



## Clinical trial results:

**A single-dose, open-label, randomized, 2-way cross-over, clinical pharmacology study of CHF 1535 35/4 NEXThaler® (DPI fixed combination of beclometasone dipropionate (BDP) 35 µg plus formoterol fumarate (FF) 4 µg versus the free combination of licensed BDP DPI and FF DPI in asthmatic children**

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-005152-10 |
| Trial protocol           | DK             |
| Global end of trial date | 08 June 2017   |

## Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 01 February 2018 |
| First version publication date | 01 February 2018 |

## Trial information

### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CCD-01535BB1-01 |
|-----------------------|-----------------|

### Additional study identifiers

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

Notes:

## Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Chiesi Farmaceutici S.p.A.                                                                    |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy,                                                               |
| Public contact               | Clinical Trial Transparency,, Clinical Trial Transparency,,<br>clinicaltrials_info@chiesi.com |
| Scientific contact           | Clinical Trial Transparency,, Clinical Trial Transparency,,<br>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:

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## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 24 October 2017 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 08 June 2017    |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

Evaluate the systemic exposure to B17MP (an active metabolite of BDP) as AUC (0-t), after inhalation of CHF 1535 35/4 NEXThaler® in comparison with a free combination of licensed products of BDP DPI and FF DPI in children with asthma.

AUC (0-t)=Area under the plasma drug concentration-time curve, calculated to the last quantifiable data point

BDP=Beclometasone dipropionate

B17MP=Beclometasone-17-monopropionate (an active metabolite of BDP)

C<sub>max</sub> =Maximum plasma concentration

DPI=Dry powder inhaler

FF=Formoterol fumarate

Protection of trial subjects:

The study was conducted according to the clinical study protocol, the current International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, any local guidelines, and the Declaration of Helsinki (1964 and amendments). Adverse events and vital signs were recorded at all visits (from screening onward).

All new clinically relevant abnormalities or relevant changes at the following visits, in the medical opinion of the Investigator, were reported as AEs in the case report form (CRF).

All described PK and safety assessments were performed according to accepted standard methods.

Background therapy: -

Evidence for comparator: -

|                                                           |                |
|-----------------------------------------------------------|----------------|
| Actual start date of recruitment                          | 19 August 2016 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

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## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 26 |
| Worldwide total number of subjects   | 26          |
| EEA total number of subjects         | 26          |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 26 |
| 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:

Children (male and female) with diagnosed asthma were screened according to the study inclusion and exclusion criteria. Overall, 28 subjects were screened; of these, 26 were randomized to treatment.

### Pre-assignment

Screening details:

Subjects attended a screening visit (2 to 21 days prior to randomisation), study entry criteria were checked; consent form signed. Eligible subjects were randomised into the study, which comprised of 2 treatment sequences that were separated by a wash-out period (min 7 days, max 3 weeks).

### Period 1

|                              |                            |
|------------------------------|----------------------------|
| Period 1 title               | Treatment (overall period) |
| Is this the baseline period? | Yes                        |
| Allocation method            | Randomised - controlled    |
| Blinding used                | Not blinded                |

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | No                       |
| <b>Arm title</b>             | Fixed combination BDP/FF |

Arm description:

Fixed combination BDP/FF 35/4 µg (total dose: BDP/FF 140/16 µg)

During the treatment, the children remained at the clinical center. They arrived at the clinical site in the morning and left on the same day, after the 8 h post-dose assessments have been performed for each treatment sequence. In the morning, the subjects inhaled a single dose (4 inhalations) of CHF 1535 using the NEXThaler®.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | CHF 1535 35/4µg NEXThaler® |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Inhalation powder          |
| Routes of administration               | Inhalation use             |

Dosage and administration details:

Fixed combination of beclometasone dipropionate (BDP) 35 µg + formoterol fumarate (FF) 4 µg.  
CHF 1535 35/4 µg NEXThaler® per inhalation (total dose: BDP/FF 140/16 µg)

A single dose was administered.

4 (four) inhalations of CHF 1535 35/4 µg via the NEXThaler® dry powder inhaler, as a fixed combination of beclometasone dipropionate 35 µg/unit dose plus formoterol fumarate 4 µg/unit dose.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Free combination BDP+FF |
|------------------|-------------------------|

Arm description:

Free combination BDP 100 µg and FF 6 µg (total dose: BDP 200 µg + FF 24 µg)

During the treatment period, the children remained at the clinical center. They arrived at the clinical site in the morning and left on the same day, after the 8 h post-dose assessments have been performed for each study period. In the morning, the subjects inhaled a single dose of BDP (2 inhalations; total dose: 200 µg) and of FF (4 inhalations total dose: 24 µg).

|                                        |                                   |
|----------------------------------------|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Beclomethasone Dipropionate (BDP) |
| Investigational medicinal product code |                                   |
| Other name                             | Clenil® Pulvinal®                 |
| Pharmaceutical forms                   | Inhalation powder                 |
| Routes of administration               | Inhalation use                    |

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Dosage and administration details:

Beclometasone dipropionate (BDP) dry powder inhaler (DPI)  
BDP 100 µg dry powder per unit dose (Clenil® Pulvinal®)

A single dose was administered.

2 (two) inhalations of BDP 100 µg (total dose: 200 µg) via a DPI.

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Formoterol Fumarate (FF) |
| Investigational medicinal product code |                          |
| Other name                             | Oxis® Turbohaler®        |
| Pharmaceutical forms                   | Inhalation powder        |
| Routes of administration               | Inhalation use           |

Dosage and administration details:

Formoterol fumarate (FF) Dry powder inhaler (DPI)  
FF 6 µg per unit dose inhalation dry powder (Oxis® Turbohaler®)

A single dose was administered.

4 (four) inhalations of FF 6 µg (total dose: 24 µg) via a DPI.

| <b>Number of subjects in period 1</b> | Fixed combination<br>BDP/FF | Free combination<br>BDP+FF |
|---------------------------------------|-----------------------------|----------------------------|
| Started                               | 12                          | 14                         |
| Completed                             | 12                          | 14                         |

## Baseline characteristics

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Fixed combination BDP/FF |
|-----------------------|--------------------------|

Reporting group description:

Fixed combination BDP/FF 35/4 µg (total dose: BDP/FF 140/16 µg)

During the treatment, the children remained at the clinical center. They arrived at the clinical site in the morning and left on the same day, after the 8 h post-dose assessments have been performed for each treatment sequence. In the morning, the subjects inhaled a single dose (4 inhalations) of CHF 1535 using the NEXThaler®.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Free combination BDP+FF |
|-----------------------|-------------------------|

Reporting group description:

Free combination BDP 100 µg and FF 6 µg (total dose: BDP 200 µg + FF 24 µg)

During the treatment period, the children remained at the clinical center. They arrived at the clinical site in the morning and left on the same day, after the 8 h post-dose assessments have been performed for each study period. In the morning, the subjects inhaled a single dose of BDP (2 inhalations; total dose: 200 µg) and of FF (4 inhalations total dose: 24 µg).

| Reporting group values | Fixed combination BDP/FF | Free combination BDP+FF | Total |
|------------------------|--------------------------|-------------------------|-------|
| Number of subjects     | 12                       | 14                      | 26    |
| Age categorical        |                          |                         |       |
| Safety population      |                          |                         |       |
| Units: Subjects        |                          |                         |       |
| Children (2-11 years)  | 12                       | 14                      | 26    |
| Age continuous         |                          |                         |       |
| Safety population      |                          |                         |       |
| Units: years           |                          |                         |       |
| arithmetic mean        | 8.6                      | 8.9                     |       |
| standard deviation     | ± 1.6                    | ± 1.7                   | -     |
| Gender categorical     |                          |                         |       |
| Safety population      |                          |                         |       |
| Units: Subjects        |                          |                         |       |
| Female                 | 6                        | 5                       | 11    |
| Male                   | 6                        | 9                       | 15    |
| Race                   |                          |                         |       |
| Safety population      |                          |                         |       |
| Units: Subjects        |                          |                         |       |
| White                  | 12                       | 12                      | 24    |
| Other                  | 0                        | 2                       | 2     |
| Body mass index (BMI)  |                          |                         |       |
| Safety population      |                          |                         |       |
| Units: kg/m2           |                          |                         |       |
| arithmetic mean        | 16.833                   | 17.207                  |       |
| standard deviation     | ± 2.355                  | ± 2.299                 | -     |
| Asthma history         |                          |                         |       |
| Units: years           |                          |                         |       |
| arithmetic mean        | 4.87                     | 6.96                    |       |
| standard deviation     | ± 2.78                   | ± 2.10                  | -     |



## End points

### End points reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Fixed combination BDP/FF |
|-----------------------|--------------------------|

Reporting group description:

Fixed combination BDP/FF 35/4 µg (total dose: BDP/FF 140/16 µg)

During the treatment, the children remained at the clinical center. They arrived at the clinical site in the morning and left on the same day, after the 8 h post-dose assessments have been performed for each treatment sequence. In the morning, the subjects inhaled a single dose (4 inhalations) of CHF 1535 using the NEXThaler®.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Free combination BDP+FF |
|-----------------------|-------------------------|

Reporting group description:

Free combination BDP 100 µg and FF 6 µg (total dose: BDP 200 µg + FF 24 µg)

During the treatment period, the children remained at the clinical center. They arrived at the clinical site in the morning and left on the same day, after the 8 h post-dose assessments have been performed for each study period. In the morning, the subjects inhaled a single dose of BDP (2 inhalations; total dose: 200 µg) and of FF (4 inhalations total dose: 24 µg).

|                            |                          |
|----------------------------|--------------------------|
| Subject analysis set title | Fixed combination BDP/FF |
|----------------------------|--------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

PK analysis set = All subjects from the safety population excluding subjects without any valid PK measurement or with major protocol deviations significantly affecting PK in at least one treatment sequence.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Free combination BDP+FF |
|----------------------------|-------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

PK analysis set = All subjects from the safety population excluding subjects without any valid PK measurement or with major protocol deviations significantly affecting PK in at least one treatment sequence.

### Primary: 1\_B17MP: AUC (0-t)

|                 |                    |
|-----------------|--------------------|
| End point title | 1_B17MP: AUC (0-t) |
|-----------------|--------------------|

End point description:

Determine the pharmacokinetic parameter AUC (0-t) for B17MP (an active metabolite of BDP).

AUC (0-t)=Area under the plasma drug concentration-time curve calculated to the last quantifiable data point

BDP=Beclometasone dipropionate

B17MP=Beclometasone-17-monopropionate

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

End point timeframe:

Pre-dose (baseline) and post-dose at 15, 30 min, 1, 2, 4, 6, and 8 h

| End point values                     | Fixed combination BDP/FF | Free combination BDP+FF |  |  |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set    |  |  |
| Number of subjects analysed          | 26 <sup>[1]</sup>        | 26 <sup>[2]</sup>       |  |  |
| Units: h.pg/mL                       |                          |                         |  |  |
| arithmetic mean (standard deviation) | 1285.66 (± 309.77)       | 854.76 (± 251.30)       |  |  |



Notes:

[1] - PK population

[2] - PK Population

## Statistical analyses

|                                                                                                                                                                                                                   |                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                 | B17MP: AUC (0-t)                                   |
| Statistical analysis description:                                                                                                                                                                                 |                                                    |
| Subjects in this analysis: N=26 (cross-over study design).<br>The value N=52, shown below is generated automatically by the EudraCT database system and is due to an innate error of the EudraCT database system. |                                                    |
| Comparison groups                                                                                                                                                                                                 | Fixed combination BDP/FF v Free combination BDP+FF |
| Number of subjects included in analysis                                                                                                                                                                           | 52                                                 |
| Analysis specification                                                                                                                                                                                            | Pre-specified                                      |
| Analysis type                                                                                                                                                                                                     | non-inferiority <sup>[3]</sup>                     |
| Parameter estimate                                                                                                                                                                                                | Adjusted geometric mean ratio                      |
| Point estimate                                                                                                                                                                                                    | 152.5                                              |
| Confidence interval                                                                                                                                                                                               |                                                    |
| level                                                                                                                                                                                                             | 90 %                                               |
| sides                                                                                                                                                                                                             | 2-sided                                            |
| lower limit                                                                                                                                                                                                       | 141.1                                              |
| upper limit                                                                                                                                                                                                       | 164.81                                             |

Notes:

[3] - Log transformed PK parameters (AUC0-t, Cmax) were analysed by an ANOVA model with fixed terms for sequence, patient-within-sequence, period, and treatment. Adjusted geometric mean ratio and its 90% confidence interval was calculated by the anti-log of the least squared (LS) means difference and the corresponding 90% CI.

## Secondary: 2\_B17MP: Cmax

|                                                                                                              |               |
|--------------------------------------------------------------------------------------------------------------|---------------|
| End point title                                                                                              | 2_B17MP: Cmax |
| End point description:                                                                                       |               |
| Determine the pharmacokinetic parameter Cmax for B17MP (an active metabolite of BDP).                        |               |
| BDP=Beclometasone dipropionate<br>B17MP=Beclometasone-17-monopropionate<br>Cmax=Maximum plasma concentration |               |
| End point type                                                                                               | Secondary     |
| End point timeframe:                                                                                         |               |
| Pre-dose (baseline) and post-dose at 15, 30 min, 1, 2, 4, 6, and 8 h                                         |               |

| End point values                     | Fixed combination BDP/FF | Free combination BDP+FF |  |  |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set    |  |  |
| Number of subjects analysed          | 26 <sup>[4]</sup>        | 26 <sup>[5]</sup>       |  |  |
| Units: pg/mL                         |                          |                         |  |  |
| arithmetic mean (standard deviation) | 447.01 (± 154.86)        | 239.41 (± 79.75)        |  |  |

Notes:

[4] - PK population

[5] - PK population

## Statistical analyses

|                                                                                                                                                                                                                   |                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                 | B17MP: Cmax                                        |
| Statistical analysis description:                                                                                                                                                                                 |                                                    |
| Subjects in this analysis: N=26 (cross-over study design).<br>The value N=52, shown below is generated automatically by the EudraCT database system and is due to an innate error of the EudraCT database system. |                                                    |
| Comparison groups                                                                                                                                                                                                 | Fixed combination BDP/FF v Free combination BDP+FF |
| Number of subjects included in analysis                                                                                                                                                                           | 52                                                 |
| Analysis specification                                                                                                                                                                                            | Pre-specified                                      |
| Analysis type                                                                                                                                                                                                     | non-inferiority <sup>[6]</sup>                     |
| Parameter estimate                                                                                                                                                                                                | Adjusted geometric mean ratio                      |
| Point estimate                                                                                                                                                                                                    | 183.82                                             |
| Confidence interval                                                                                                                                                                                               |                                                    |
| level                                                                                                                                                                                                             | 90 %                                               |
| sides                                                                                                                                                                                                             | 2-sided                                            |
| lower limit                                                                                                                                                                                                       | 163.18                                             |
| upper limit                                                                                                                                                                                                       | 207.07                                             |

Notes:

[6] - Log transformed PK parameters (AUC0-t, Cmax) were analysed by an ANOVA model with fixed terms for sequence, patient-within-sequence, period, and treatment. Adjusted geometric mean ratio and its 90% confidence interval was calculated by the anti-log of the least squared (LS) means difference and the corresponding 90% CI.

## Secondary: 3\_Formoterol: AUC (0-t)

|                                                                                                               |                         |
|---------------------------------------------------------------------------------------------------------------|-------------------------|
| End point title                                                                                               | 3_Formoterol: AUC (0-t) |
| End point description:                                                                                        |                         |
| Determine the pharmacokinetic parameter AUC (0-t) for formoterol.                                             |                         |
| AUC (0-t) =Area under the plasma drug concentration-time curve calculated to the last quantifiable data point |                         |
| End point type                                                                                                | Secondary               |
| End point timeframe:                                                                                          |                         |
| Pre-dose (baseline) and post-dose at 15, 30 min, 1, 2, 4, 6, and 8 h                                          |                         |

| End point values                     | Fixed combination BDP/FF | Free combination BDP+FF |  |  |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set    |  |  |
| Number of subjects analysed          | 26 <sup>[7]</sup>        | 23 <sup>[8]</sup>       |  |  |
| Units: h.pg/mL                       |                          |                         |  |  |
| arithmetic mean (standard deviation) | 82.13 (± 26.24)          | 95.03 (± 44.02)         |  |  |

Notes:

[7] - PK population

[8] - PK population

## Statistical analyses

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | Formoterol: AUC (0-t) |
|-----------------------------------|-----------------------|

Statistical analysis description:

Subjects in this analysis: N=26 (cross-over study design).

The value N=49, shown below is generated automatically by the EudraCT database system and is due to an innate error of the EudraCT database system.

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Comparison groups                       | Fixed combination BDP/FF v Free combination BDP+FF |
| Number of subjects included in analysis | 49                                                 |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | non-inferiority <sup>[9]</sup>                     |
| Parameter estimate                      | Adjusted geometric mean ratio                      |
| Point estimate                          | 91.51                                              |
| Confidence interval                     |                                                    |
| level                                   | 90 %                                               |
| sides                                   | 2-sided                                            |
| lower limit                             | 84                                                 |
| upper limit                             | 99.69                                              |

Notes:

[9] - Log transformed PK parameters (AUC0-t, Cmax) were analysed by an ANOVA model with fixed terms for sequence, patient-within-sequence, period, and treatment. Adjusted geometric mean ratio and its 90% confidence interval was calculated by the anti-log of the least squared (LS) means difference and the corresponding 90% CI.

## Secondary: 4\_Formoterol: Cmax

|                 |                    |
|-----------------|--------------------|
| End point title | 4_Formoterol: Cmax |
|-----------------|--------------------|

End point description:

Determine the pharmacokinetic parameter Cmax for formoterol.

Cmax=Maximum plasma concentration

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

End point timeframe:

Pre-dose (baseline) and post-dose at 15, 30 min, 1, 2, 4, 6, and 8 h

| End point values                     | Fixed combination BDP/FF | Free combination BDP+FF |  |  |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set    |  |  |
| Number of subjects analysed          | 26 <sup>[10]</sup>       | 26 <sup>[11]</sup>      |  |  |
| Units: pg/mL                         |                          |                         |  |  |
| arithmetic mean (standard deviation) | 36.01 (± 13.15)          | 33.85 (± 18.51)         |  |  |

Notes:

[10] - PK population

[11] - PK population

## Statistical analyses

|                                                                                                                                                                                                                                                        |                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                      | Formoterol: Cmax                                   |
| Statistical analysis description:<br>Subjects in this analysis: N=26 (cross-over study design).<br>The value N=52, shown below is generated automatically by the EudraCT database system and is due to an innate error of the EudraCT database system. |                                                    |
| Comparison groups                                                                                                                                                                                                                                      | Fixed combination BDP/FF v Free combination BDP+FF |
| Number of subjects included in analysis                                                                                                                                                                                                                | 52                                                 |
| Analysis specification                                                                                                                                                                                                                                 | Pre-specified                                      |
| Analysis type                                                                                                                                                                                                                                          | non-inferiority <sup>[12]</sup>                    |
| Parameter estimate                                                                                                                                                                                                                                     | Adjusted geometric mean ratio                      |
| Point estimate                                                                                                                                                                                                                                         | 114.57                                             |
| Confidence interval                                                                                                                                                                                                                                    |                                                    |
| level                                                                                                                                                                                                                                                  | 90 %                                               |
| sides                                                                                                                                                                                                                                                  | 2-sided                                            |
| lower limit                                                                                                                                                                                                                                            | 99.81                                              |
| upper limit                                                                                                                                                                                                                                            | 131.5                                              |

### Notes:

[12] - Log transformed PK parameters (AUC0-t, Cmax) were analysed by an ANOVA model with fixed terms for sequence, patient-within-sequence, period, and treatment. Adjusted geometric mean ratio and its 90% confidence interval was calculated by the anti-log of the least squared (LS) means difference and the corresponding 90% CI.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing the informed consent until the end of the study.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Fixed combination CHF 1535 (BDP/FF) |
|-----------------------|-------------------------------------|

Reporting group description: -

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Free combination (BDP+FF) |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events                            | Fixed combination<br>CHF 1535 (BDP/FF) | Free combination<br>(BDP+FF) |  |
|---------------------------------------------------|----------------------------------------|------------------------------|--|
| Total subjects affected by serious adverse events |                                        |                              |  |
| subjects affected / exposed                       | 0 / 26 (0.00%)                         | 0 / 26 (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: 0 %

| Non-serious adverse events                            | Fixed combination<br>CHF 1535 (BDP/FF) | Free combination<br>(BDP+FF) |  |
|-------------------------------------------------------|----------------------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events |                                        |                              |  |
| subjects affected / exposed                           | 1 / 26 (3.85%)                         | 2 / 26 (7.69%)               |  |
| General disorders and administration site conditions  |                                        |                              |  |
| Catheter site discolouration                          |                                        |                              |  |
| subjects affected / exposed                           | 0 / 26 (0.00%)                         | 1 / 26 (3.85%)               |  |
| occurrences (all)                                     | 0                                      | 1                            |  |
| Renal and urinary disorders                           |                                        |                              |  |
| Glycosuria                                            |                                        |                              |  |
| subjects affected / exposed                           | 1 / 26 (3.85%)                         | 1 / 26 (3.85%)               |  |
| occurrences (all)                                     | 1                                      | 1                            |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                     |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 March 2016 | Changes versus the previous version of the protocol were implemented to limit assessments only to those deemed to be necessary and to minimize children's stress and improve their compliance to the study; this amendment included reducing the number of blood sample collections and of vital sign testing procedures, and removing the Holter monitoring. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported