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,, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency,, Clinical Trial Transparency,, 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	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:

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)
Cmax =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:

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:

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)	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
Arm title	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.

Arm title	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

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.

Number of subjects in period 1	Fixed combination BDP/FF	Free combination 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[1]	26[2]		
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

Statistical analysis title	B17MP: AUC (0-t)

Statistical analysis description:

Subjects in this analysis: N=26 (cross-over study design).
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[3]
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
B17MP=Beclometasone-17-monopropionate
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[4]	26[5]		
Units: pg/mL				
arithmetic mean (standard deviation)	447.01 (± 154.86)	239.41 (± 79.75)		

Notes:

[4] - PK population

[5] - PK population

Statistical analyses

Statistical analysis title	B17MP: Cmax

Statistical analysis description:

Subjects in this analysis: N=26 (cross-over study design).
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[6]
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[7]	23[8]		
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

Statistical analysis title	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[9]
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[10]	26[11]		
Units: pg/mL				
arithmetic mean (standard deviation)	36.01 (± 13.15)	33.85 (± 18.51)		

Notes:

[10] - PK population

[11] - PK population

Statistical analyses

Statistical analysis title	Formoterol: Cmax

Statistical analysis description:

Subjects in this analysis: N=26 (cross-over study design).
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[12]
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 CHF 1535 (BDP/FF)	Free combination (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 CHF 1535 (BDP/FF)	Free combination (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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported