

**Clinical trial results:**

A phase II, multinational, multicentre, double blind, double dummy, randomised, cross-over, active - and placebo-controlled clinical study to compare the bronchodilator effect of single administration of CHF 1535 pMDI (fixed combination of extrafine beclomethasone dipropionate 50 g + formoterol fumarate 6 g/metered dose, total dose 100/12 g) given with spacer vs. free combination of licensed extrafine beclomethasone dipropionate pMDI given with spacer (total dose 100 g) plus formoterol pMDI given with spacer (total dose 12 g) in terms of FEV1 AUC0-12h in asthmatic children

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-002060-24 |
| Trial protocol | PL Outside EU/EEA |
| Global end of trial date | 26 February 2013 |

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-0903-PR-0060 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01584492 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Chiesi Farmaceutici SpA |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy, 43122 |
| Public contact | Clinical Trial Transparency Manager, Chiesi Farmaceutici SpA, clinicalTrials_info@chiesi.com |
| Scientific contact | Clinical Trial Transparency Manager, Chiesi Farmaceutici SpA, clinicalTrials_info@chiesi.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000548-PIP01-09 |
| 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? | Yes |
|--|-----|

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 February 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 February 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 February 2013 |
| 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 bronchodilator effect of single administration of CHF 1535 50/6 pMDI (fixed combination of extrafine beclomethasone dipropionate 50 µg + formoterol fumarate 6 µg/metered dose, 2 inhalations, total dose 100/12 µg) given with spacer vs. free combination of extrafine beclomethasone dipropionate 50 µg/metered dose pMDI (2 inhalations, total dose 100 µg) given with spacer plus formoterol 6 µg/metered dose pMDI (2 inhalations, total dose 12 µg) given with spacer in terms of FEV1 AUC 0-12 hours corrected by time for the 12 hours study period in asthmatic children

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: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 27 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Ukraine: 39 |
| Country: Number of subjects enrolled | Poland: 20 |
| Worldwide total number of subjects | 59 |
| EEA total number of subjects | 20 |

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) | 59 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 81 patients were screened, of whom 59 patients were randomised from eight sites. Twenty-two patients failed screening because they did not meet the inclusion criteria. 1-week \pm 3 days run-in period was followed by five single-day randomised

treatment periods separated by wash-out periods of 14 \pm 7 days.

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:

Two matched placebos were provided to achieve a complete double-blind, double-dummy design. The canisters/actuators of CHF 1535 and FF pMDI were identical.

The randomisation list was provided to the labelling facility but was not available to patients, investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data, unless in case of emergency. The Sponsor's clinical team was also blinded during the study.

Arms

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

Arm description:

- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 μ g/FF 6 μ g) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 μ g/FF 12 μ g) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 μ g/FF 24 μ g) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 μ g/FF 24 μ g) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 μ g HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 μ g) + extrafine BDP 50 μ g, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 μ g) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.. Each patient will have 6 inhalations at each

| | |
|--|---|
| Arm type | experimental - active comparator - placebo |
| Investigational medicinal product name | CHF 1535 pMDI - formoterol pMDI + BDP pMDI - placebo pMDI |
| Investigational medicinal product code | |
| Other name | beclomethasone dipropionate, formoterol fumarate, placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

A 1-week \pm 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14 \pm 7 days. A safety follow-up phone contact was made 7 \pm 3 days after the last treatment visit or premature discontinuation, for safety purposes.

During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 μ g extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 μ g) administered with AeroChamber Plus™ spacer device.

| | |
|-----------|--------------------|
| Arm title | Sequence B/C/D/E/A |
|-----------|--------------------|

Arm description:

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

| | |
|--|---|
| Arm type | experimental - active comparator - placebo |
| Investigational medicinal product name | CHF 1535 pMDI - formoterol pMDI + BDP pMDI - placebo pMDI |
| Investigational medicinal product code | |
| Other name | beclomethasone dipropionate, formoterol fumarate, placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.

During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

| | |
|------------------|--------------------|
| Arm title | Sequence C/D/E/A/B |
|------------------|--------------------|

Arm description:

- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

| | |
|--|---|
| Arm type | experimental - active comparator - placebo |
| Investigational medicinal product name | CHF 1535 pMDI - formoterol pMDI + BDP pMDI - placebo pMDI |
| Investigational medicinal product code | |
| Other name | beclomethasone dipropionate, formoterol fumarate, placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.

During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

| | |
|------------------|--------------------|
| Arm title | Sequence D/E/A/B/C |
|------------------|--------------------|

Arm description:

- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

| | |
|--|---|
| Arm type | experimental - active comparator - placebo |
| Investigational medicinal product name | CHF 1535 pMDI - formoterol pMDI + BDP pMDI - placebo pMDI |
| Investigational medicinal product code | |
| Other name | beclomethasone dipropionate, formoterol fumarate, placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.
During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

| | |
|------------------|--------------------|
| Arm title | Sequence E/A/B/C/D |
|------------------|--------------------|

Arm description:

- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

| | |
|--|---|
| Arm type | experimental - active comparator - placebo |
| Investigational medicinal product name | CHF 1535 pMDI - formoterol pMDI + BDP pMDI - placebo pMDI |
| Investigational medicinal product code | |
| Other name | beclomethasone dipropionate, formoterol fumarate, placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.
During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

| Number of subjects in period 1 | Sequence A/B/C/D/E | Sequence B/C/D/E/A | Sequence C/D/E/A/B |
|---------------------------------------|--------------------|--------------------|--------------------|
| Started | 13 | 13 | 13 |
| Completed | 12 | 13 | 12 |
| Not completed | 1 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | 1 | - | - |

| Number of subjects in period 1 | Sequence D/E/A/B/C | Sequence E/A/B/C/D |
|---------------------------------------|--------------------|--------------------|
| Started | 11 | 9 |
| Completed | 10 | 9 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | - | - |

Baseline characteristics

Reporting groups

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

Reporting group description:

- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.. Each patient will have 6 inhalations at each

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

Reporting group description:

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Reporting group description:

- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Reporting group description:

- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
 - Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
 - Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
 - Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
 - Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Reporting group description:

- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

| Reporting group values | Sequence A/B/C/D/E | Sequence B/C/D/E/A | Sequence C/D/E/A/B |
|---|--------------------|--------------------|--------------------|
| Number of subjects | 13 | 13 | 13 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (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 Units: years | | | |
| arithmetic mean | 8.5 | 9.4 | 8.6 |
| standard deviation | ± 1.9 | ± 1.4 | ± 1.3 |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 4 | 6 |
| Male | 11 | 9 | 7 |

| Reporting group values | Sequence D/E/A/B/C | Sequence E/A/B/C/D | Total |
|---|--------------------|--------------------|---|
| Number of subjects | 11 | 9 | 59 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (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 | | | 0 0 0 0 0 0 0 0 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 8.8 | 9 | - |
| standard deviation | ± 1.7 | ± 1.7 | - |

| | | | |
|--------------------|---|---|----|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 2 | 18 |
| Male | 7 | 7 | 41 |

End points

End points reporting groups

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

Reporting group description:

- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.. Each patient will have 6 inhalations at each

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

Reporting group description:

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Reporting group description:

- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Reporting group description:

- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
 - Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
 - Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
 - Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
 - Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Reporting group description:

- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
 - Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
 - Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
 Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

| | |
|----------------------------|------------------------|
| Subject analysis set title | CHF 1535 50/6 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomised patients who received at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | CHF 1535 100/12 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | CHF 1535 200/24 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | BDP 100 µg + FF 12 µg - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

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

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | CHF 1535 50/6 µg - Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | CHF 1535 100/12 µg - Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | CHF 1535 200/24 µg - Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

| | |
|----------------------------|--------------------------------|
| Subject analysis set title | BDP 100 µg + FF 12 µg - Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

| | |
|----------------------------|------------------|
| Subject analysis set title | Placebo - Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

Primary: FEV1 AUC0-12h standardised by time

| | |
|--|------------------------------------|
| End point title | FEV1 AUC0-12h standardised by time |
| End point description: | |
| FEV1 AUC corrected by time measured over 12 hours (10 min pre-dose and 10 min, 30 min, 1, 2, 4, 6, 8, 10, 12 hours postdose) following the morning dose of study medication. | |
| End point type | Primary |
| End point timeframe: | |
| At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period) | |

| End point values | CHF 1535 50/6 µg - ITT | CHF 1535 100/12 µg - ITT | CHF 1535 200/24 µg - ITT | BDP 100 µg + FF 12 µg - ITT |
|--------------------------------------|---------------------------|--------------------------------|--------------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 1.789 (± 0.388) | 1.81 (± 0.405) | 1.82 (± 0.416) | 1.821 (± 0.416) |

| End point values | Placebo - ITT | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 1.738 (± 0.365) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF1535 100/12 µg vs BDP 100 µg + FF 12 µg |
| Comparison groups | CHF 1535 100/12 µg - ITT v BDP 100 µg + FF 12 µg - ITT |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.909 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | -0.003 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.047 |
| upper limit | 0.042 |

| | |
|---|--|
| Statistical analysis title | CHF 1535 50/6 µg vs placebo |
| Comparison groups | CHF 1535 50/6 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.048 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.045 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.089 |

| | |
|---|--|
| Statistical analysis title | CHF 1535 100/12 µg vs placebo |
| Comparison groups | CHF 1535 100/12 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.076 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.032 |
| upper limit | 0.121 |

| | |
|---|--|
| Statistical analysis title | CHF1535 200/24 µg vs placebo |
| Comparison groups | CHF 1535 200/24 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.086 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.041 |
| upper limit | 0.131 |

| | |
|---|---|
| Statistical analysis title | BDP 100 µg + FF 12 µg vs placebo |
| Comparison groups | Placebo - ITT v BDP 100 µg + FF 12 µg - ITT |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.079 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.034 |
| upper limit | 0.123 |

Secondary: Peak FEV1

| | |
|------------------------|--|
| End point title | Peak FEV1 |
| End point description: | Peak FEV1 is intended as the maximum value of the post-dose measurements during a 12 hour interval |
| End point type | Secondary |
| End point timeframe: | At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period) |

| End point values | CHF 1535 50/6 µg - ITT | CHF 1535 100/12 µg - ITT | CHF 1535 200/24 µg - ITT | BDP 100 µg + FF 12 µg - ITT |
|--------------------------------------|------------------------|--------------------------|--------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 1.923 (± 0.4) | 2 (± 0.427) | 1.971 (± 0.404) | 1.961 (± 0.426) |

| End point values | Placebo - ITT | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 1.879 (± 0.371) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CHF1535 100/12 µg vs BDP 100 µg + FF 12 µg |
| Comparison groups | CHF 1535 100/12 µg - ITT v BDP 100 µg + FF 12 µg - ITT |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.198 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.034 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.018 |
| upper limit | 0.086 |

| | |
|---|--|
| Statistical analysis title | CHF1535 50/6 µg vs placebo |
| Comparison groups | CHF 1535 50/6 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.16 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.037 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.015 |
| upper limit | 0.089 |

| | |
|-----------------------------------|--|
| Statistical analysis title | CHF1535 100/12 µg vs placebo |
| Comparison groups | Placebo - ITT v CHF 1535 100/12 µg - ITT |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.119 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.067 |
| upper limit | 0.171 |

| | |
|---|--|
| Statistical analysis title | CHF1535 200/24 µg vs placebo |
| Comparison groups | Placebo - ITT v CHF 1535 200/24 µg - ITT |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.094 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.042 |
| upper limit | 0.146 |

| | |
|---|---|
| Statistical analysis title | BDP 100 µg + FF 12 µg vs placebo |
| Comparison groups | Placebo - ITT v BDP 100 µg + FF 12 µg - ITT |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.085 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.033 |
| upper limit | 0.137 |

Secondary: FEV1 at 12 h post-dose

| | |
|--|------------------------|
| End point title | FEV1 at 12 h post-dose |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period) | |

| End point values | CHF 1535 50/6 µg - ITT | CHF 1535 100/12 µg - ITT | CHF 1535 200/24 µg - ITT | BDP 100 µg + FF 12 µg - ITT |
|--------------------------------------|------------------------|--------------------------|--------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 1.721 (± 0.423) | 1.754 (± 0.395) | 1.799 (± 0.432) | 1.794 (± 0.424) |

| End point values | Placebo - ITT | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 1.733 (± 0.368) | | | |

Statistical analyses

| Statistical analysis title | CHF1535 100/12 µg vs BDP 100 µg + FF 12 µg |
|---|--|
| Comparison groups | CHF 1535 100/12 µg - ITT v BDP 100 µg + FF 12 µg - ITT |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.24 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | -0.037 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.098 |
| upper limit | 0.025 |

| Statistical analysis title | CHF1535 50/6 µg vs placebo |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

| | |
|---|--|
| Comparison groups | CHF 1535 50/6 µg - ITT v Placebo - ITT |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.76 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | -0.009 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.071 |
| upper limit | 0.052 |

| | |
|---|--|
| Statistical analysis title | CHF1535 100/12 µg vs placebo |
| Comparison groups | Placebo - ITT v CHF 1535 100/12 µg - ITT |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.283 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.033 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.028 |
| upper limit | 0.094 |

| | |
|---|--|
| Statistical analysis title | CHF1535 200/24 µg vs placebo |
| Comparison groups | Placebo - ITT v CHF 1535 200/24 µg - ITT |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.013 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.078 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.017 |
| upper limit | 0.139 |

| | |
|---|---|
| Statistical analysis title | BDP 100 µg + FF 12 µg vs placebo |
| Comparison groups | Placebo - ITT v BDP 100 µg + FF 12 µg - ITT |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.025 |
| Method | ANCOVA |
| Parameter estimate | adjusted mean difference |
| Point estimate | 0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.009 |
| upper limit | 0.131 |

Secondary: Pre-dose heart rate

| | |
|--|---------------------|
| End point title | Pre-dose heart rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period) | |

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|---------------------------|-----------------------------|-----------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: beats/min | | | | |
| arithmetic mean (standard deviation) | 80.2 (± 13.7) | 80.3 (± 13.1) | 80.4 (± 14.2) | 81.7 (± 12.6) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: beats/min | | | | |
| arithmetic mean (standard deviation) | 81.5 (± 15.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose heart rate

| | |
|-----------------|----------------------|
| End point title | Post-dose heart rate |
|-----------------|----------------------|

End point description:

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

End point timeframe:

30 minutes post-dose at each clinic visit from Visit 2 to Visit 6

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: beats/min | | | | |
| arithmetic mean (standard deviation) | 79 (± 11.9) | 80.7 (± 12.7) | 81.6 (± 14.1) | 80.1 (± 14.1) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: beats/min | | | | |
| arithmetic mean (standard deviation) | 79.7 (± 13.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose systolic blood pressure

| | |
|-----------------|----------------------------------|
| End point title | Pre-dose systolic blood pressure |
|-----------------|----------------------------------|

End point description:

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

End point timeframe:

Sitting systolic blood pressure at each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 102.1 (± 6.7) | 101.4 (± 6.8) | 101.2 (± 7) | 101.3 (± 6.7) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 102 (± 6.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose systolic blood pressure

| | |
|-----------------|-----------------------------------|
| End point title | Post-dose systolic blood pressure |
|-----------------|-----------------------------------|

End point description:

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

End point timeframe:

30 minutes post-dose, sitting systolic blood pressure at each visit from Visit 2 to Visit 6 (treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 102.2 (± 6.5) | 101.9 (± 7.2) | 101.4 (± 7.4) | 102.2 (± 6.2) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 102.5 (± 6.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose distolic blood pressure

| | |
|-----------------|----------------------------------|
| End point title | Pre-dose distolic blood pressure |
|-----------------|----------------------------------|

End point description:

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

End point timeframe:

Pre-dose, sitting diastolic blood pressure at each visit from Visit 1 (screening visit, run-in) to Visit 6 (from Visit 2 to Visit 6: treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|---------------------------|-----------------------------|-----------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 66.2 (± 6.4) | 65.2 (± 6.6) | 65.8 (± 6.9) | 65.9 (± 6.7) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 66.3 (± 6.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose diastolic blood pressure

| | |
|-----------------|------------------------------------|
| End point title | Post-dose diastolic blood pressure |
|-----------------|------------------------------------|

End point description:

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

End point timeframe:

30 minutes post-dose, sitting diastolic blood pressure at each visit from Visit 2 to Visit 6 (treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 65.7 (± 5.9) | 66.1 (± 5.8) | 65.6 (± 6.3) | 65.9 (± 6.3) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 66.1 (± 5.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose QTcF

| | |
|-----------------|---------------|
| End point title | Pre-dose QTcF |
|-----------------|---------------|

End point description:

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

End point timeframe:

15 minutes pre-dose at each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 405.4 (± 12.6) | 400.9 (± 13.6) | 401.4 (± 14.9) | 402.4 (± 15.4) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 402.6 (± 14.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 30 min post-dose QTcF

| | |
|-----------------|-----------------------|
| End point title | 30 min post-dose QTcF |
|-----------------|-----------------------|

End point description:

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

End point timeframe:

30 minutes post-dose at each visit from Visit 2 to Visit 6 (treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|---------------------------|-----------------------------|-----------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 404.3 (± 14) | 405.5 (± 13.2) | 406.4 (± 16.4) | 402.5 (± 18.1) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 401.1 (± 15.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 1 hour post-dose QTcF

| | |
|-----------------|-----------------------|
| End point title | 1 hour post-dose QTcF |
|-----------------|-----------------------|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 1 hour post-dose at each visit from Visit 2 to Visit 6 (treatment period). | |

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 405.7 (± 12.8) | 400.7 (± 16.1) | 406.4 (± 16.3) | 402.8 (± 14.5) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 402.2 (± 14.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 2 hour QTcF

| | |
|---|-------------|
| End point title | 2 hour QTcF |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 2 hours post-dose at each visit from Visit 2 to Visit 6 (treatment period). | |

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 403.2 (± 13.4) | 400.8 (± 12.9) | 405.1 (± 16.7) | 402.5 (± 13.8) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 403.1 (± 15.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 6 hour post-dose QTcF

| | |
|-----------------|-----------------------|
| End point title | 6 hour post-dose QTcF |
|-----------------|-----------------------|

End point description:

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

End point timeframe:

6 hours post-dose at each visit from Visit 2 to Visit 6 (treatment period).

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|---------------------------|-----------------------------|-----------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 402.5 (± 13.8) | 402.1 (± 15.9) | 403.2 (± 14.1) | 402 (± 15.3) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | 402 (± 15.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 12 hour post-dose QTcF

| | |
|-----------------|------------------------|
| End point title | 12 hour post-dose QTcF |
|-----------------|------------------------|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 hours post-dose at each visit from Visit 2 to Visit 6 (treatment period). | |

| End point values | CHF 1535 50/6 µg - Safety | CHF 1535 100/12 µg - Safety | CHF 1535 200/24 µg - Safety | BDP 100 µg + FF 12 µg - Safety |
|--------------------------------------|------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 58 | 57 | 58 | 59 |
| Units: mesc | | | | |
| arithmetic mean (standard deviation) | 399.3 (± 12.6) | 398.3 (± 13.3) | 402.5 (± 13.8) | 398.6 (± 12.3) |

| End point values | Placebo - Safety | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: mesc | | | | |
| arithmetic mean (standard deviation) | 399.1 (± 15.3) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period) to follow-up.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Safety population - CHF 1535 50/6 µg |
|-----------------------|--------------------------------------|

Reporting group description:

CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations.

| | |
|-----------------------|--|
| Reporting group title | Safety population - CHF 1535 100/12 µg |
|-----------------------|--|

Reporting group description:

CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

| | |
|-----------------------|--|
| Reporting group title | Safety population - CHF 1535 200/24 µg |
|-----------------------|--|

Reporting group description:

CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations

| | |
|-----------------------|---|
| Reporting group title | Safety population - BDP 100 µg + FF 12 µg |
|-----------------------|---|

Reporting group description:

Formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations

| | |
|-----------------------|-----------------------------|
| Reporting group title | Safety population - Placebo |
|-----------------------|-----------------------------|

Reporting group description:

Placebo pMDI with spacer, 6 inhalations in the morning at the clinic

| Serious adverse events | Safety population - CHF 1535 50/6 µg | Safety population - CHF 1535 100/12 µg | Safety population - CHF 1535 200/24 µg |
|---|--------------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 57 (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 | Safety population - BDP 100 µg + FF 12 µg | Safety population - Placebo | |
|---|---|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 57 (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 %

| Non-serious adverse events | Safety population - CHF 1535 50/6 µg | Safety population - CHF 1535 100/12 µg | Safety population - CHF 1535 200/24 µg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 2 / 58 (3.45%) | 3 / 57 (5.26%) | 4 / 58 (6.90%) |
| Nervous system disorders Tremor subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | 0 / 57 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 1 / 58 (1.72%) 1 0 / 58 (0.00%) 0 | 0 / 57 (0.00%) 0 1 / 57 (1.75%) 1 1 / 57 (1.75%) 1 | 0 / 58 (0.00%) 0 0 / 58 (0.00%) 0 0 / 58 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | 0 / 57 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection | 0 / 58 (0.00%) 0 0 / 58 (0.00%) 0 | 0 / 57 (0.00%) 0 0 / 57 (0.00%) 0 | 0 / 58 (0.00%) 0 2 / 58 (3.45%) 2 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 1 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| Non-serious adverse events | Safety population - BDP 100 µg + FF 12 µg | Safety population - Placebo | |
|---|--|--------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 4 / 57 (7.02%) | |
| Nervous system disorders | | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 57 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 57 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 57 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Throat irritation | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 57 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 57 (1.75%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 57 (1.75%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 57 (3.51%) | |
| occurrences (all) | 1 | 2 | |
| Respiratory tract infection | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 57 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 57 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 06 July 2012 | <p>This substantial amendment was introduced:</p> <ol style="list-style-type: none">1. To modify the inclusion criterion n.6 about reversibility test at the screening visit lowering the positive threshold to 12% improvement with 200 µg salbutamol from pre-dose value instead of 15% in this children population under stable inhaled corticosteroid therapy;2. To increase the time window between the 12-hour spirometry visits, and the relevant tolerance, from 7±3 to 14±7 days, in order to improve the acceptability of the study by patients and their parents, and to better match the availability of study personnel at the sites;3. To provide also parents/patients with instructions for cleaning of AeroChamber Plus™ spacers in case of delay in attending clinic visits;4. To decrease the number of participating Countries, keeping the same number of involved investigational sites;5. To update the planned study start and end;6. To allow the concomitant treatment with leukotriene antagonists if taken at stable dose in the 4 weeks prior to study entry and to be continued at the same dose throughout all the study period;7. To correct some typing errors. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported