



## Clinical trial results:

**A phase II, multicentre, double blind, randomised, 5-way cross-over study to test the non-inferiority of the acute bronchodilator effect of CHF 1535 200/6 µg NEXThaler® versus CHF 1535 100/6 µg NEXThaler® in partially controlled and uncontrolled adult asthmatic patients.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2013-004826-27  |
| Trial protocol           | GB              |
| Global end of trial date | 14 October 2014 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 11 July 2016   |
| First version publication date | 09 August 2015 |

### Trial information

#### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CCD-01535BA1-01 |
|-----------------------|-----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02000609 |
| 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 Manager, Chiesi Farmaceutici S.p.A., clinicalTrials_info@chiesi.com |
| Scientific contact           | Clinical Trial Transparency Manager, Chiesi Farmaceutici S.p.A., 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                       | 14 October 2014 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 14 October 2014 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 14 October 2014 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority in terms of acute bronchodilator effect (FEV1 AUC0-12h) between a single dose of CHF 1535 NEXThaler® 200 + 6 µg and a single dose of CHF 1535 NEXThaler® 100 + 6 µg at two dose levels (1 and 4 inhalations) in partially-controlled and uncontrolled adult asthmatic patients.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements . Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy:

BDP HFA 100 µg (QVAR), 2 inhalations bid (total daily dose BDP 400 µg)

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 10 April 2014 |
| 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 | United Kingdom: 60 |
| Worldwide total number of subjects   | 60                 |
| EEA total number of subjects         | 60                 |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 60 |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

#### Recruitment details:

Sixty subjects were randomised to one of the 5 treatment sequences and received study drugs: A-B-C-D-E (N=11), B-C-D-E-A (N=11), C-D-E-A-B (N=14), D-E-A-B-C (N=13) and E-A-B-C-D (N=11). Fifty eight (96.7%) subjects completed the study. Two (3.3%) subjects discontinued the study prematurely; 1 (1.7%) subject withdrew consent after randomisation.

### Pre-assignment

#### Screening details:

In total, 208 subjects were screened. One hundred forty-eight subjects were not randomised (i.e., screening failures), of whom 140 subjects were not eligible to enter the study, 3 subjects withdrew consent before randomisation, 1 subject was lost to follow-up and 4 subjects were not randomized for other reasons.

### 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:

This was a double-blind study. The randomisation list was provided to the labelling facility but was not be available to the subjects, Investigators, monitors or employees of the centre involved in the management of the study before unblinding of the data, unless in case of emergency. The Sponsor's clinical team was also blinded during the study as they did not have direct access to the randomisation list.

### Arms

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

#### Arm description:

Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

|  |   |
|--|---|
| Arm type                               | experimental - active comparator - placebo  |
| Investigational medicinal product name | CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use  |

#### Dosage and administration details:

##### Test treatments:

CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.

- Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
- Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

## Reference treatments:

- Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
- Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
- Treatment E: placebo.

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

## Arm description:

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

|  |   |
|--|---|
| Arm type                               | experimental - active comparator - placebo  |
| Investigational medicinal product name | CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use  |

## Dosage and administration details:

## Test treatments:

CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.

- Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
- Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

## Reference treatments:

- Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
- Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
- Treatment E: placebo.

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

## Arm description:

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

|          |  |
|----------|--|
| Arm type | experimental - active comparator - placebo |
|----------|--|

|  |   |
|--|---|
| Investigational medicinal product name | CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

Test treatments:

CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.

- Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
- Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:

- Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
- Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
- Treatment E: placebo.

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

Arm description:

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

|  |   |
|--|---|
| Arm type                               | experimental - active comparator - placebo  |
| Investigational medicinal product name | CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

Test treatments:

CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.

- Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
- Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:

- Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
- Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
- Treatment E: placebo.

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

Arm description:

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler®

BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

|  |   |
|--|---|
| Arm type                               | experimental - active comparator - placebo  |
| Investigational medicinal product name | CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

Test treatments:

CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.

- Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
- Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:

- Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
- Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
- Treatment E: placebo.

| <b>Number of subjects in period 1</b> | Sequence A-B-C-D-E | Sequence B-C-D-E-A | Sequence C-D-E-A-B |
|---------------------------------------|--------------------|--------------------|--------------------|
| Started                               | 11                 | 11                 | 14                 |
| Completed                             | 10                 | 11                 | 14                 |
| Not completed                         | 1                  | 0                  | 0                  |
| personal issues                       | 1                  | -                  | -                  |
| Consent withdrawn by subject          | -                  | -                  | -                  |

| <b>Number of subjects in period 1</b> | Sequence D-E-A-B-C | Sequence E-A-B-C-D |
|---------------------------------------|--------------------|--------------------|
| Started                               | 13                 | 11                 |
| Completed                             | 12                 | 11                 |
| Not completed                         | 1                  | 0                  |
| personal issues                       | -                  | -                  |
| Consent withdrawn by subject          | 1                  | -                  |

## Baseline characteristics

### Reporting groups

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

#### Reporting group description:

Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

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

#### Reporting group description:

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

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

#### Reporting group description:

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

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

#### Reporting group description:

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;



NEXThaler®;

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

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

Reporting group description:

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

| Reporting group values                                | Sequence A-B-C-D-E | Sequence B-C-D-E-A | Sequence C-D-E-A-B |
|---|--------------------|--------------------|--------------------|
| Number of subjects                                    | 11                 | 11                 | 14                 |
| Age categorical<br>Units: Subjects                    |                    |                    |                    |
| In utero  |                    |                    |                    |
| Preterm newborn infants<br>(gestational age < 37 wks) |                    |                    |                    |
| Newborns (0-27 days)                                  |                    |                    |                    |
| Infants and toddlers (28 days-23<br>months)           |                    |                    |                    |
| Children (2-11 years)                                 |                    |                    |                    |
| Adolescents (12-17 years)                             |                    |                    |                    |
| Adults (18-64 years)                                  |                    |                    |                    |
| From 65-84 years                                      |                    |                    |                    |
| 85 years and over                                     |                    |                    |                    |
| Age continuous<br>Units: years                        |                    |                    |                    |
| arithmetic mean                                       | 43.4               | 36.2               | 35.8               |
| standard deviation                                    | ± 14.5             | ± 9.6              | ± 13.9             |
| Gender categorical<br>Units: Subjects                 |                    |                    |                    |
| Female  | 4                  | 5                  | 7                  |
| Male  | 7                  | 6                  | 7                  |

| Reporting group values                                | Sequence D-E-A-B-C | Sequence E-A-B-C-D | Total |
|---|--------------------|--------------------|-------|
| Number of subjects                                    | 13                 | 11                 | 60    |
| Age categorical<br>Units: Subjects                    |                    |                    |       |
| In utero  |                    |                    | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |                    |                    | 0     |
| Newborns (0-27 days)                                  |                    |                    | 0     |

|  |       |      |    |
|--|-------|------|----|
| Infants and toddlers (28 days-23 months) |       |      | 0  |
| Children (2-11 years)                    |       |      | 0  |
| Adolescents (12-17 years)                |       |      | 0  |
| Adults (18-64 years)                     |       |      | 0  |
| From 65-84 years                         |       |      | 0  |
| 85 years and over                        |       |      | 0  |
| Age continuous                           |       |      |    |
| Units: years                             |       |      |    |
| arithmetic mean                          | 35    | 40.9 |    |
| standard deviation                       | ± 9.2 | ± 11 | -  |
| Gender categorical                       |       |      |    |
| Units: Subjects                          |       |      |    |
| Female                                   | 7     | 5    | 28 |
| Male                                     | 6     | 6    | 32 |

### Subject analysis sets

|   |                    |
|---|--------------------|
| Subject analysis set title  | Treatment A - ITT  |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.  |                    |
| Subject analysis set title  | Treatment B - ITT  |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.  |                    |
| Subject analysis set title  | Treatment C - ITT  |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.  |                    |
| Subject analysis set title  | Treatment D - ITT  |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.  |                    |
| Subject analysis set title  | Treatment E - ITT  |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.  |                    |
| Subject analysis set title  | Treatment A - PP   |
| Subject analysis set type   | Per protocol       |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                    |
| Subject analysis set title  | Treatment B - PP   |
| Subject analysis set type   | Per protocol       |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                    |

|   |                      |
|---|----------------------|
| Subject analysis set title  | Treatment C - PP     |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                      |
| Subject analysis set title  | Treatment D - PP     |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                      |
| Subject analysis set title  | Treatment E - PP     |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                      |
| Subject analysis set title  | Treatment A - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment B - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment C - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment D - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment E - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |

| Reporting group values                                | Treatment A - ITT | Treatment B - ITT | Treatment C - ITT |
|---|-------------------|-------------------|-------------------|
| Number of subjects                                    | 60                | 58                | 58                |
| Age categorical<br>Units: Subjects                    |                   |                   |                   |
| In utero  |                   |                   |                   |
| Preterm newborn infants<br>(gestational age < 37 wks) |                   |                   |                   |
| Newborns (0-27 days)                                  |                   |                   |                   |
| Infants and toddlers (28 days-23 months)              |                   |                   |                   |
| Children (2-11 years)                                 |                   |                   |                   |
| Adolescents (12-17 years)                             |                   |                   |                   |
| Adults (18-64 years)                                  |                   |                   |                   |
| From 65-84 years                                      |                   |                   |                   |
| 85 years and over                                     |                   |                   |                   |

|   |    |    |    |
|---|----|----|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ±  | ±  | ±  |
| Gender categorical<br>Units: Subjects                                   |    |    |    |
| Female  | 28 | 27 | 27 |
| Male  | 32 | 31 | 31 |

| Reporting group values  | Treatment D - ITT | Treatment E - ITT | Treatment A - PP |
|---|-------------------|-------------------|------------------|
| Number of subjects  | 59                | 59                | 60               |
| Age categorical<br>Units: Subjects  |                   |                   |                  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                   |                   |                  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | ±                 | ±                 | ±                |
| Gender categorical<br>Units: Subjects   |                   |                   |                  |
| Female  | 28                | 28                | 28               |
| Male  | 31                | 31                | 32               |

| Reporting group values  | Treatment B - PP | Treatment C - PP | Treatment D - PP |
|---|------------------|------------------|------------------|
| Number of subjects  | 57               | 58               | 59               |
| Age categorical<br>Units: Subjects  |                  |                  |                  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                  |                  |                  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | ±                | ±                | ±                |

|                                       |    |    |    |
|---------------------------------------|----|----|----|
| Gender categorical<br>Units: Subjects |    |    |    |
| Female                                | 26 | 27 | 28 |
| Male                                  | 31 | 31 | 31 |

| Reporting group values  | Treatment E - PP | Treatment A - safety | Treatment B - safety |
|---|------------------|----------------------|----------------------|
| Number of subjects  | 59               | 60                   | 58                   |
| Age categorical<br>Units: Subjects  |                  |                      |                      |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                  |                      |                      |
| Age continuous<br>Units: years  |                  |                      |                      |
| arithmetic mean   |                  |                      |                      |
| standard deviation  | ±                | ±                    | ±                    |
| Gender categorical<br>Units: Subjects   |                  |                      |                      |
| Female  | 28               | 28                   | 27                   |
| Male  | 31               | 32                   | 31                   |

| Reporting group values  | Treatment C - safety | Treatment D - safety | Treatment E - safety |
|---|----------------------|----------------------|----------------------|
| Number of subjects  | 58                   | 59                   | 59                   |
| Age categorical<br>Units: Subjects  |                      |                      |                      |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                      |                      |                      |
| Age continuous<br>Units: years  |                      |                      |                      |
| arithmetic mean   |                      |                      |                      |
| standard deviation  | ±                    | ±                    | ±                    |
| Gender categorical<br>Units: Subjects   |                      |                      |                      |
| Female  | 27                   | 28                   | 28                   |
| Male  | 31                   | 31                   | 31                   |



## End points

### End points reporting groups

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

Reporting group description:

Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

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

Reporting group description:

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

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

Reporting group description:

- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

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

Reporting group description:

- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

NEXThaler®;

• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

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

Reporting group description:

- Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
- Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
- Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
- Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
- Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Treatment A - ITT  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Treatment B - ITT  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Treatment C - ITT  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Treatment D - ITT  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Treatment E - ITT  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Treatment A - PP |
| Subject analysis set type  | Per protocol     |

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Treatment B - PP |
| Subject analysis set type  | Per protocol     |

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.



|   |                      |
|---|----------------------|
| Subject analysis set title  | Treatment C - PP     |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                      |
| Subject analysis set title  | Treatment D - PP     |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                      |
| Subject analysis set title  | Treatment E - PP     |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis. |                      |
| Subject analysis set title  | Treatment A - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment B - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment C - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment D - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |
| Subject analysis set title  | Treatment E - safety |
| Subject analysis set type   | Safety analysis      |
| Subject analysis set description:<br>All randomised subjects who received at least one dose of study drug.  |                      |

### Primary: FEV1 AUC0-12h/12h

|   |                   |
|---|-------------------|
| End point title   | FEV1 AUC0-12h/12h |
| End point description:<br>FEV1 AUC0-12h was measured standardised by time (L)   |                   |
| End point type  | Primary           |
| End point timeframe:<br>FEV1 was measured from visit 3 to visit 7, at the following timepoints: at pre-dose within 60 min of the dose and at 10 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose. |                   |

| End point values                          | Treatment A - PP       | Treatment B - PP       | Treatment C - PP      | Treatment D - PP      |
|---|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type                        | Subject analysis set   | Subject analysis set   | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed               | 60                     | 57                     | 58                    | 59                    |
| Units: Liters                             |                        |                        |                       |                       |
| arithmetic mean (confidence interval 95%) | 2.754 (2.722 to 2.786) | 2.783 (2.749 to 2.818) | 2.87 (2.837 to 2.903) | 2.897 (2.863 to 2.93) |

| End point values                          | Treatment E - PP      |  |  |  |
|---|-----------------------|--|--|--|
| Subject group type                        | Subject analysis set  |  |  |  |
| Number of subjects analysed               | 59                    |  |  |  |
| Units: Liters                             |                       |  |  |  |
| arithmetic mean (confidence interval 95%) | 2.477 (2.444 to 2.51) |  |  |  |

### Statistical analyses

| Statistical analysis title              | Treatment B vs Treatment A          |
|---|-------------------------------------|
| Comparison groups                       | Treatment A - PP v Treatment B - PP |
| Number of subjects included in analysis | 117                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | non-inferiority                     |
| P-value                                 | = 0.224                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.029                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.018                              |
| upper limit                             | 0.076                               |

| Statistical analysis title              | Treatment D vs Treatment C          |
|---|-------------------------------------|
| Comparison groups                       | Treatment D - PP v Treatment C - PP |
| Number of subjects included in analysis | 117                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | non-inferiority                     |
| P-value                                 | = 0.258                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.027                               |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.02   |
| upper limit         | 0.073   |

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment E          |
| Comparison groups                       | Treatment E - PP v Treatment D - PP |
| Number of subjects included in analysis | 118                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | other <sup>[1]</sup>                |
| P-value                                 | < 0.001                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.42                                |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.374                               |
| upper limit                             | 0.466                               |

Notes:

[1] - Assay sensitivity analysis

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment E          |
| Comparison groups                       | Treatment C - PP v Treatment E - PP |
| Number of subjects included in analysis | 117                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | other <sup>[2]</sup>                |
| P-value                                 | < 0.001                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.393                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.347                               |
| upper limit                             | 0.439                               |

Notes:

[2] - Assy sensitivity analysis

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Treatment B vs Treatment E          |
| Comparison groups                 | Treatment B - PP v Treatment E - PP |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 116                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[3]</sup>     |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.306                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.259                    |
| upper limit                             | 0.354                    |

Notes:

[3] - Assay sensitivity analysis

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Treatment A vs Treatment E          |
| Comparison groups                       | Treatment A - PP v Treatment E - PP |
| Number of subjects included in analysis | 119                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | other <sup>[4]</sup>                |
| P-value                                 | < 0.001                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.277                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.231                               |
| upper limit                             | 0.324                               |

Notes:

[4] - Assay sensitivity analysis

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment A          |
| Comparison groups                       | Treatment A - PP v Treatment C - PP |
| Number of subjects included in analysis | 118                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | other <sup>[5]</sup>                |
| P-value                                 | < 0.001                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.116                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.069                               |
| upper limit                             | 0.162                               |

Notes:

[5] - dose-effect analysis

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Treatment D vs Treatment B |
|-----------------------------------|----------------------------|

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Treatment D - PP v Treatment B - PP |
| Number of subjects included in analysis | 116                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | other <sup>[6]</sup>                |
| P-value                                 | < 0.001                             |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | adjusted mean difference            |
| Point estimate                          | 0.113                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.066                               |
| upper limit                             | 0.161                               |

Notes:

[6] - dose-effect analysis

### Secondary: FEV1 AUC0-4h/4h

|  |                 |
|--|-----------------|
| End point title  | FEV1 AUC0-4h/4h |
| End point description:   |                 |
| FEV1 AUC0-4h standardised by time (L)  |                 |
| End point type   | Secondary       |
| End point timeframe:   |                 |
| FEV1 was measured from visit 3 to visit 7 (treatment visits) at the following timepoints: at pre-dose within 60 min of the dose and at 10 min, 30 min, 1 h, 2 h, 3 h, 4 h post-dose. |                 |

| End point values                          | Treatment A - ITT      | Treatment B - ITT     | Treatment C - ITT      | Treatment D - ITT    |
|---|------------------------|-----------------------|------------------------|----------------------|
| Subject group type                        | Subject analysis set   | Subject analysis set  | Subject analysis set   | Subject analysis set |
| Number of subjects analysed               | 60                     | 58                    | 58                     | 59                   |
| Units: Liters                             |                        |                       |                        |                      |
| arithmetic mean (confidence interval 95%) | 2.773 (2.742 to 2.804) | 2.802 (2.77 to 2.834) | 2.887 (2.855 to 2.919) | 2.9 (2.869 to 2.931) |

| End point values                          | Treatment E - ITT     |  |  |  |
|---|-----------------------|--|--|--|
| Subject group type                        | Subject analysis set  |  |  |  |
| Number of subjects analysed               | 59                    |  |  |  |
| Units: Liters                             |                       |  |  |  |
| arithmetic mean (confidence interval 95%) | 2.52 (2.488 to 2.551) |  |  |  |

### Statistical analyses

|                            |                                       |
|----------------------------|---------------------------------------|
| Statistical analysis title | Treatment B vs Treatment A            |
| Comparison groups          | Treatment A - ITT v Treatment B - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 118                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | non-inferiority          |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.029                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -0.015                   |
| upper limit                             | 0.074                    |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment C            |
| Comparison groups                       | Treatment C - ITT v Treatment D - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.013                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.031                                |
| upper limit                             | 0.057                                 |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment E            |
| Comparison groups                       | Treatment D - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[7]</sup>                  |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.38                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.336                                 |
| upper limit                             | 0.424                                 |

Notes:

[7] - Sensitivity analysis

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Treatment C vs Treatment E            |
| Comparison groups                 | Treatment C - ITT v Treatment E - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 117                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[8]</sup>     |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.367                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.323                    |
| upper limit                             | 0.412                    |

Notes:

[8] - sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment B vs Treatment E            |
| Comparison groups                       | Treatment B - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[9]</sup>                  |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.283                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.238                                 |
| upper limit                             | 0.327                                 |

Notes:

[9] - sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment A vs Treatment E            |
| Comparison groups                       | Treatment E - ITT v Treatment A - ITT |
| Number of subjects included in analysis | 119                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[10]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.253                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.208                                 |
| upper limit                             | 0.298                                 |

Notes:

[10] - sensitivity analysis

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Treatment C vs Treatment A |
|-----------------------------------|----------------------------|

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Treatment A - ITT v Treatment C - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[11]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.114                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.07                                  |
| upper limit                             | 0.159                                 |

Notes:

[11] - Dose-effect analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment B            |
| Comparison groups                       | Treatment B - ITT v Treatment D - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[12]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.098                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.053                                 |
| upper limit                             | 0.142                                 |

Notes:

[12] - Dose-effect analysis

### Secondary: FEV1 AUC4-12h/8h

|  |                  |
|--|------------------|
| End point title  | FEV1 AUC4-12h/8h |
| End point description:<br>FEV1 AUC4-12h was measured in a standardised by time (L) way.  |                  |
| End point type   | Secondary        |
| End point timeframe:<br>FEV1 was measured from visit 3 to visit 7 (treatment visits) at the following time points: pre-dose within 60 min of the dose and at 10 min, 30 min, 1 h, 2 h, 3 h, 4 h post-dose. |                  |



| End point values                          | Treatment A - ITT     | Treatment B - ITT      | Treatment C - ITT      | Treatment D - ITT     |
|---|-----------------------|------------------------|------------------------|-----------------------|
| Subject group type                        | Subject analysis set  | Subject analysis set   | Subject analysis set   | Subject analysis set  |
| Number of subjects analysed               | 60                    | 58                     | 58                     | 59                    |
| Units: Liters                             |                       |                        |                        |                       |
| arithmetic mean (confidence interval 95%) | 2.74 (2.706 to 2.775) | 2.768 (2.732 to 2.803) | 2.857 (2.821 to 2.892) | 2.89 (2.855 to 2.926) |

| End point values                          | Treatment E - ITT      |  |  |  |
|---|------------------------|--|--|--|
| Subject group type                        | Subject analysis set   |  |  |  |
| Number of subjects analysed               | 59                     |  |  |  |
| Units: Liters                             |                        |  |  |  |
| arithmetic mean (confidence interval 95%) | 2.449 (2.413 to 2.484) |  |  |  |

### Statistical analyses

| Statistical analysis title              | Treatment B vs Treatment A            |
|---|---------------------------------------|
| Comparison groups                       | Treatment A - ITT v Treatment B - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.027                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.022                                |
| upper limit                             | 0.077                                 |

| Statistical analysis title              | Treatment D vs Treatment C            |
|---|---------------------------------------|
| Comparison groups                       | Treatment D - ITT v Treatment C - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.033                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.016                                |
| upper limit                             | 0.083                                 |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment E            |
| Comparison groups                       | Treatment D - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[13]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.442                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.392                                 |
| upper limit                             | 0.491                                 |

Notes:

[13] - sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment E            |
| Comparison groups                       | Treatment C - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[14]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.408                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.359                                 |
| upper limit                             | 0.458                                 |

Notes:

[14] - sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment B vs Treatment E            |
| Comparison groups                       | Treatment E - ITT v Treatment B - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[15]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.319                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.269   |
| upper limit         | 0.369   |

Notes:

[15] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment A vs Treatment E            |
| Comparison groups                       | Treatment A - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 119                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[16]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.292                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.242                                 |
| upper limit                             | 0.342                                 |

Notes:

[16] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment A            |
| Comparison groups                       | Treatment C - ITT v Treatment A - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[17]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.117                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.067                                 |
| upper limit                             | 0.167                                 |

Notes:

[17] - Dose-effect analysis

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Treatment D vs Treatment B            |
| Comparison groups                 | Treatment D - ITT v Treatment B - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 117                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[18]</sup>    |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.123                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.073                    |
| upper limit                             | 0.172                    |

Notes:

[18] - Dose-effect analysis

## Secondary: Peak FEV1

|   |           |
|---|-----------|
| End point title   | Peak FEV1 |
| End point description:                                      |           |
| Maximum FEV1 value over 12h post-dose                       |           |
| End point type  | Secondary |
| End point timeframe:  |           |
| FEV1 was measured over 12 hours after single administration |           |

| End point values                          | Treatment A - ITT     | Treatment B - ITT      | Treatment C - ITT      | Treatment D - ITT      |
|---|-----------------------|------------------------|------------------------|------------------------|
| Subject group type                        | Subject analysis set  | Subject analysis set   | Subject analysis set   | Subject analysis set   |
| Number of subjects analysed               | 60                    | 58                     | 58                     | 59                     |
| Units: Liters                             |                       |                        |                        |                        |
| arithmetic mean (confidence interval 95%) | 2.898 (2.865 to 2.93) | 2.919 (2.886 to 2.953) | 3.008 (2.975 to 3.041) | 3.023 (2.991 to 3.056) |

| End point values                          | Treatment E - ITT      |  |  |  |
|---|------------------------|--|--|--|
| Subject group type                        | Subject analysis set   |  |  |  |
| Number of subjects analysed               | 59                     |  |  |  |
| Units: Liters                             |                        |  |  |  |
| arithmetic mean (confidence interval 95%) | 2.641 (2.608 to 2.673) |  |  |  |

## Statistical analyses

|                            |                                       |
|----------------------------|---------------------------------------|
| Statistical analysis title | Treatment B vs Treatment A            |
| Comparison groups          | Treatment A - ITT v Treatment B - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 118                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | non-inferiority          |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.022                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -0.024                   |
| upper limit                             | 0.068                    |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment C            |
| Comparison groups                       | Treatment C - ITT v Treatment D - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.016                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.03                                 |
| upper limit                             | 0.061                                 |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment E            |
| Comparison groups                       | Treatment D - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[19]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.383                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.337                                 |
| upper limit                             | 0.429                                 |

Notes:

[19] - Sensitivity analysis

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Treatment C vs Treatment E            |
| Comparison groups                 | Treatment C - ITT v Treatment E - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 117                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[20]</sup>    |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.367                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.321                    |
| upper limit                             | 0.413                    |

Notes:

[20] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment B vs Treatment E            |
| Comparison groups                       | Treatment B - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[21]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.279                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.232                                 |
| upper limit                             | 0.325                                 |

Notes:

[21] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment A vs Treatment E            |
| Comparison groups                       | Treatment A - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 119                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[22]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.257                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.211                                 |
| upper limit                             | 0.303                                 |

Notes:

[22] - Sensitivity analysis

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Treatment C vs Treatment A |
|-----------------------------------|----------------------------|

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Treatment C - ITT v Treatment A - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[23]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.11                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.064                                 |
| upper limit                             | 0.157                                 |

Notes:

[23] - Dose-effect analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment B            |
| Comparison groups                       | Treatment B - ITT v Treatment D - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[24]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.104                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.058                                 |
| upper limit                             | 0.15                                  |

Notes:

[24] - Dose-effect analysis

## Secondary: Peak FVC

|                        |  |
|------------------------|--|
| End point title        | Peak FVC   |
| End point description: | maximum FEV1 value over 12h post-dose                      |
| End point type         | Secondary  |
| End point timeframe:   | FVC was measured over 12 hours after single administration |

| End point values                          | Treatment A - ITT     | Treatment B - ITT      | Treatment C - ITT     | Treatment D - ITT     |
|---|-----------------------|------------------------|-----------------------|-----------------------|
| Subject group type                        | Subject analysis set  | Subject analysis set   | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed               | 60                    | 58                     | 58                    | 59                    |
| Units: Liters                             |                       |                        |                       |                       |
| arithmetic mean (confidence interval 95%) | 4.121 (4.09 to 4.153) | 4.149 (4.116 to 4.182) | 4.172 (4.14 to 4.205) | 4.187 (4.155 to 4.22) |

|   |                        |  |  |  |
|---|------------------------|--|--|--|
| <b>End point values</b>                   | Treatment E - ITT      |  |  |  |
| Subject group type                        | Subject analysis set   |  |  |  |
| Number of subjects analysed               | 59                     |  |  |  |
| Units: Liters                             |                        |  |  |  |
| arithmetic mean (confidence interval 95%) | 4.014 (3.982 to 4.046) |  |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment B vs Treatment A            |
| Comparison groups                       | Treatment A - ITT v Treatment B - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.028                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.018                                |
| upper limit                             | 0.073                                 |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment C            |
| Comparison groups                       | Treatment C - ITT v Treatment D - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.015                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.03                                 |
| upper limit                             | 0.06                                  |

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Treatment D vs Treatment E            |
| Comparison groups                 | Treatment D - ITT v Treatment E - ITT |



|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 118                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[25]</sup>    |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.173                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.128                    |
| upper limit                             | 0.218                    |

Notes:

[25] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment E            |
| Comparison groups                       | Treatment C - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[26]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.158                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.113                                 |
| upper limit                             | 0.204                                 |

Notes:

[26] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment B vs Treatment E            |
| Comparison groups                       | Treatment B - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[27]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.135                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.089                                 |
| upper limit                             | 0.181                                 |

Notes:

[27] - Sensitivity analysis

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Treatment A vs Treatment E |
|-----------------------------------|----------------------------|

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Treatment A - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 119                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[28]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.107                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.062                                 |
| upper limit                             | 0.152                                 |

Notes:

[28] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment A            |
| Comparison groups                       | Treatment A - ITT v Treatment C - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[29]</sup>                 |
| P-value                                 | = 0.027                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.051                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.006                                 |
| upper limit                             | 0.096                                 |

Notes:

[29] - Dose-effect analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment B            |
| Comparison groups                       | Treatment D - ITT v Treatment B - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[30]</sup>                 |
| P-value                                 | = 0.102                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.038                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.008                                |
| upper limit                             | 0.084                                 |

Notes:

[30] - Dose-effect analysis

**Secondary: FVC AUC0-12/12h**

|                 |                 |
|-----------------|-----------------|
| End point title | FVC AUC0-12/12h |
|-----------------|-----------------|

End point description:

AUC0-12h was measured in a standardised by time (L) way.

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

End point timeframe:

FVC was measured at the following time points during treatment visits (visit 3 to visit 7): at pre-dose within 60 min of the dose and at 10 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose.

| End point values                          | Treatment A - ITT     | Treatment B - ITT      | Treatment C - ITT      | Treatment D - ITT      |
|---|-----------------------|------------------------|------------------------|------------------------|
| Subject group type                        | Subject analysis set  | Subject analysis set   | Subject analysis set   | Subject analysis set   |
| Number of subjects analysed               | 60                    | 58                     | 58                     | 59                     |
| Units: LIters                             |                       |                        |                        |                        |
| arithmetic mean (confidence interval 95%) | 3.97 (3.941 to 3.998) | 3.986 (3.956 to 4.016) | 4.023 (3.993 to 4.053) | 4.042 (4.013 to 4.072) |

| End point values                          | Treatment E - ITT      |  |  |  |
|---|------------------------|--|--|--|
| Subject group type                        | Subject analysis set   |  |  |  |
| Number of subjects analysed               | 59                     |  |  |  |
| Units: LIters                             |                        |  |  |  |
| arithmetic mean (confidence interval 95%) | 3.835 (3.805 to 3.864) |  |  |  |

**Statistical analyses**

| Statistical analysis title              | Treatment B vs Treatment A            |
|---|---------------------------------------|
| Comparison groups                       | Treatment B - ITT v Treatment A - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | non-inferiority                       |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.016                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.025                                |
| upper limit                             | 0.058                                 |

| Statistical analysis title | Treatment D vs Treatment C            |
|----------------------------|---------------------------------------|
| Comparison groups          | Treatment C - ITT v Treatment D - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 117                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | non-inferiority          |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.019                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -0.022                   |
| upper limit                             | 0.06                     |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment D vs Treatment E            |
| Comparison groups                       | Treatment D - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[31]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.208                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.166                                 |
| upper limit                             | 0.249                                 |

Notes:

[31] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment E            |
| Comparison groups                       | Treatment C - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[32]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.188                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.147                                 |
| upper limit                             | 0.23                                  |

Notes:

[32] - Sensitivity analysis

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Treatment B vs Treatment E            |
| Comparison groups                 | Treatment B - ITT v Treatment E - ITT |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 117                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[33]</sup>    |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | adjusted mean difference |
| Point estimate                          | 0.151                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.109                    |
| upper limit                             | 0.193                    |

Notes:

[33] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment A vs Treatment E            |
| Comparison groups                       | Treatment A - ITT v Treatment E - ITT |
| Number of subjects included in analysis | 119                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[34]</sup>                 |
| P-value                                 | < 0.001                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.135                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.094                                 |
| upper limit                             | 0.176                                 |

Notes:

[34] - Sensitivity analysis

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Treatment C vs Treatment A            |
| Comparison groups                       | Treatment C - ITT v Treatment A - ITT |
| Number of subjects included in analysis | 118                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[35]</sup>                 |
| P-value                                 | = 0.011                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.053                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.014                                 |
| upper limit                             | 0.098                                 |

Notes:

[35] - Dose-effect analysis

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Treatment D vs Treatment B |
|-----------------------------------|----------------------------|

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Treatment D - ITT v Treatment B - ITT |
| Number of subjects included in analysis | 117                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[36]</sup>                 |
| P-value                                 | = 0.009                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | adjusted mean difference              |
| Point estimate                          | 0.056                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.014                                 |
| upper limit                             | 0.098                                 |

Notes:

[36] - Dose-effect analysis

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent until follow-up phone call.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Treatment A - safety population |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Treatment B - safety population |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Treatment C - safety population |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Treatment D - safety population |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Treatment E - safety population |
|-----------------------|---------------------------------|

Reporting group description: -

| Serious adverse events                            | Treatment A - safety population | Treatment B - safety population | Treatment C - safety population |
|---|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events |                                 |                                 |                                 |
| subjects affected / exposed                       | 0 / 60 (0.00%)                  | 0 / 58 (0.00%)                  | 0 / 58 (0.00%)                  |
| number of deaths (all causes)                     | 0                               | 0                               | 0                               |
| number of deaths resulting from adverse events    | 0                               | 0                               | 0                               |

| Serious adverse events                            | Treatment D - safety population | Treatment E - safety population |  |
|---|---------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events |                                 |                                 |  |
| subjects affected / exposed                       | 0 / 59 (0.00%)                  | 0 / 59 (0.00%)                  |  |
| number of deaths (all causes)                     | 0                               | 0                               |  |
| number of deaths resulting from adverse events    | 0                               | 0                               |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>  | Treatment A - safety population | Treatment B - safety population | Treatment C - safety population |
|--|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 8 / 60 (13.33%)                 | 9 / 58 (15.52%)                 | 5 / 58 (8.62%)                  |
| Injury, poisoning and procedural complications                                       |                                 |                                 |                                 |
| Contusion  |                                 |                                 |                                 |
| subjects affected / exposed  | 1 / 60 (1.67%)                  | 0 / 58 (0.00%)                  | 0 / 58 (0.00%)                  |
| occurrences (all)  | 1                               | 0                               | 0                               |
| Fall   |                                 |                                 |                                 |
| subjects affected / exposed  | 1 / 60 (1.67%)                  | 0 / 58 (0.00%)                  | 0 / 58 (0.00%)                  |
| occurrences (all)  | 1                               | 0                               | 0                               |
| Laceration   |                                 |                                 |                                 |
| subjects affected / exposed  | 1 / 60 (1.67%)                  | 0 / 58 (0.00%)                  | 0 / 58 (0.00%)                  |
| occurrences (all)  | 1                               | 0                               | 0                               |
| Cardiac disorders  |                                 |                                 |                                 |
| Palpitations   |                                 |                                 |                                 |
| subjects affected / exposed  | 0 / 60 (0.00%)                  | 0 / 58 (0.00%)                  | 0 / 58 (0.00%)                  |
| occurrences (all)  | 0                               | 0                               | 0                               |
| Nervous system disorders   |                                 |                                 |                                 |
| Dizziness  |                                 |                                 |                                 |
| subjects affected / exposed  | 0 / 60 (0.00%)                  | 0 / 58 (0.00%)                  | 1 / 58 (1.72%)                  |
| occurrences (all)  | 0                               | 0                               | 1                               |
| Headache   |                                 |                                 |                                 |
| subjects affected / exposed  | 2 / 60 (3.33%)                  | 4 / 58 (6.90%)                  | 1 / 58 (1.72%)                  |
| occurrences (all)  | 2                               | 4                               | 2                               |
| Hypersomnia  |                                 |                                 |                                 |
| subjects affected / exposed  | 0 / 60 (0.00%)                  | 1 / 58 (1.72%)                  | 0 / 58 (0.00%)                  |
| occurrences (all)  | 0                               | 1                               | 0                               |
| Tremor   |                                 |                                 |                                 |
| subjects affected / exposed  | 0 / 60 (0.00%)                  | 0 / 58 (0.00%)                  | 4 / 58 (6.90%)                  |
| occurrences (all)  | 0                               | 0                               | 4                               |
| General disorders and administration site conditions                                 |                                 |                                 |                                 |
| Chest discomfort   |                                 |                                 |                                 |
| subjects affected / exposed  | 1 / 60 (1.67%)                  | 0 / 58 (0.00%)                  | 0 / 58 (0.00%)                  |
| occurrences (all)  | 1                               | 0                               | 0                               |
| Immune system disorders  |                                 |                                 |                                 |



|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 60 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Eye disorders<br>Eye pruritus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 60 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 | 1 / 58 (1.72%)<br>1 |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 60 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 60 (0.00%)<br>0 | 1 / 58 (1.72%)<br>1 | 0 / 58 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 60 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 60 (0.00%)<br>0 | 1 / 58 (1.72%)<br>1 | 0 / 58 (0.00%)<br>0 |
| Reproductive system and breast disorders<br>Prostatomegaly<br>subjects affected / exposed<br>occurrences (all)            | 1 / 60 (1.67%)<br>1 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 60 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)  | 1 / 60 (1.67%)<br>1 | 1 / 58 (1.72%)<br>1 | 0 / 58 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Eczema<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 60 (1.67%)<br>1 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Rash  |                     |                     |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 60 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 | 0 / 58 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders  |                     |                     |                     |
| Back pain  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 60 (1.67%)      | 0 / 58 (0.00%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Myalgia  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 60 (0.00%)      | 1 / 58 (1.72%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 0                   | 2                   | 0                   |
| Infections and infestations                      |                     |                     |                     |
| Conjunctivitis bacterial                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 60 (0.00%)      | 0 / 58 (0.00%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Nasopharyngitis                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 60 (0.00%)      | 1 / 58 (1.72%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Rhinitis   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 60 (0.00%)      | 0 / 58 (0.00%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Tooth infection                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 60 (0.00%)      | 0 / 58 (0.00%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Upper respiratory tract infection                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 60 (0.00%)      | 1 / 58 (1.72%)      | 0 / 58 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |

| <b>Non-serious adverse events</b>                     | Treatment D - safety population | Treatment E - safety population |  |
|---|---------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events |                                 |                                 |  |
| subjects affected / exposed                           | 9 / 59 (15.25%)                 | 13 / 59 (22.03%)                |  |
| Injury, poisoning and procedural complications        |                                 |                                 |  |
| Contusion   |                                 |                                 |  |
| subjects affected / exposed                           | 0 / 59 (0.00%)                  | 0 / 59 (0.00%)                  |  |
| occurrences (all)                                     | 0                               | 0                               |  |
| Fall  |                                 |                                 |  |
| subjects affected / exposed                           | 0 / 59 (0.00%)                  | 0 / 59 (0.00%)                  |  |
| occurrences (all)                                     | 0                               | 0                               |  |

|  |  |   |  |
|--|--|---|--|
| Laceration<br>subjects affected / exposed<br>occurrences (all)   | 0 / 59 (0.00%)<br>0  | 0 / 59 (0.00%)<br>0   |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)  | 1 / 59 (1.69%)<br>1  | 0 / 59 (0.00%)<br>0   |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypersomnia<br>subjects affected / exposed<br>occurrences (all)<br><br>Tremor<br>subjects affected / exposed<br>occurrences (all) | 1 / 59 (1.69%)<br>1<br><br>2 / 59 (3.39%)<br>2<br><br>0 / 59 (0.00%)<br>0<br><br>1 / 59 (1.69%)<br>1 | 0 / 59 (0.00%)<br>0<br><br>7 / 59 (11.86%)<br>7<br><br>1 / 59 (1.69%)<br>1<br><br>0 / 59 (0.00%)<br>0 |  |
| General disorders and administration<br>site conditions<br>Chest discomfort<br>subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0  | 1 / 59 (1.69%)<br>1   |  |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0  | 1 / 59 (1.69%)<br>1   |  |
| Eye disorders<br>Eye pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 59 (0.00%)<br>0<br><br>1 / 59 (1.69%)<br>1   | 0 / 59 (0.00%)<br>0<br><br>0 / 59 (0.00%)<br>0  |  |
| Gastrointestinal disorders   |  |   |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 59 (0.00%)<br>0 | 1 / 59 (1.69%)<br>1 |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 59 (1.69%)<br>1 | 0 / 59 (0.00%)<br>0 |  |
| Reproductive system and breast disorders<br>Prostatomegaly<br>subjects affected / exposed<br>occurrences (all)            | 0 / 59 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 59 (1.69%)<br>1 | 0 / 59 (0.00%)<br>0 |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders<br>Eczema<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 59 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0 | 1 / 59 (1.69%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)          | 0 / 59 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0 |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 59 (0.00%)<br>0 | 0 / 59 (0.00%)<br>0 |  |
| Infections and infestations   |                     |                     |  |

|                                   |                |                |  |
|-----------------------------------|----------------|----------------|--|
| Conjunctivitis bacterial          |                |                |  |
| subjects affected / exposed       | 1 / 59 (1.69%) | 0 / 59 (0.00%) |  |
| occurrences (all)                 | 1              | 0              |  |
| Nasopharyngitis                   |                |                |  |
| subjects affected / exposed       | 1 / 59 (1.69%) | 1 / 59 (1.69%) |  |
| occurrences (all)                 | 1              | 1              |  |
| Rhinitis                          |                |                |  |
| subjects affected / exposed       | 1 / 59 (1.69%) | 0 / 59 (0.00%) |  |
| occurrences (all)                 | 1              | 0              |  |
| Tooth infection                   |                |                |  |
| subjects affected / exposed       | 0 / 59 (0.00%) | 1 / 59 (1.69%) |  |
| occurrences (all)                 | 0              | 1              |  |
| Upper respiratory tract infection |                |                |  |
| subjects affected / exposed       | 0 / 59 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences (all)                 | 0              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|   |
|---|
| No limitations or caveats are applicable to this summary of results |
|---|

Notes: