Clinical trial results:
A SINGLE-DOSE, OPEN-LABEL, 2-WAY CROSS-OVER, CLINICAL PHARMACOLOGY STUDY OF CHF 1535 50/6 HFA pMDI (FIXED COMBINATION OF BECLOMETHASONE DIPROPIONATE 50µg PLUS FORMOTEROL FUMARATE 6 µg) USING THE AEROCHAMBER PLUS™ SPACER DEVICE VERSUS THE FREE COMBINATION OF BECLOMETHASONE HFA pMDI AND FORMOTEROL HFA pMDI AVAILABLE ON THE MARKET USING THE AEROCHAMBER PLUS™ SPACER DEVICE IN ASTHMATIC CHILDREN

Summary

EudraCT number	2009-010434-22
Trial protocol	DK
Global end of trial date	07 December 2010

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-0902-PR-0013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01848769
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici SpA
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Chiesi Clinical Trials, ClinicalTrials_info@chiesi.com, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com
Scientific contact	Chiesi Clinical Trials, ClinicalTrials_info@chiesi.com, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	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	17 February 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective(s).
To evaluate, in children, the systemic exposure to B17MP (active metabolite of BDP) as AUC0-t , after inhalation of CHF 1535 pMDI 50/6 with AeroChamber Plus spacer device in comparison with an already approved free combination of BDP pMDI and formoterol pMDI with AeroChamber Plus spacer device.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2009
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: -

Pre-assignment

Screening details:

A total of 27 patients were screened. Twenty six (26) were randomised. Three patients did not receive any treatment and therefore the safety population consisted of 23 patients.

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 study, blinding procedures were not applicable.

Arms

Are arms mutually exclusive?	No
Arm title	Sequence T--R

Arm description:

Test treatment (fixed combination): CHF 1535 HFA pMDI (fixed combination of BDP 50 µg + Formoterol 6 µg) using AeroChamber PlusTM spacer device, 4 puffs. Total dose: BDP 200 µg and formoterol 24 µg

Reference treatment (free combination): BDP HFA pMDI (Aerobec® 50 µg, Teva) plus Formoterol HFA pMDI (Atimos 6 µg) using AeroChamber PlusTM spacer device, 2+2 puffs respectively and this sequence will be repeated 2 times. Total dose: BDP 200 µg and formoterol 24 µg.

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

Dosage and administration details:

The study included a screening visit, followed by a wash out period (from 7 days to 3 weeks), first treatment visits followed by a wash out period (from 7 days to 3 weeks) and a second treatment visit followed by a follow-up visit within 7 days.

Test treatment:
Product: Aerobec®
Dose: Beclomethasone dipropionate 50 µg.Total dose 200 µg (4 puffs)
Administration: Inhalation
Duration of Treatment: single dose

Reference treatment:
Product: Atimos®
Dose: Formoterol fumarate 6 µg. Total dose 24 µg (4 puffs),
Administration: Inhalation
Duration of Treatment: single dose

Arm title	Sequence R--T

Arm description:

Reference treatment (free combination): BDP HFA pMDI (Aerobec® 50 µg, Teva) plus Formoterol HFA pMDI (Atimos 6 µg) using AeroChamber PlusTM spacer device, 2+2 puffs respectively and this sequence will be repeated 2 times. Total dose: BDP 200 µg and formoterol 24 µg.

Test treatment (fixed combination): CHF 1535 HFA pMDI (fixed combination of BDP 50 µg + Formoterol 6 µg) using AeroChamber PlusTM spacer device, 4 puffs. Total dose: BDP 200 µg and formoterol 24 µg

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

Dosage and administration details:

The study included a screening visit, followed by a wash out period (from 7 days to 3 weeks), first treatment visits followed by a wash out period (from 7 days to 3 weeks) and a second treatment visit followed by a follow-up visit within 7 days.

Reference treatment:
Product: Atimos®
Dose: Formoterol fumarate 6 µg. Total dose 24 µg (4 puffs),
Administration: Inhalation
Duration of Treatment: single dose

Test treatment:
Product: Aerobec®
Dose: Beclomethasone dipropionate 50 µg.Total dose 200 µg (4 puffs)
Administration: Inhalation
Duration of Treatment: single dose

Number of subjects in period 1	Sequence T--R	Sequence R--T
Started	11	12
Completed	11	11
Not completed	0	1
Technical problem with blood sampling	-	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall trial by sequence
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Twenty-six patients were randomised; 3 patients did not receive any treatment and, therefore, the safety population consisted of 23 patients. Baseline characteristics are reported for those 23 patients.

Reporting group values	Overall trial by sequence	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 10 7.6 to 11.9	 -	
Gender categorical Units: Subjects			
Female	5	5	
Male	18	18	

Subject analysis sets	
Subject analysis set title	Test treatment - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised subjects who used at least one dose of study medication.	

Subject analysis set title	Reference treatment - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised subjects who used at least one dose of study	
Subject analysis set title	Test treatment - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic population: subpopulation of the safety population without any major protocol deviation that could affect the PK.	
Subject analysis set title	Reference treatment - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subpopulation of the safety population without any major protocol deviation that could affect the PK.	

Reporting group values	Test treatment - Safety	Reference treatment - Safety	Test treatment - PK
Number of subjects	22	23	20

Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female	5	5	5
Male	17	18	15

Reporting group values	Reference treatment - PK		
Number of subjects	20		
Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female	5		
Male	15		

End points

End points reporting groups

Reporting group title	Sequence T--R

Reporting group description:

Test treatment (fixed combination): CHF 1535 HFA pMDI (fixed combination of BDP 50 µg + Formoterol 6 µg) using AeroChamber PlusTM spacer device, 4 puffs. Total dose: BDP 200 µg and formoterol 24 µg

Reference treatment (free combination): BDP HFA pMDI (Aerobec® 50 µg, Teva) plus Formoterol HFA pMDI (Atimos 6 µg) using AeroChamber PlusTM spacer device, 2+2 puffs respectively and this sequence will be repeated 2 times. Total dose: BDP 200 µg and formoterol 24 µg.

Reporting group title	Sequence R--T

Reporting group description:

Reference treatment (free combination): BDP HFA pMDI (Aerobec® 50 µg, Teva) plus Formoterol HFA pMDI (Atimos 6 µg) using AeroChamber PlusTM spacer device, 2+2 puffs respectively and this sequence will be repeated 2 times. Total dose: BDP 200 µg and formoterol 24 µg.

Test treatment (fixed combination): CHF 1535 HFA pMDI (fixed combination of BDP 50 µg + Formoterol 6 µg) using AeroChamber PlusTM spacer device, 4 puffs. Total dose: BDP 200 µg and formoterol 24 µg

Subject analysis set title	Test treatment - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Subject analysis set title	Reference treatment - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who used at least one dose of study

Subject analysis set title	Test treatment - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pharmacokinetic population: subpopulation of the safety population without any major protocol deviation that could affect the PK.

Subject analysis set title	Reference treatment - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subpopulation of the safety population without any major protocol deviation that could affect the PK.

Primary: AUC0-t of B17MP (active metabolite of beclomethasone dipropionate)

End point title	AUC0-t of B17MP (active metabolite of beclomethasone dipropionate)

End point description:

V1 = screening visit
wash out period (7 days to 3 weeks)
V2 = treatment period 1
wash out period (7 days to 3 weeks)
V3 = treatment period 2
V4 = follow-up visit

End point type	Primary

End point timeframe:

Visit 2 and Visit 3

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours*pg/mL				
geometric mean (full range (min-max))	1165 (613.7 to 2145)	1433 (727.5 to 2307)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Statistical analysis description:	
ANOVA of the log transformed AUC0-t parameter values, where subject nested within sequence is included as a random effect and sequence, period and treatment are included as fixed effects.	
Comparison groups	Reference treatment - PK v Test treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.697
upper limit	0.948
Variability estimate	Standard deviation

Secondary: AUC0-∞ for B17MP (active metabolite of beclomethasone dipropionate)

End point title	AUC0-∞ for B17MP (active metabolite of beclomethasone dipropionate)
End point description:	
V1 = screening visit wash out period (7 days to 3 weeks) V2 = treatment period 1 wash out period (7 days to 3 weeks) V3 = treatment period 2 V4 = follow-up visit	
End point type	Secondary
End point timeframe:	
V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours*pg/mL				
geometric mean (confidence interval 95%)	1336 (764.2 to 2281)	1615 (877.6 to 2427)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.724
upper limit	0.945

Secondary: Cmax for B17MP (active metabolite of beclomethasone dipropionate)

End point title	Cmax for B17MP (active metabolite of beclomethasone dipropionate)
End point description: V1 = screening visit wash out period (7 days to 3 weeks) V2 = treatment period 1 wash out period (7 days to 3 weeks) V3 = treatment period 2 V4 = follow-up visit	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: pg/mL				
geometric mean (confidence interval 95%)	535.2 (279 to 994)	656 (382 to 1068)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Reference treatment - PK v Test treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.701
upper limit	0.947

Secondary: AUC0-0.5h of B17MP (active metabolite of beclomethasone dipropionate)

End point title	AUC0-0.5h of B17MP (active metabolite of beclomethasone dipropionate)
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours*pg/mL				
geometric mean (confidence interval 95%)	138.5 (72.1 to 256.8)	170.5 (98.7 to 275.9)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Reference treatment - PK v Test treatment - PK

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.697
upper limit	0.943

Secondary: Tmax for B17MP (active metabolite of beclomethasone dipropionate)

End point title	Tmax for B17MP (active metabolite of beclomethasone dipropionate)
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours				
median (full range (min-max))	0.517 (0.517 to 0.533)	0.517 (0.517 to 0.55)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: T1/2 for B17MP (active metabolite of beclomethasone dipropionate)	
End point title	T1/2 for B17MP (active metabolite of beclomethasone dipropionate)
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours				
median (full range (min-max))	1.714 (1.261 to 2.123)	1.756 (1.137 to 2.403)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Reference treatment - PK v Test treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	0.044
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.068
upper limit	0.196

Secondary: AUC0-t of formoterol	
End point title	AUC0-t of formoterol
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours*pg/mL				
geometric mean (confidence interval 95%)	65 (31.8 to 105)	66.3 (36 to 95.2)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.85
upper limit	1.1

Secondary: AUC0-∞ for formoterol

End point title	AUC0-∞ for formoterol
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours*pg/mL				
geometric mean (full range (min-max))	85.4 (44 to 141)	87.4 (46 to 143.9)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Reference treatment - PK v Test treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.84
upper limit	1.12

Secondary: AUC0-0.5h for formoterol

End point title	AUC0-0.5h for formoterol
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours*pg/mL				
geometric mean (full range (min-max))	4.5 (1.8 to 7.3)	4.9 (3.4 to 8.6)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.91
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.06

Secondary: Cmax for formoterol	
End point title	Cmax for formoterol
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: pg/mL				
geometric mean (full range (min-max))	17.8 (6.9 to 28.4)	19 (13.1 to 33.1)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	1.08

Secondary: Tmax for formoterol	
End point title	Tmax for formoterol
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours				
arithmetic mean (standard deviation)	0.592 (± 0.183)	0.545 (± 0.115)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: T1/2 for formoterol

End point title	T1/2 for formoterol

End point description:

End point type	Secondary

End point timeframe:

V2 and V3

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours				
arithmetic mean (standard deviation)	3.526 (± 0.718)	3.44 (± 0.591)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	-0.046
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.371
upper limit	0.325

Secondary: Serum potassium, AUC0-8h

End point title	Serum potassium, AUC0-8h
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: mEq/L*hours				
arithmetic mean (standard deviation)	31.1 (± 1.9)	30.7 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum potassium, Cmin

End point title	Serum potassium, Cmin
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: mEq/L				
arithmetic mean (standard deviation)	3.7 (± 0.3)	3.7 (± 0.2)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Reference treatment - PK v Test treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.03

Secondary: Serum potassium, Tmin

End point title	Serum potassium, Tmin
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hours				
arithmetic mean (standard deviation)	3.4 (± 2.1)	3.3 (± 2)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7963
Method	Friedman's test

Secondary: Urinary glucose excretion

End point title	Urinary glucose excretion
End point description: Number of patients who present glucose in the urine	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: number of subject	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Cortisol urinary excretion 0-8h

End point title	Cortisol urinary excretion 0-8h
End point description:	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: mcg				
arithmetic mean (standard deviation)	14.6 (± 9.3)	13.4 (± 8.4)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.69

Secondary: Cortisol/creatinine ratio	
End point title	Cortisol/creatinine ratio
End point description: Cortisol urinary excretion 0-8h normalised for creatinine excretion 0-8h	
End point type	Secondary
End point timeframe: V2 and V3	

End point values	Test treatment - PK	Reference treatment - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: mcg/g				
arithmetic mean (standard deviation)	61 (± 23.7)	60.6 (± 33.5)		

Statistical analyses

Statistical analysis title	Comparison between treatments (T vs R)
Comparison groups	Test treatment - PK v Reference treatment - PK

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	adjusted least square mean in ln
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.44

Secondary: Heart rate, AUC(0-8h)/8

End point title	Heart rate, AUC(0-8h)/8

End point description:

End point type	Secondary

End point timeframe:

V2 and V3

End point values	Test treatment - Safety	Reference treatment - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	23		
Units: bpm				
geometric mean (confidence interval 95%)	82.5 (76.4 to 89.2)	81.8 (75.4 to 88.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

V1,V2, V3 and V4

Adverse event reporting additional description:

Adverse events were fully described and coded according to the MedDRA Dictionary (version 12.0). Frequency of subjects presenting with treatment-emergent AEs (TEAEs), IMP-related AEs (ADR) and SAEs was tabulated for each treatment group by system organ class (SOC) and preferred term (PT).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Safety population (N=23)

Reporting group description:

Only one adverse event occurred during the study. In the afternoon 8.5 hours after the second study drug administration (test drug) an 11 year old male reported vertigo with a duration of 3.75 hours (Source EOT list 8 (Appendix 16.4.1)). The condition resolved spontaneously. The event was considered of mild intensity and not related to study drug administration.

Serious adverse events	Safety population (N=23)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety population (N=23)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)		
Nervous system disorders			
vertigo	Additional description: Only one adverse event occurred during the study; 8.5 hours after the second drug administration (test drug) an 11 year old male reported vertigo (duration 3.75 h). The condition was mild, not related to study drug, and resolved spontaneously.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2009	- Avoid the blood sampling for potassium and glucose determination. This allowed the use of less sampling tubes to be filled in. In this way, there was more blood to separate plasma for the primary endpoint (pharmacokinetic). This also allowed avoiding the fasting condition for children and thus the reduction of discomfort. - Increase the time deviations permitted for the sampling points, taking into account the objective difficulties in the procedure. - Measure PEF instead of FEV1 for all children, in order to simplify the study process for the children. The PEF values were tested as already described in the protocol. - Avoid the training with Vitalograph AIM: this device was conceived to reduce coordination problems when using pMDIs, but children used spacers, according to the guidelines, to avoid these problems, therefore, this training was not necessary. - Measure heart rate manually: the use of pulseoximeter was a more complex procedure and it would have delayed the PK sampling - Repeatedly breath into the spacer instead of breathing once deeply, taking into account that this was the common practice in children for the use of pMDIs with spacers.
25 January 2010	- Change of the Principal Investigator. - Issues related to technical aspects and timelines. The present study has been inserted into a Paediatric Investigational Plan (PIP) and is subjected to the revision and approval of the EMEA Paediatric Committee (PDCO). PDCO provided scientific input and: agreed to avoid the fasting conditions and noted that fasting is not rigidly necessary to assess plasma potassium (and urinary glucose). Potassium and glucose were very important safety measures that cannot be waived in this kind of study. Suggested that the study protocol was to be further amended in order to keep the determination of potassium in plasma and to replace blood glucose by urinary glucose. Suggested to use a more precise method to measure the heart rate: the use of pulseoximeter was recommended. Suggested that children older than 5 years were able to perform the inhalation manoeuvre with spacers and suggested that one single deep inhalation was preferable than tidal breathing through the spacer device (AeroChamber Plus™).

Notes:

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 and caveats are specified to this summary of the results

Notes: