Clinical trial results:
A single centre, randomised, double-blind, double-dummy, 2-way cross over study to compare safety assessed by knemometry and urinary cortisol measurements of CHF1535 50/6 pMDI (fixed combination of beclomethasone dipropionate and formoterol fumarate) and the free combination of licensed beclomethasone dipropionate and formoterol fumarate in asthmatic children already treated with inhaled corticosteroids.

Summary

EudraCT number	2010-023637-29
Trial protocol	DK
Global end of trial date	18 November 2013

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	CCD-1012-PR-0051

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01450774
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A
Sponsor organisation address	Via Palermo, 26/A, Parma, Italy, 43126
Public contact	Chiesi Clinical Trials, Chiesi Farmaceutici S.p.A, clinicaltrials_info@chiesi.com
Scientific contact	Chiesi Clinical Trials, 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	18 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2013
Global end of trial reached?	Yes
Global end of trial date	18 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to show that the fixed combination CHF 1535 50/6µg (CHF 1535) pMDI, 2 inhalations twice a day (bid), using AeroChamber Plus™ spacer device is non-inferior to a corresponding free combination (CHF 1535+FF) of BDP 50µg pMDI, 2 inhalations bid plus FF 6µg pMDI, 2 inhalations bid, using AeroChamber Plus™ spacer device in terms of lower leg growth rate (LLGR), measured by knemometry, over a 2-week treatment period.

Cross-over part of the study: 2 treatments (each part 2 weeks), wash-out (2 weeks); follow-up (2 weeks).

Study visits: V0 (pre-screening), V1 (screening), V2 (randomization, start treatment 1), V3 (end treatment 1), V4 (start treatment 2) , V5 (end treatment 2), follow-up.

BDP: beclomethasone dipropionate
bid: twice daily
CHF 1535: CHF 1535 50/6µg; fixed combination of BDP and FF
CHF 1535+FF: free combination of BDP and FF
FF: formoterol fumarate
LLGR: lower leg growth rate
pMDI: pressurised metered dose inhaler

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	62
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 72 patients were screened; of these 62 patients were randomized.

Pre-assignment

Screening details:

Following a pre-screening and screening visit, eligible patients entered a 2-week placebo run-in period and training.

Period 1

Period 1 title	Overall trial by sequence (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Sequence A -- B

Arm description:

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI
2 inhalations b.i.d of placebo pMDI

THEN CROSSOVER

Treatment B: Free combination of extrafine BDP 50 µg pMDI with AeroChamber Plus™ spacer device plus FF 6 µg pMDI with AeroChamber Plus™ spacer device.
Total daily dose: BDP 200 µg + FF 24 µg
Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of extrafine BDP 50 µg pMDI
2 inhalations b.i.d. of FF 6 µg pMDI

Arm type	Experimental
Investigational medicinal product name	CHF 1535 50µg/6µg pMDI with AeroChamber Plus™ spacer device
Investigational medicinal product code	
Other name	Treatment A, fixed dose combination
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

Treatment A: CHF 1535 50µg/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50µg/6 µg pMDI (fixed combination of extrafine BDP 50 µg with FF 6 µg / metered dose) with AeroChamber Plus™ spacer device; double dummy administration.

Total daily dose: BDP 200 µg/FF 24 µg

2 puffs every morning and evening via inhaler with the spacer device for 2 weeks

- 2 inhalations b.i.d. of CHF 1535 50µg/6 µg pMDI

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

2 puffs of placebo pMDI every morning and evening via inhaler with the spacer device for 2 weeks.
- 2 inhalations b.i.d of placebo pMDI

Investigational medicinal product name	Beclomethasone Dipropionate (BDP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for two weeks.
2 inhalations b.i.d. of BDP 50 µg pMDI
BDP=Beclomethasone Dipropionate

Investigational medicinal product name	Formoterol Fumarate (FF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for two weeks.
2 inhalations b.i.d. of FF 6 µg pMDI
FF=Formoterol Fumarate

Arm title	Sequence B -- A

Arm description:

Treatment B: Free combination of extrafine BDP 50 µg pMDI with AeroChamber Plus™ spacer device plus FF 6 µg pMDI with AeroChamber Plus™ spacer device.
Total daily dose: BDP 200 µg + FF 24 µg
Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of extrafine BDP 50 µg pMDI
2 inhalations b.i.d. of FF 6 µg pMDI

THEN CROSSOVER

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI
2 inhalations b.i.d of placebo pMDI

Arm type	Experimental
Investigational medicinal product name	Beclomethasone Dipropionate (BDP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

Double dummy administration: two puffs every morning and evening from each inhaler with the spacer

device for two weeks.
2 inhalations b.i.d. of BDP 50 µg pMDI
BDP=Beclomethasone Dipropionate

Investigational medicinal product name	Formoterol Fumarate (FF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for two weeks.
2 inhalations b.i.d. of FF 6 µg pMDI
FF=Formoterol Fumarate

Investigational medicinal product name	CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device
Investigational medicinal product code	
Other name	CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Total daily dose: BDP 200 µg/FF 24 µg

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for two weeks.
- 2 inhalations b.i.d of BDP placebo pMDI
- 2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Respiratory use

Dosage and administration details:

2 puffs of placebo pMDI every morning and evening via inhaler with the spacer device for 2 weeks.
- 2 inhalations b.i.d of placebo pMDI

Number of subjects in period 1	Sequence A -- B	Sequence B -- A
Started	31	31
Completed	29	30
Not completed	2	1
Consent withdrawn by subject	1	-
Erroneously withdrawn	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence A -- B

Reporting group description:

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI
2 inhalations b.i.d of placebo pMDI

THEN CROSSOVER

Treatment B: Free combination of extrafine BDP 50 µg pMDI with AeroChamber Plus™ spacer device plus FF 6 µg pMDI with AeroChamber Plus™ spacer device.
Total daily dose: BDP 200 µg + FF 24 µg
Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of extrafine BDP 50 µg pMDI
2 inhalations b.i.d. of FF 6 µg pMDI

Reporting group title	Sequence B -- A

Reporting group description:

Treatment B: Free combination of extrafine BDP 50 µg pMDI with AeroChamber Plus™ spacer device plus FF 6 µg pMDI with AeroChamber Plus™ spacer device.
Total daily dose: BDP 200 µg + FF 24 µg
Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of extrafine BDP 50 µg pMDI
2 inhalations b.i.d. of FF 6 µg pMDI

THEN CROSSOVER

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI
2 inhalations b.i.d of placebo pMDI

Reporting group values	Sequence A -- B	Sequence B -- A	Total
Number of subjects	31	31	62
Age categorical Units: Subjects			
Children (2-11 years)	31	31	62
Age continuous Units: years			
arithmetic mean	9.5	9.5	
standard deviation	± 1.59	± 2.06	-

Gender categorical Units: Subjects			
Female	12	18	30
Male	19	13	32
Race Units: Subjects			
Asian	3	2	5
White	28	29	57

End points reporting groups

Reporting group title	Sequence A -- B

Reporting group description:

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI
2 inhalations b.i.d of placebo pMDI

THEN CROSSOVER

Treatment B: Free combination of extrafine BDP 50 µg pMDI with AeroChamber Plus™ spacer device plus FF 6 µg pMDI with AeroChamber Plus™ spacer device.
Total daily dose: BDP 200 µg + FF 24 µg
Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of extrafine BDP 50 µg pMDI
2 inhalations b.i.d. of FF 6 µg pMDI

Reporting group title	Sequence B -- A

Reporting group description:

Treatment B: Free combination of extrafine BDP 50 µg pMDI with AeroChamber Plus™ spacer device plus FF 6 µg pMDI with AeroChamber Plus™ spacer device.
Total daily dose: BDP 200 µg + FF 24 µg
Double dummy administration: two puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of extrafine BDP 50 µg pMDI
2 inhalations b.i.d. of FF 6 µg pMDI

THEN CROSSOVER

Treatment A: CHF 1535 50/6 µg pMDI with AeroChamber Plus™ spacer device = fixed dose combination.

CHF 1535 50/6 µg pMDI (fixed combination of extrafine BDP 50 µg + FF 6 µg / metered dose) with AeroChamber Plus™ spacer device.

Double dummy administration: 2 puffs every morning and evening from each inhaler with the spacer device for 2 weeks:
2 inhalations b.i.d. of CHF 1535 50/6 µg pMDI
2 inhalations b.i.d of placebo pMDI

Subject analysis set title	Subjects who received CHF 1535 50/6 µg treatment
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who received at least one administration of the treatment (CHF 1535).

Subject analysis set title	Subjects who received BDP+FF treatment
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who received at least one administration of the treatment (BDP+FF).

Subject analysis set title	Subjects who received placebo during the run-in phase
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who received at least one administration of the placebo during the run-in phase.

Primary: 1_Lower Leg Growth Rate (LLGR) comparison of active treatments

End point title	1_Lower Leg Growth Rate (LLGR) comparison of active treatments

End point description:

The primary safety endpoint was the Lower Leg Growth Rate (LLGR) after 2-week treatment with active drug. Comparison was made between the active treatments i.e. fixed combination (CHF 1535 50/6 µg) and the free combination (BDP+FF).

LLGR = Lower Leg Growth Rate
BDP = Beclomethasone dipropionate
FF=Formoterol fumarate
CHF 1535 50/6 µg=Fixed combination of BDP and FF

End point type	Primary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment	Subjects who received placebo during the run-in phase	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60[1]	59[2]	62[3]	
Units: mm/week				
least squares mean (standard error)	0.182 (± 0.07)	0.355 (± 0.07)	0.526 (± 0.06)	

Notes:

[1] - Safety analysis population

[2] - Safety analysis population

[3] - Safety analysis population

Statistical analyses

Statistical analysis title	Difference in LLGR between active treatments

Statistical analysis description:

The Lower Leg Growth Rate (LLGR) after 2 weeks of treatment was compared between the active treatments, using an analysis of co-variance (ANCOVA). The model included the treatment and period as fixed effects, subject as random effect, and baseline LLGR as co-variable.

Cross-over study, groups examined should not be added up. The number N=119 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.073
Method	ANCOVA
Parameter estimate	Least Square Means
Point estimate	-0.173

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.363
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[4] - Non-inferiority testing, comparing the lower confidence limit with greater than or equal to -0.20 mm/week.
Point estimate represents Least Square (LS) adjusted mean.

Statistical analysis title	Difference in LLGR CHF 1535 50/6 µg - Placebo

Statistical analysis description:

The Lower Leg Growth Rate (LLGR) after 2 weeks of treatment was compared between the CHF 1535 50/6 µg - Placebo. Results from ANOVA with treatment (Placebo, CHF 1535 50/6 µg, BDP+FF) as fixed effect, subject as random effect.

Cross-over study, groups examined should not be added up. The number N=122 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received placebo during the run-in phase
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	ANOVA
Parameter estimate	Least Square Means
Point estimate	-0.346
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.527
upper limit	-0.165
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[5] - Point estimate represents Least Square (LS) adjusted mean.

Statistical analysis title	Difference in LLGR BDP+FF - Placebo

Statistical analysis description:

The Lower Leg Growth Rate (LLGR) after 2 weeks of treatment was compared between the BDP+FF - Placebo. Results from ANOVA with treatment (Placebo, CHF 1535 50/6 µg, BDP+FF) as fixed effect, subject as random effect.

Cross-over study, groups examined should not be added up. The number N=121 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received placebo during the run-in phase v Subjects who received BDP+FF treatment

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.066
Method	ANOVA
Parameter estimate	Least Square Means
Point estimate	-0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.352
upper limit	0.011
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[6] - Point estimate represents Least Square (LS) adjusted mean.

Secondary: 2_24-h Urinary Free Cortisol (UFC) corrected for creatinine; active treatments

End point title	2_24-h Urinary Free Cortisol (UFC) corrected for creatinine; active treatments

End point description:

Determine 24-h urinary free cortisol (UFC), corrected for creatinine (ratio cortisol/creatinine). Comparison was made for this parameter between the active treatments, considering the change in UFC between the start and end of each treatment (2 weeks).

Patients collected urine over 24 h to measure free cortisol and creatinine on the day before and after 2 weeks of active treatment (free combination CHF 1535 and fixed combination BDP+FF). The urine collection started in the morning at the time when the patient woke up and ended in the morning of the following day, at the time when the patient woke up.

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[7]	45[8]		
Units: nmol/mmol				
geometric mean (standard error)	0.974 (± 1.09)	0.919 (± 1.09)		

Notes:

[7] - Safety analysis population

[8] - Safety analysis population

Statistical analyses

Statistical analysis title	24-h UFC (corrected) comparison active treatments

Statistical analysis description:

Comparison of 24-h urinary free cortisol (UFC), corrected for creatinine, between the start vs end of

each active treatments after 2 weeks.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	= 0.5738
Method	ANCOVA
Parameter estimate	Log ratio
Point estimate	1.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.862
upper limit	1.302
Variability estimate	Standard error of the mean
Dispersion value	1.11

Notes:

[9] - Comparison of data for 24-h UFC levels (corrected for creatinine); change after treatment with CHF 1535 (fixed combination) and with BDP+FF (free combination) was evaluated using an ANCOVA model with treatment and period as fixed effects, subject as a random effect, and the baseline (run-in) 24-h UFC/creatinine as covariates.

Cross-over study, groups examined should not be added. The number N=93 (subjects in this analysis set) is an innate error of the EudraCT.

Secondary: 3_24-h Urinary Free Cortisol (UFC) corrected for creatinine; active treatment vs placebo

End point title	3_24-h Urinary Free Cortisol (UFC) corrected for creatinine; active treatment vs placebo

End point description:

24-hour urinary free cortisol (UFC) levels (corrected for creatinine), at the end of the active treatment phase, compared with UFC (corrected for creatinine), at the end of the placebo run-in, training phase.

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment	Subjects who received placebo during the run-in phase	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	50[10]	48[11]	58[12]	
Units: nmol/mmol				
least squares mean (standard error)	5.37 (± 1.1)	4.94 (± 1.1)	5.7 (± 1.1)	

Notes:

[10] - Safety analysis population

[11] - Safety analysis population

[12] - Safety analysis population

Statistical analyses

Statistical analysis title	24-h UFC (cor) CHF 1535 50/6 µg vs Placebo run-in

Statistical analysis description:

24-h UFC levels (corrected for creatinine), after active treatment CHF 1535 50/6 µg compared with the 24-h UFC levels (corrected for creatinine), after Placebo (run-in, training time).

Cross-over study, groups examined should not be added up. The number N=108 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received placebo during the run-in phase
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.5307
Method	ANOVA
Parameter estimate	Log ratio
Point estimate	0.943
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.785
upper limit	1.134
Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[13] - The comparison of the 24-h UFC (corrected for creatinine) excretion of each of the two active treatments with placebo was done using an analysis of variance (ANOVA) with treatment (CHF 1535 and placebo run-in, training time) as fixed effect and subject as random effect.

Statistical analysis title	24-h UFC (corr) BDP+FF vs Placebo run-in

Statistical analysis description:

24-h UFC, corrected for creatinine ratio levels, after active treatment BDP+FF compared with the 24-h UFC corrected for creatinine ratio levels, after Placebo (run-in, training time).

Cross-over study, groups examined should not be added up. The number N=106 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received BDP+FF treatment v Subjects who received placebo during the run-in phase
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.1381
Method	ANOVA
Parameter estimate	Log ratio
Point estimate	0.867
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.718
upper limit	1.048
Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[14] - The comparison of the 24-h UFC/creatinine ratio excretion of each of the two active treatments with placebo was done using an analysis of variance (ANOVA) with treatment (BDP+FF and run-in placebo) as fixed effect and subject as random effect.

Secondary: 4_Incidence of adverse events during active treatment

End point title	4_Incidence of adverse events during active treatment

End point description:

The incidence of adverse events (AEs) was presented with descriptive statistics. Information was collected on treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs), serious adverse events (SAEs) (if any), Serious adverse drug reaction (SADRs) (if any), and AEs leading to study withdrawal (if any).

A TEAE was defined as any AE with onset at or after first study drug administration. If the time of onset of AE was missing and the start date of the AE was on the day of first study drug administration, this AE was considered as treatment-emergent.
AEs starting in the wash-out phase or follow-up period were considered TEAEs. AEs starting during the wash-out phase were accounted to preceding phase with active treatment and AEs starting during follow-up time were accounted to preceding phase with active treatment.

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61[15]	60[16]		
Units: events	34	26		

Notes:

[15] - Safety analysis population

[16] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Heart rate change between start and end of active treatment

End point title	5_Heart rate change between start and end of active treatment

End point description:

Heart rate was recorded during the treatment period and the changes within each treatment period were summarised with descriptive statistics by treatment group.

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60[17]	59[18]		
Units: beats/min				
arithmetic mean (standard deviation)	1.7 (± 10.64)	2.2 (± 10.12)		

Notes:

[17] - Safety analysis population

[18] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Secondary: 6_Mean expiratory flow (PEF) active treatment, change from baseline

End point title	6_Mean expiratory flow (PEF) active treatment, change from baseline

End point description:

Peak expiratory flow (PEF) in L/min was measured twice daily (in the morning and in the evening) and documented in the patient's diary. The morning and evening mean daily PEF shown as change from baseline, during the baseline (placebo, run-in phase) and during the active treatment phase.

End point type	Secondary

End point timeframe:

After 2 weeks of baseline (placebo run-in phase), after 2 weeks of treatment phase with CHF 1535 50/6 µg, and after 2 weeks of treatment phase with BDP+FF.

INPUT needed from Chiesi stats. - please check whether OK to use only overall means;

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60[19]	60[20]		
Units: L/min				
arithmetic mean (standard deviation)				
PEF morning	20.274 (± 26.5019)	18.212 (± 27.6377)		
PEF evening	19.132 (± 25.5557)	18.055 (± 32.1549)		

Notes:

[19] - Intention-to-treat analysis population

[20] - Intention-to-treat analysis population

Statistical analyses

Statistical analysis title	PEF morning treatment difference

Statistical analysis description:

Mean change from baseline in PEF (morning); treatment difference CHF 1535 50/6 µg - BDP+FF.

Cross-over study, groups examined should not be added. The number N=120 (subject in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	= 0.647
Method	ANCOVA
Parameter estimate	LS adjusted mean
Point estimate	1.852
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.209
upper limit	9.913
Variability estimate	Standard error of the mean
Dispersion value	4.02

Notes:

[21] - Results from ANCOVA with treatment (CHF 1535 50/6 µg, BDP+FF) and period as fixed effects, subject as random effect and baseline. Change from baseline. Intention-to-treat analysis population.

Cross-over study, groups examined should not be added. The number N=120 (subjects in this analysis set) is an innate error of the EudraCT database system.

Statistical analysis title	PEF evening treatment difference

Statistical analysis description:

Mean change from baseline in PEF (evening); treatment difference CHF1535 - BDP+FF.

Cross-over study, groups examined should not be added. The number N=120 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received BDP+FF treatment v Subjects who received CHF 1535 50/6 µg treatment
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
P-value	= 0.843
Method	ANCOVA
Parameter estimate	LS adjusted mean
Point estimate	0.826
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.483
upper limit	9.135
Variability estimate	Standard error of the mean
Dispersion value	4.15

Notes:

[22] - Results from ANCOVA with treatment (CHF 1535, BDP+FF) and period as fixed effects, subject as random effect and baseline. Change from baseline. Intention-to-treat analysis population.

Secondary: 7_Overall asthma symptom score, active treatment, change from baseline

End point title	7_Overall asthma symptom score, active treatment, change from baseline

End point description:

Change in overall asthma symptom score. Data are presented as the overall asthma symptom score, for the daytime (evening measurement), nighttime (morning measurement), and whole day. Comparison

was made between active treatments CHF 1535 50/6 µg vs BDP+FF from baseline (run-in, training to the last visit of treatment period 2). The asthma scores is presented as descriptive measures.

Asthma symptoms were recorded twice daily during the run-in, active treatment , and during the wash-out. Asthma symptoms were assessed as cough, wheeze, chest tightness, breathlessness, and overall. The scores were evaluated on a scale from 0 (none) to 3 (severe).

The mean daily asthma scores for each symptom (daytime, nighttime, overall=defined as the average of the morning and evening score) averaged over all days of the run-in period and of the 2-week treatment periods (also wash out period).

End point type	Secondary

End point timeframe:

The patient was required to complete a diary card daily from screening to the last visit of treatment 2.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60[23]	60[24]		
Units: symptom score				
arithmetic mean (standard deviation)				
Daytime	-0.212 (± 0.5778)	-0.074 (± 0.8123)		
Nighttime	-0.155 (± 0.4175)	-0.055 (± 0.678)		
Whole day	-0.185 (± 0.4655)	-0.066 (± 0.7262)		

Notes:

[23] - Intention-to-treat-population

[24] - Intention-to-treat-population

Statistical analyses

Statistical analysis title	Asthma score (difference btw treatments) daytime

Statistical analysis description:

Results from ANCOVA with treatment (CHF 1535 50/6 µg, BDP+FF) and period as fixed effects, subject as random effect and baseline score as covariable. The average score of the run-in period is used as baseline for active treatment phase 1 and the average score of the wash out period is used as the baseline for active treatment phase 2.

Cross-over study, groups examined should not be added up. The number N=120 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
P-value	= 0.146
Method	ANCOVA
Parameter estimate	LS adjusted mean
Point estimate	-0.111

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.262
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[25] - Daytime
Results from ANCOVA with treatment (CHF1535 50/6 µg, BDP+FF) and period as fixed effects, subject as random effect and baseline score as covariable. The average score of the run-in is used as baseline for period 1 and the average score of the wash out period is used as the baseline for period 2.

Statistical analysis title	Asthma score (difference btw treatments) nighttime

Statistical analysis description:

Results from ANCOVA with treatment (CHF 1535, BDP+FF) and period as fixed effects, subject as random effect and baseline score as covariable. The average score of the run-in period is used as baseline for active treatment phase 1 and the average score of the wash out period is used as the baseline for active treatment phase 2.

Cross-over study, groups examined should not be added up. The number N=120 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
P-value	= 0.247
Method	ANCOVA
Parameter estimate	LS mean adjusted
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.243
upper limit	0.064
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[26] - Nighttime
Results from ANCOVA with treatment (CHF1535, BDP+FF) and period as fixed effects, subject as random effect and baseline score as covariable. The average score of the run-in is used as baseline for period 1 and the average score of the wash out period is used as the baseline for period 2.

Statistical analysis title	Asthma score (difference btw treatments) whole day

Statistical analysis description:

Results from ANCOVA with treatment (CHF 1535, BDP+FF) and period as fixed effects, subject as random effect and baseline score as covariable. The average score of the run-in period is used as baseline for active treatment phase 1 and the average score of the wash out period is used as the baseline for active treatment phase 2.

Cross-over study, groups examined should not be added up. The number N=120 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
P-value	= 0.183
Method	ANCOVA
Parameter estimate	LS adjusted mean
Point estimate	-0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.259
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[27] - Whole day
Results from ANCOVA with treatment (CHF1535, BDP+FF) and period as fixed effects, subject as random effect and baseline score as covariable. The average score of the run-in is used as baseline for period 1 and the average score of the wash out period is used as the baseline for period 2.

Secondary: 8_Change in FEV1 active treatment, change from baseline

End point title	8_Change in FEV1 active treatment, change from baseline

End point description:

Measurement of forced expiratory volume in 1 second (FEV1) in liters (L) was performed at each study visit.

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51[28]	56[29]		
Units: Liter				
arithmetic mean (standard deviation)	0.054 (± 0.1854)	0.049 (± 0.1229)		

Notes:

[28] - Intention-to-treat population

[29] - Intention-to-treat population

Statistical analyses

Statistical analysis title	FEV1 treatment difference

Statistical analysis description:

Mean change from baseline in FEV1; treatment difference CHF 1535 50/6 µg - BDP+FF.

Cross-over study, groups examined should not be added. The number N=107 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority[30]
P-value	= 0.893
Method	ANCOVA
Parameter estimate	LS adjusted mean
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.056
upper limit	0.064
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[30] - Results from ANCOVA with treatment (CHF1535 50/6 µg, BDP+FF) and period as fixed effects, subject as
random effect and pre-dose FEV1 values at visit 2 for period 1 and at visit 4 for period 2 as covariable.

Change from baseline. Treatment difference CHF 1535 50/6 µg - BDP+FF. Intention-to-treat analysis population.

Secondary: 9_Change in forced vital capacity (FVC) active treatment, change from baseline

End point title	9_Change in forced vital capacity (FVC) active treatment, change from baseline

End point description:

Measurement of Forced vital capacity (FVC) in liters (L) was performed at each study visit.

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51[31]	56[32]		
Units: Liter				
arithmetic mean (standard deviation)	0.008 (± 0.1944)	0.045 (± 0.1461)		

Notes:

[31] - Intention-to-treat population

[32] - Intention-to-treat population

Statistical analyses

Statistical analysis title	FVC treatment difference

Statistical analysis description:

Mean change from baseline in FVC; treatment difference CHF 1535 50/6 µg - BDP+FF.

Cross-over study, groups examined should not be added. The number N=121 (subjects in this analysis set) is an innate error of the EudraCT database system.

Comparison groups	Subjects who received CHF 1535 50/6 µg treatment v Subjects who received BDP+FF treatment
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
P-value	= 0.275
Method	ANCOVA
Parameter estimate	LS mean adjusted
Point estimate	-0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.103
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[33] - Results from ANCOVA with treatment (CHF1535 50/6 µg, BDP+FF) and period as fixed effects, subject as
random effect and pre-dose FVC values at visit 2 for period 1 and at visit 4 for period 2 as covariable.

Change from baseline. Treatment difference CHF 1535 50/6 µg - BDP+FF. Intention-to-treat analysis population.

Secondary: 10_Days of use of rescue medication, comparison of active treatments

End point title	10_Days of use of rescue medication, comparison of active treatments

End point description:

Intake of rescue medication was analysed descriptively, collecting information per treatment group. Comparison was made for the time when active treatments were administered (2 weeks).

End point type	Secondary

End point timeframe:

After treatment with CHF 1535 50/6 µg (fixed dose combination) and BDP+FF (free dose combination); each treatment was for 2 weeks.

End point values	Subjects who received CHF 1535 50/6 µg treatment	Subjects who received BDP+FF treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17[34]	20[35]		
Units: days				
arithmetic mean (standard deviation)	4.3 (± 3.72)	3.5 (± 3.55)		

Notes:

[34] - Safety analysis population

[35] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the overall duration of the study (from screening to the end of follow-up).

Adverse event reporting additional description:

Patients entered a 2-week placebo run-in period, including a training period. The cross-over part of the study was: 2 treatment periods of 2 weeks, each separated by a wash-out period of 2 weeks. Study visits were at start and end of each treatment period. A follow-up phone call was performed 2 weeks after the last visit to monitor unresolved AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	CHF 1535

Reporting group description:

For this reporting group, the Subjects affected by non-serious adverse events is 25 instead of 23. Due to an ERROR of the system this value couldn't be entered successfully. Therefore the correct ratio: Total subjects affected by non-serious adverse events / subject exposed is 25/61 is 41%

Reporting group title	BDP+FF

Reporting group description: -

Serious adverse events	CHF 1535	BDP+FF	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (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: 5 %

Non-serious adverse events	CHF 1535	BDP+FF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 61 (37.70%)	18 / 60 (30.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 61 (9.84%)	4 / 60 (6.67%)	
occurrences (all)	6	4	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 7	7 / 60 (11.67%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2012	The planned end date of the study was postponed from March 2012 to January 2014 due to the low recruitment.
12 April 2013	An amendment to the Investigational Medicinal Product Dossier (approved on 07 March 2013) included an update of the placebo shelf-life according to the updated stability data of the active product BDP pMDI. The new proposed shelf-life was 36 months below 25°C instead of previously 30°C. The changes were applied to the batches used to prepare the study kits produced from March 2013.

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.

None.

Notes: