Clinical trial results:
A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, 2-WAY CROSS-OVER, CLINICAL PHARMACOLOGY STUDY OF CHF 1535 50/6 NEXT DPI® (FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE 50 µg PLUS FORMOTEROL FUMARATE 6 µg) VERSUS THE FREE COMBINATION OF LICENSED BECLOMETASONE DPI AND FORMOTEROL DPI IN ASTHMATIC CHILDREN

Summary

EudraCT number	2011-001208-36
Trial protocol	DK
Global end of trial date	21 August 2012

Results information

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

Trial information

Trial identification

Sponsor protocol code	CCD-1103-PR-0058

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01468272
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	21 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 August 2012
Global end of trial reached?	Yes
Global end of trial date	21 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
- To evaluate, in children, the systemic exposure to B17MP (active metabolite of BDP) as AUC0-t , after inhalation of CHF 1535 NEXT DPI® in comparison with a free combination of licensed BDP DPI and formoterol DPI.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 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	Denmark: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	27
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 29 patients were screened. Two patients were screening failures: one patient did not meet the inclusion and exclusion criteria and one patient withdrew his/her consent (see Section 14.1.2). A total of 27 patients were randomised, 6 in the age range 5-8 years and 21 in the age range 9-11 (see Section 14.1.6); 14 patients in the sequenc

Period 1

Period 1 title	Overall trial by sequence (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this was an open-label study, no blinding procedure was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence T-R

Arm description:

Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.

Reference Treatment:Free combination of
- Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®)
- Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)

Arm type	experimental - active comparator
Investigational medicinal product name	CHF 1535 NEXT DPI - BDP DPI + FF DPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test Treatment:
CHF 1535 50/6µg NEXT DPI® (total dose: BDP/FF 200/24 µg)
- 4 (four) inhalations of CHF 1535 50/6 NEXT DPI®
Reference Treatment:
BDP 100 µg DPI + FF 6 µg DPI (total dose: BDP 200 µg + FF 24 µg)
- 2 (two) inhalations of BDP 100µg DPI
- 4 (four) inhalations of FF 6 µg DPI
Eligible subjects were randomized to one of the two treatment sequences.

Arm title	Sequence R-T

Arm description:

Reference Treatment:Free combination of
- Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®)
- Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)

Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.

Arm type	active comparator - experimental

Investigational medicinal product name	BDP DPI + FF DPI - CHF 1535 NEXT DPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test Treatment:
CHF 1535 50/6µg NEXT DPI® (total dose: BDP/FF 200/24 µg)
- 4 (four) inhalations of CHF 1535 50/6 NEXT DPI®
Reference Treatment:
BDP 100 µg DPI + FF 6 µg DPI (total dose: BDP 200 µg + FF 24 µg)
- 2 (two) inhalations of BDP 100µg DPI
- 4 (four) inhalations of FF 6 µg DPI
Eligible subjects were randomized to one of the two treatment sequences.

Number of subjects in period 1	Sequence T-R	Sequence R-T
Started	14	13
Completed	13	13
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence T-R
Reporting group description:	
Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler. Reference Treatment:Free combination of - Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®) - Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)	
Reporting group title	Sequence R-T
Reporting group description:	
Reference Treatment:Free combination of - Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®) - Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®) Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.	

Reporting group values	Sequence T-R	Sequence R-T	Total
Number of subjects	14	13	27
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	9.6	9	
standard deviation	± 1.39	± 1.53	-
Gender categorical Units: Subjects			
Female	3	5	8
Male	11	8	19

End points

End points reporting groups

Reporting group title	Sequence T-R

Reporting group description:

Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.

Reference Treatment:Free combination of
- Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®)
- Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)

Reporting group title	Sequence R-T

Reporting group description:

Reference Treatment:Free combination of
- Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®)
- Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)

Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.

Subject analysis set title	CHF 1535 NEXT DPI - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who used at least one dose of study medication.

Subject analysis set title	BDP DPI + FF DPI - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who used at least one dose of study medication.

Subject analysis set title	CHF 1535 NEXT DPI - PK/PD population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients from the safety population excluding subjects without any valid PK/PD measurement or with major protocol deviations significantly affecting PK/PD

Subject analysis set title	PMI DPI + FF DPI - PK/PD population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients from the safety population excluding subjects without any valid PK/PD measurement or with major protocol deviations significantly affecting PK/PD

Primary: Plasma AUC0-t for B17MP

End point title	Plasma AUC0-t for B17MP

End point description:

The area under the plasma concentration vs. time curve observed from time 0 up to the last measurable concentration, computed using the linear trapezoidal rule [16]. An 8 hour value was required for derivation of AUC0-t.

Eight blood samples were to be collected in the 0-8 h interval after dosing (pre-dose, 15 min, 30 min, 1, 2, 4, 6, and 8 hours post-dose) to determine BDP, its metabolite B17MP and formoterol

End point type	Primary

End point timeframe:

At Visits 2 and 3

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*pg/mL				
geometric mean (full range (min-max))	2099.057 (1105.17 to 2926.97)	1446.354 (553.86 to 2252.89)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.453
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.31
upper limit	1.62

Secondary: Plasma AUC0-t for BDP

End point title	Plasma AUC0-t for BDP
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*pg/mL				
geometric mean (full range (min-max))	258.919	187.13 (85 to		

(129.13 to 489.13)	374.85)

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.3836
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.19
upper limit	1.61

Secondary: Plasma BDP AUC0-inf

End point title	Plasma BDP AUC0-inf
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*pg/mL				
geometric mean (full range (min-max))	331.983 (172.44 to 548.66)	260.101 (130.32 to 441.54)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI -

	PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.2497
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1
upper limit	1.42

Secondary: Plasma BDP Cmax

End point title	Plasma BDP Cmax
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: pg/mL				
geometric mean (full range (min-max))	585.817 (346 to 1176)	353.58 (151 to 723)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.6568
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.45
upper limit	1.89

Secondary: Plasma BDP t1/2

End point title	Plasma BDP t1/2
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
geometric mean (full range (min-max))	0.307 (0.21 to 0.8)	0.413 (0.27 to 0.68)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	0.6995
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	0.77

Secondary: Plasma BDP tmax

End point title	Plasma BDP tmax
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
geometric mean (full range (min-max))	0.256 (0.25 to 0.28)	0.257 (0.22 to 0.52)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of median differ
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Plasma formoterol AUC0-t

End point title	Plasma formoterol AUC0-t
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*pg/mL				
geometric mean (full range (min-max))	156.55 (89.37 to 284.29)	106.771 (58.49 to		

	172.39)

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.4662
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.31
upper limit	1.64

Secondary: Plasma formoterol AUC0-inf

End point title	Plasma formoterol AUC0-inf
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*pg/mL				
geometric mean (full range (min-max))	200.112 (109.01 to 363.61)	133.779 (65.49 to 227.8)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI -

	PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.4958
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.33
upper limit	1.68

Secondary: Plasma formoterol Cmax

End point title	Plasma formoterol Cmax
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: pg/mL				
geometric mean (full range (min-max))	72.098 (44.4 to 112)	37.724 (26.2 to 53.1)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.9112
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.68
upper limit	2.17

Secondary: Plasma formoterol t1/2

End point title	Plasma formoterol t1/2
End point description:	

End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
geometric mean (full range (min-max))	3.511 (2.71 to 5.03)	3.261 (1.87 to 4.98)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.0768
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.18

Secondary: Plasma formoterol Tmax

End point title	Plasma formoterol Tmax
End point description:	

End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
geometric mean (full range (min-max))	0.256 (0.25 to 0.28)	0.286 (0.22 to 0.98)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of median differ
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Plasma B17MP AUC0-inf

End point title	Plasma B17MP AUC0-inf
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*pg/mL				
geometric mean (full range (min-max))	2411.667 (1327.77 to	1704.533 (730.77 to		

4095.76)	2446.76)

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.4161
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.29
upper limit	1.55

Secondary: Plasma B17MP Cmax

End point title	Plasma B17MP Cmax
End point description:	

End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: pg/mL				
geometric mean (full range (min-max))	705.119 (363 to 1298)	451.857 (199 to 793)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.5605
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.4
upper limit	1.74

Secondary: Plasma B17MP t1/2

End point title	Plasma B17MP t1/2
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
geometric mean (full range (min-max))	2.49 (1.48 to 4.47)	2.353 (1.48 to 3.39)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.0587
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.15

Secondary: Plasma B17MP tmax	
End point title	Plasma B17MP tmax
End point description:	

End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
geometric mean (full range (min-max))	0.443 (0.25 to 1)	0.832 (0.28 to 2.02)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of median differ
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5
upper limit	1.1

Secondary: Plasma potassium Cmin	
End point title	Plasma potassium Cmin
End point description:	

End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: mEq/L				
geometric mean (full range (min-max))	3.224 (2.8 to 3.7)	3.241 (1.4 to 4)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	0.9947
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.1

Secondary: Plasma potassium AUC0-t

End point title	Plasma potassium AUC0-t
End point description:	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: h*mEq/L				
geometric mean (full range (min-max))	28.182 (24.36 to 31.28)	29.959 (26.42 to 32.71)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	0.9396
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	0.96

Secondary: Plasma potassium tmin

End point title	Plasma potassium tmin
End point description:	

End point type	Secondary
End point timeframe:	
At Visits 2 and 3	

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: hours				
arithmetic mean (standard deviation)	1.782 (± 1.141)	1.948 (± 1.446)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	PMI DPI + FF DPI - PK/PD population v CHF 1535 NEXT DPI - PK/PD population

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of median differ
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2

Secondary: PEF

End point title	PEF

End point description:

PEF was measured pre-dose and 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h post-dose.
Only data at 8 h post-dose are reported here.

End point type	Secondary

End point timeframe:

At Visits 2 and 3

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: L/min				
arithmetic mean (standard deviation)	290 (± 76.07)	271.4 (± 64.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ae/Aecreat

End point title	Ae/Aecreat

End point description:

Ae/Aecreat: 8h urinary excretion of cortisol, normalized for 8h creatinine excretion (Aecreat).

End point type	Secondary

End point timeframe:

At Visits 2 and 3

End point values	CHF 1535 NEXT DPI - Safety population	BDP DPI + FF DPI - Safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: integer				
geometric mean (full range (min-max))	0.036 (0 to 0.2)	0.043 (0 to 0.1)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - Safety population v BDP DPI + FF DPI - Safety population
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least square mean ratio
Point estimate	0.8549
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.08

Secondary: Glucose concentration in urine

End point title	Glucose concentration in urine

End point description:

Glucose concentration was evaluated in urine. Urinary glucose reference interval was: 0 - 30 mg/dL. The reference PK/PD population is 25 patients because for one patient (S026) no result for glucose was reported after inhalation of the reference product, hence the patient was excluded for both the test and reference.

End point type	Secondary

End point timeframe:

At Visits 2 and 3

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: n. subjects with urine glucose >30 mg/dL	10	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate as AUC0-8h/8h

End point title	Heart rate as AUC0-8h/8h

End point description:

End point type	Secondary

End point timeframe:

At each clinic visit from Visit 1 to Visit 4.

End point values	CHF 1535 NEXT DPI - PK/PD population	PMI DPI + FF DPI - PK/PD population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: bpm				
geometric mean (full range (min-max))	101.13 (86.9 to 129.3)	95.68 (80.8 to 120.4)		

Statistical analyses

Statistical analysis title	Test treatment vs Reference treatment
Comparison groups	CHF 1535 NEXT DPI - PK/PD population v PMI DPI + FF DPI - PK/PD population
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	least square mean ratio
Point estimate	1.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each clinic visit from Visit 1 to Visit 4

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Sequence T-R

Reporting group description:

Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.

Reference Treatment:Free combination of
- Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®)
- Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)

Reporting group title	Sequence R-T

Reporting group description:

Reference Treatment:Free combination of
- Beclometasone dipropionate 100 µg inhalation powder (Clenil® Pulvinal®)
- Formoterol fumarate 6 µg inhalation powder (Oxis® Turbohaler®)

Test treatment:CHF 1535 50/6 NEXT DPI®: fixed combination of beclometasone dipropionate 50 µg/unit dose plus formoterol fumarate 6 µg/unit dose, administered via the NEXT DPI® dry powder inhaler.

Serious adverse events	Sequence T-R	Sequence R-T	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Sequence T-R	Sequence R-T	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No limitations or caveat are reported for this trial.

Notes: