



Clinical trial results:

A phase III, 12-week, multicentre, multinational, randomised, double-blind, double-dummy, 3 arm-parallel group study to test the efficacy of CHF 1535 50/6 microgram (fixed combination of beclomethasone dipropionate plus formoterol fumarate) versus a free combination of beclomethasone dipropionate 50 microgram plus formoterol fumarate 6 microgram and versus a monotherapy of beclomethasone dipropionate 50 microgram, in partly controlled asthmatic children.

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2009-016757-18 |
| Trial protocol | DE FR HU SK ES BG IT Outside EU/EEA |
| Global end of trial date | 28 September 2012 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 31 July 2016 |
| First version publication date | 31 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | CCD-0807-PR-0024 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01475032 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Chiesi Farmaceutici SpA |
| Sponsor organisation address | Via Palermo, 26/A, Parma, Italy, 43126 |
| Public contact | Chiesi Clinical Trials, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com |
| Scientific contact | Chiesi Clinical Trials, 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 | 28 September 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 September 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Demonstrate that CHF 1535 50/6 µg pMDI (daily dose: BDP 200 µg/FF 24 µg) is superior to the corresponding monotherapy with beclomethasone dipropionate 50 µg pMDI (daily dose: BDP 200 µg) and non-inferior relative to the corresponding free combination of beclomethasone dipropionate 50 µg pMDI (daily dose: BDP 200 µg) plus formoterol fumarate 6 µg pMDI (daily dose: FF 24 µg) (all treatments administered via the AeroChamber Plus™ spacer device) in terms of pulmonary function (change from baseline in pre-dose morning FEV1 after a 12-week treatment period) in paediatric patients with "partly controlled" persistent asthma.

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP and FF

pMDI=Pressurised metered dose inhaler

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices (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 | 25 September 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 185 |
| Country: Number of subjects enrolled | Slovakia: 35 |
| Country: Number of subjects enrolled | Bulgaria: 111 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Hungary: 108 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Russian Federation: 74 |
| Country: Number of subjects enrolled | Ukraine: 77 |
| Country: Number of subjects enrolled | Romania: 15 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 638 |
| EEA total number of subjects | 487 |

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) | 638 |
| 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:

Overall, 779 patients were screened; of these 638 patients were randomized.

Pre-assignment

Screening details:

Pre-screening visit was performed 3-7 days before screening visit. At screening visit, inclusion/exclusion criteria were assessed, followed by a Run-in period of 2 weeks when patients stopped their current asthma treatment and received BDP 100mcg pMDI.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial (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:

Placebo was provided to assure a complete double-blind, double-dummy design. The canisters/actuators of CHF 1535 and FF pMDI were of identical appearance.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment A - fixed combination CHF 1535 50/6 µg |

Arm description:

Treatment A: CHF 1535 50/6 µg (total daily dose: BDP 200 µg/FF 24 µg)

- 2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP 50µg and FF 6 µg

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 1535 50/6 µg |
| Investigational medicinal product code | |
| Other name | BDP/FF, Fixed combination of beclomethasone dipropionate and formoterol fumarate |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device

- 2 inhalations twice a day

CHF 1535 50/6 µg=Fixed combination of BDPµg and FF 50µg/6 µg

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

pMDI=pressurised Metered Dose Inhaler

| | |
|--|-----------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Extrafine BDP placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

2 inhalations twice a day

| | |
|------------------|---|
| Arm title | Treatment B - free combination BDP + FF |
|------------------|---|

Arm description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)

- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Beclomethasone dipropionate (BDP) |
| Investigational medicinal product code | |
| Other name | Beclomethasone dipropionate, Ventolair |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

BDP 50 µg pMDI via AeroChamber Plus spacer device

- 2 inhalations twice a day

BDP=Beclomethasone dipropionate

pMDI=pressurised Metered Dose Inhaler

| | |
|--|--------------------------|
| Investigational medicinal product name | Formoterol fumarate (FF) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

FF 6 µg pMDI via AeroChamber Plus spacer device

- 2 inhalations twice a day.

FF=Formoterol fumarate

pMDI=pressurised Metered Dose Inhaler

| | |
|------------------|-------------------------------|
| Arm title | Treatment C - monotherapy BDP |
|------------------|-------------------------------|

Arm description:

Treatment C: (total daily dose: BDP 200 µg)

- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Beclomethasone dipropionate (BDP) |
| Investigational medicinal product code | |
| Other name | Beclomethasone dipropionate, Ventolair |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

BDP 50 µg pMDI via AeroChamber Plus spacer device

- 2 inhalations twice a day

BDP=Beclomethasone dipropionate

pMDI=pressurised Metered Dose Inhaler

| | |
|--|-----------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | CHF 1535 placebo pMDI |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate
 FF=Formoterol fumarate
 CHF 1535=Fixed combination of BDP and FF
 pMDI=pressurised Metered Dose Inhaler

| Number of subjects in period 1 | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP |
|---|--|---|-------------------------------|
| Started | 211 | 213 | 214 |
| Completed | 208 | 205 | 204 |
| Not completed | 3 | 8 | 10 |
| Consent withdrawn by subject | 2 | 4 | 6 |
| inclusion/exclusion criteria not met | - | 2 | 2 |
| Technical issues: metered dose inhaler & spacer | 1 | 1 | 1 |
| Lost to follow-up | - | 1 | - |
| Protocol deviation | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Treatment A - fixed combination CHF 1535 50/6 µg |
|-----------------------|--|

Reporting group description:

Treatment A: CHF 1535 50/6 µg (total daily dose: BDP 200 µg/FF 24 µg)

- 2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP 50µg and FF 6 µg

| | |
|-----------------------|---|
| Reporting group title | Treatment B - free combination BDP + FF |
|-----------------------|---|

Reporting group description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)

- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

| | |
|-----------------------|-------------------------------|
| Reporting group title | Treatment C - monotherapy BDP |
|-----------------------|-------------------------------|

Reporting group description:

Treatment C: (total daily dose: BDP 200 µg)

- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

| Reporting group values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP |
|------------------------|--|---|-------------------------------|
| Number of subjects | 211 | 213 | 214 |
| Age categorical | | | |
| Units: Subjects | | | |
| 5-8 years | 98 | 95 | 95 |
| 9-12 years | 112 | 113 | 114 |
| not recorded | 1 | 5 | 5 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 78 | 69 | 71 |
| Male | 132 | 139 | 138 |
| not recorded | 1 | 5 | 5 |
| Race | | | |
| Units: Subjects | | | |
| White | 208 | 207 | 207 |
| Asian | 0 | 0 | 1 |
| Other | 1 | 1 | 1 |
| Not Available | 1 | 0 | 0 |
| Not part of ITT | 1 | 5 | 5 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 638 | | |

| | | | |
|--------------------|-----|--|--|
| Age categorical | | | |
| Units: Subjects | | | |
| 5-8 years | 288 | | |
| 9-12 years | 339 | | |
| not recorded | 11 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 218 | | |
| Male | 409 | | |
| not recorded | 11 | | |
| Race | | | |
| Units: Subjects | | | |
| White | 622 | | |
| Asian | 1 | | |
| Other | 3 | | |
| Not Available | 1 | | |
| Not part of ITT | 11 | | |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Treatment A - fixed combination CHF 1535 50/6 µg |
|-----------------------|--|

Reporting group description:

Treatment A: CHF 1535 50/6 µg (total daily dose: BDP 200 µg/FF 24 µg)

- 2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP 50µg and FF 6 µg

| | |
|-----------------------|---|
| Reporting group title | Treatment B - free combination BDP + FF |
|-----------------------|---|

Reporting group description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)

- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

| | |
|-----------------------|-------------------------------|
| Reporting group title | Treatment C - monotherapy BDP |
|-----------------------|-------------------------------|

Reporting group description:

Treatment C: (total daily dose: BDP 200 µg)

- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

Primary: 1_FEV1 change from baseline to end of treatment (week 12)

| | |
|-----------------|---|
| End point title | 1_FEV1 change from baseline to end of treatment (week 12) |
|-----------------|---|

End point description:

Pre-dose morning FEV1.

Shown value is the mean change from baseline, after 12 weeks of treatment.

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

End point timeframe:

Baseline to end of treatment (Week 12).

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 194 ^[1] | 193 ^[2] | 192 ^[3] | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 0.153 (± 0.231) | 0.194 (± 0.294) | 0.135 (± 0.248) | |

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Comparison between treatments (A vs C) |
| Statistical analysis description: | |
| Primary endpoint analysis: adjusted mean difference between treatments at week 12. | |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 386 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.482 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.018 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.033 |
| upper limit | 0.07 |

| | |
|--|---|
| Statistical analysis title | Comparison between treatments (A vs B) |
| Statistical analysis description: | |
| Primary endpoint analysis: adjusted mean difference between treatments at week 12. | |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.099 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.043 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.094 |
| upper limit | 0.008 |

Secondary: 2a_FEV1 change from baseline to week 4, 8

| | |
|-----------------|---|
| End point title | 2a_FEV1 change from baseline to week 4, 8 |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline to week 4, 8. For statistical analysis in relation to week12, see primary endpoint.

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 210 ^[4] | 208 ^[5] | 209 ^[6] | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | 0.135 (± 0.245) | 0.143 (± 0.233) | 0.125 (± 0.244) | |
| Week 8 | 0.177 (± 0.232) | 0.178 (± 0.239) | 0.155 (± 0.249) | |
| Week 12 | 0.153 (± 0.231) | 0.194 (± 0.294) | 0.135 (± 0.248) | |

Notes:

[4] - ITT population

For week 4 N=197

For week 8 N=197

For week 12 N=194

[5] - ITT population

For week 4 N=196

For week 8 N=193

For week 12 N=193

[6] - ITT population

For week 4 N=191

For week 8 N=192

For week 12 N=192

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 4 (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 419 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.527 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.032 |
| upper limit | 0.063 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 8 (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 419 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.317 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.024 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.023 |
| upper limit | 0.071 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 4 (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 418 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.965 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -0.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.048 |
| upper limit | 0.046 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 8 (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 418 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.977 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.001 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.046 |
| upper limit | 0.048 |

Secondary: 2b_FVC change from baseline to week 4, 8, 12

| | |
|----------------------------|--|
| End point title | 2b_FVC change from baseline to week 4, 8, 12 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to week 4, 8, 12. | |

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 210 ^[7] | 208 ^[8] | 209 ^[9] | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | 0.099 (± 0.256) | 0.119 (± 0.22) | 0.123 (± 0.265) | |
| Week 8 | 0.161 (± 0.274) | 0.152 (± 0.232) | 0.153 (± 0.24) | |
| Week 12 | 0.139 (± 0.261) | 0.166 (± 0.275) | 0.14 (± 0.25) | |

Notes:

[7] - ITT population

For week 4 N=197

For week 8 N=197

For week 12 N=193

[8] - ITT population

For week 4 N=194

For week 8 N=191

For week 12 N=191

[9] - ITT population

For week 4 N=190

For week 8 N=191

For week 12 N=191

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Comparison between treatments at week 4 (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 419 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.477 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.018 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.067 |
| upper limit | 0.031 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 8 (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 419 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.035 |
| upper limit | 0.063 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 12 (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 419 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.994 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.051 |
| upper limit | 0.052 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 4 (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 418 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.677 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.059 |
| upper limit | 0.039 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 8 (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 418 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.5 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.017 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.032 |
| upper limit | 0.066 |

| | |
|---|---|
| Statistical analysis title | Comparison between treatments at week 12 (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 418 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.282 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.028 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.023 |

Secondary: 3a_Morning PEF - change from baseline to end of treatment (week 12)

| | |
|-----------------|---|
| End point title | 3a_Morning PEF - change from baseline to end of treatment (week 12) |
|-----------------|---|

End point description:

Pre-dose morning PEF was recorded on the electronic peak flow meter during each inter-visit period in the randomised population.

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

End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|---|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 199 ^[10] | 199 ^[11] | 199 ^[12] | |
| Units: liters/min | | | | |
| arithmetic mean (standard deviation) | 18.73 (± 27.28) | 14.83 (± 31.38) | 9.13 (± 30.6) | |

Notes:

[10] - ITT population

[11] - ITT population

[12] - ITT population

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
|----------------------------|---|

Statistical analysis description:

Only morning PEF measurements performed before morning study medication intake were considered.

| | |
|-------------------|--|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
|-------------------|--|

| | |
|---|-----|
| Number of subjects included in analysis | 398 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|---------|
| P-value | = 0.002 |
|---------|---------|

| | |
|--------|--------|
| Method | ANCOVA |
|--------|--------|

| | |
|--------------------|--------------------------|
| Parameter estimate | Adjusted mean difference |
|--------------------|--------------------------|

| | |
|----------------|-------|
| Point estimate | 8.904 |
|----------------|-------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|-------|
| lower limit | 3.296 |
|-------------|-------|

| | |
|-------------|--------|
| upper limit | 14.512 |
|-------------|--------|

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.336 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 2.751 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.861 |
| upper limit | 8.362 |

Secondary: 3b_Evening PEF - change from baseline to end of treatment (week 12)

| | |
|--|---|
| End point title | 3b_Evening PEF - change from baseline to end of treatment (week 12) |
| End point description: Pre-dose evening PEF was recorded on the electronic peak flow meter during each inter-visit period in the randomised population. | |
| End point type | Secondary |
| End point timeframe: Baseline to end of treatment (week 12); entire treatment period. | |

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|---|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 199 ^[13] | 199 ^[14] | 199 ^[15] | |
| Units: liters/minute | | | | |
| arithmetic mean (standard deviation) | 12.4 (± 29.02) | 11.37 (± 32.4) | 6.7 (± 28.99) | |

Notes:

[13] - ITT population

[14] - ITT population

[15] - ITT population

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
| Statistical analysis description: Only evening PEF measurements performed before evening study medication intake were considered. | |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.053 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 5.574 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.062 |
| upper limit | 11.21 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
|-----------------------------------|---|

Statistical analysis description:

Only evening PEF measurements performed before evening study medication intake were considered.

| | |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 398 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.919 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.294 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.344 |
| upper limit | 5.932 |

Secondary: 4_PEF - change from baseline in daily variability

| | |
|-----------------|---|
| End point title | 4_PEF - change from baseline in daily variability |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 196 ^[16] | 192 ^[17] | 194 ^[18] | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -1.79 (± 6.73) | -1.01 (± 7.57) | -0.43 (± 6.39) | |

Notes:

[16] - ITT population

[17] - ITT population

[18] - ITT population

Statistical analyses

| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 390 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -1.118 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.051 |
| upper limit | -0.184 |

| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 388 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.454 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.357 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.292 |
| upper limit | 0.578 |

Secondary: 5a_Asthma symptom score - daytime - change from baseline

| | |
|-----------------|--|
| End point title | 5a_Asthma symptom score - daytime - change from baseline |
|-----------------|--|

End point description:

Asthma symptom score was recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening.

Shown value is the mean change from baseline, after 12 weeks of treatment.

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

End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 208 ^[19] | 205 ^[20] | 207 ^[21] | |
| Units: asthma symptom score | | | | |
| arithmetic mean (standard deviation) | -0.53 (± 1.12) | -0.48 (± 0.98) | -0.51 (± 1.07) | |

Notes:

[19] - ITT population

[20] - ITT population

[21] - ITT population

Statistical analyses

| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 415 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.646 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.043 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.227 |
| upper limit | 0.141 |

| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
|----------------------------|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 413 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.571 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.053 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.237 |
| upper limit | 0.131 |

Secondary: 5b_Asthma symptom score - evening - change from baseline

| | |
|---|--|
| End point title | 5b_Asthma symptom score - evening - change from baseline |
| End point description: | |
| Asthma symptom scores was recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. Shown value is the mean change from baseline, after 12 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to end of treatment (week 12); entire treatment period. | |

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 207 ^[22] | 206 ^[23] | 207 ^[24] | |
| Units: asthma symptom score | | | | |
| arithmetic mean (standard deviation) | -0.41 (± 1.05) | -0.29 (± 0.92) | -0.36 (± 1) | |

Notes:

[22] - ITT population

[23] - ITT population

[24] - ITT population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.499 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.06 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.235 |
| upper limit | 0.114 |

| | |
|---|--|
| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
| Comparison groups | Treatment B - free combination BDP + FF v Treatment A - fixed combination CHF 1535 50/6 µg |
| Number of subjects included in analysis | 413 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.213 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.111 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.285 |
| upper limit | 0.064 |

Secondary: 6_Asthma symptom-free days - change from baseline

| | |
|--|---|
| End point title | 6_Asthma symptom-free days - change from baseline |
| End point description: | |
| Asthma symptom scores were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. | |
| An asthma symptom-free day is a day with total day-time and night-time asthma symptom scores = 0. | |
| Shown value is the mean change from baseline, after 12 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to end of treatment (week 12); entire treatment period. | |

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|---|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 208 ^[25] | 206 ^[26] | 206 ^[27] | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 22.01 (± 33.35) | 25.44 (± 30.71) | 23.39 (± 31.19) | |

Notes:

[25] - ITT population

[26] - ITT population

[27] - ITT population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.734 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.939 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.353 |
| upper limit | 4.475 |

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.428 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -2.189 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.604 |
| upper limit | 3.226 |

Secondary: 7_Rescue medication use - change from baseline

| | |
|-----------------|--|
| End point title | 7_Rescue medication use - change from baseline |
|-----------------|--|

End point description:

Use of rescue medication (number of salbutamol puffs) were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. The recorded data was downloaded and checked by the investigator at each visit.

Shown value is the adjusted mean change from baseline (number of puffs per day), after 12 weeks of

treatment.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to end of treatment (week 12); entire treatment period. | |

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 207 ^[28] | 204 ^[29] | 205 ^[30] | |
| Units: number of puffs per day | | | | |
| arithmetic mean (standard deviation) | -0.18 (± 0.77) | -0.09 (± 0.71) | -0.17 (± 0.87) | |

Notes:

[28] - ITT population

[29] - ITT population

[30] - ITT population

Statistical analyses

| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 412 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.857 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.013 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.151 |
| upper limit | 0.126 |

| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
|---|---|
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 411 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.402 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -0.059 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.198 |
| upper limit | 0.079 |

Secondary: 8_Rescue medication-free days - percentage - change from baseline

| | |
|-----------------|---|
| End point title | 8_Rescue medication-free days - percentage - change from baseline |
|-----------------|---|

End point description:

Use of rescue medication (number of salbutamol puffs) were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. The recorded data was downloaded and checked by the investigator at each visit.

Shown value is the mean change from baseline (percentage of rescue medication use-free days), after 12 weeks of treatment.

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

End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|---|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 208 ^[31] | 206 ^[32] | 206 ^[33] | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 16.41 (± 28.31) | 13.17 (± 26.78) | 11.76 (± 31.18) | |

Notes:

[31] - ITT population

[32] - ITT population

[33] - ITT population

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.077 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 3.819 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.417 |
| upper limit | 8.054 |

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.21 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 2.704 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.529 |
| upper limit | 6.937 |

Secondary: 9_Asthma control days - change from baseline

| | |
|--|--|
| End point title | 9_Asthma control days - change from baseline |
| End point description: | |
| Asthma control days were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. An asthma control day is a day with total day-time and night-time asthma symptom scores = 0 and no puffs of rescue medication taken. | |
| Shown value is the percentage asthma control days, presented as the adjusted mean change from baseline, after 12 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to end of treatment (week 12); entire treatment period. | |

| End point values | Treatment A - fixed combination CHF 1535 50/6 µg | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP | |
|--------------------------------------|--|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 208 ^[34] | 206 ^[35] | 206 ^[36] | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 22.25 (± 32.59) | 26.48 (± 31.88) | 22.44 (± 31.44) | |

Notes:

[34] - ITT population

[35] - ITT population

[36] - ITT population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs C) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.92 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.284 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.233 |
| upper limit | 5.801 |

| | |
|---|---|
| Statistical analysis title | Change from baseline to entire treatment (A vs B) |
| Comparison groups | Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.338 |
| Method | ANCOVA |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -2.695 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.216 |
| upper limit | 2.826 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Run-in phase (week -2) to Follow-up (week 14)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Treatment A - fixed combination BDP/FF |
|-----------------------|--|

Reporting group description:

Treatment A: (total daily dose: BDP 200 µg/FF 24 µg)

2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device + 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day.

| | |
|-----------------------|---|
| Reporting group title | Treatment B - free combination BDP + FF |
|-----------------------|---|

Reporting group description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)

2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device + 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Treatment C - monotherapy BDP |
|-----------------------|-------------------------------|

Reporting group description:

Treatment C: (total daily dose: BDP 200 µg)

2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device + 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day.

| Serious adverse events | Treatment A - fixed combination BDP/FF | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP |
|---|--|---|-------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 211 (0.95%) | 2 / 210 (0.95%) | 1 / 213 (0.47%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Chest injury | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 210 (0.48%) | 0 / 213 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 210 (0.48%) | 0 / 213 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Enteritis | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 210 (0.00%) | 0 / 213 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 210 (0.00%) | 0 / 213 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Post streptococcal glomerulonephritis | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 210 (0.00%) | 1 / 213 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 210 (0.00%) | 0 / 213 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Treatment A - fixed combination BDP/FF | Treatment B - free combination BDP + FF | Treatment C - monotherapy BDP |
|---|--|---|-------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 63 / 211 (29.86%) | 61 / 210 (29.05%) | 56 / 213 (26.29%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | Additional description: "Asthma" is the Preferred Term of the event "asthma exacerbation". | | |
| subjects affected / exposed | 11 / 211 (5.21%) | 7 / 210 (3.33%) | 11 / 213 (5.16%) |
| occurrences (all) | 12 | 8 | 12 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 16 / 211 (7.58%) | 9 / 210 (4.29%) | 11 / 213 (5.16%) |
| occurrences (all) | 23 | 10 | 13 |
| Pharyngitis | | | |

| | | | |
|-----------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 5 / 211 (2.37%) | 16 / 210 (7.62%) | 8 / 213 (3.76%) |
| occurrences (all) | 5 | 17 | 8 |

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.

| |
|-------|
| None. |
|-------|

Notes: