysis | 44  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| P-value                                 | = 0.0006  |
| Method                                  | Mixed models analysis                           |
| Parameter estimate                      | Adjusted Mean Change                            |
| Point estimate                          | -66.95  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -81.4   |
| upper limit                             | -41.27  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Percent change from V3 post to V3 pre-dose; FRC |
|-----------------------------------|---|

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value. The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.  
The correct value for subjects in the analysis is N=22.

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | V3 pre-dose, FRC v V3 post-dose, FRC |
| Number of subjects included in analysis | 44                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other                                |
| P-value                                 | = 0.3855                             |
| Method                                  | Mixed models analysis                |
| Parameter estimate                      | Adjusted Mean Change                 |
| Point estimate                          | -29.28                               |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -68.62                               |
| upper limit                             | 59.42                                |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs starting on or after first administration of study drug (CHF5993 DPI) were classified as Treatment-Emergent AEs (TEAEs).

Adverse event reporting additional description:

The safety data were summarised in 3 phases: 1)Screening: starting from date signing the ICF until first FP/SLM DPI administration date-1 min/day, 2)Run-in: starting from first FP/SLM DPI administration date until first CHF5993 DPI administration date-1 min/day, 3)Treatment: from first CHF5993 DPI administration date until date of last contact.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | CHF5993 DPI 100/6/12.5 µg - Safety set |
|-----------------------|--|

Reporting group description:

The safety set, defined as all patients who received at least one dose of study drug (CHF5993 DPI), included 25 patients.

| Serious adverse events                            | CHF5993 DPI<br>100/6/12.5 µg -<br>Safety set |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 0 / 25 (0.00%)                               |  |  |
| number of deaths (all causes)                     | 0  |  |  |
| number of deaths resulting from adverse events    | 0  |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | CHF5993 DPI<br>100/6/12.5 µg -<br>Safety set |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 11 / 25 (44.00%)                             |  |  |
| Nervous system disorders                              |  |  |  |
| Headache  |  |  |  |
| subjects affected / exposed                           | 3 / 25 (12.00%)                              |  |  |
| occurrences (all)                                     | 3  |  |  |
| Sciatica  |  |  |  |
| subjects affected / exposed                           | 1 / 25 (4.00%)                               |  |  |
| occurrences (all)                                     | 1  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Gastrointestinal disorders                      |                |  |  |
| Hiatus hernia                                   |                |  |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Pleural calcification                           |                |  |  |
| subjects affected / exposed                     | 2 / 25 (8.00%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Bronchiectasis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Pulmonary fibrosis                              |                |  |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Hepatic steatosis                               |                |  |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) |  |  |
| occurrences (all)                               | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 22 March 2021  | The following changes have been implemented:<br>-IMP storage conditions updated accordingly to EMA requirements;<br>-Typo corrections.  |
| 09 August 2021 | The following substantial changes have been implemented:<br>-Blood chemistry updated considering the creatinine test replacing BUN analysis;<br>-RSI is now referred to Summary of;<br>-Product Characteristics instead of IB;<br>-Sponsor medical expert contacts updated;<br>-Typo corrections. |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported