Clinical trial results:
A 12-WEEK, MULTICENTER, MULTINATIONAL, RANDOMISED, DOUBLE BLIND, DOUBLE-DUMMY (OPEN LABEL FOR THE SPACER GROUP), 3-ARM PARALLEL GROUP STUDY COMPARING THE EFFICACY AND THE SAFETY OF CHF 1535 HFA pMDI (BDP/FF 100/6 µg per actuation) 2 PUFFS BID VERSUS BDP HFA pMDI (250 µg per actuation) 2 PUFFS BID, IN ADOLESCENT PATIENTS WITH MODERATE TO SEVERE PERSISTENT ASTHMA

Summary

EudraCT number	2007-000522-46
Trial protocol	CZ HU PL SK
Global end of trial date	29 May 2008

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-0606-PR-0019

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, 43126
Public contact	Clinical Trial Transparency Manager, Chiesi Clinical Trials, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency Manager, Chiesi Clinical Trials, 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	29 May 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2008
Global end of trial reached?	Yes
Global end of trial date	29 May 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical superiority in terms of pulmonary function (change from baseline in pre-dose morning PEF) of CHF 1535 versus a corresponding dose of beclomethasone monotherapy in adolescent patients with partly controlled moderate to severe persistent asthma over a 12-week treatment period, the two study treatments being administered via a pMDI standard actuator (without spacer).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2007
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	Czech Republic: 45
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	Poland: 75
Country: Number of subjects enrolled	Russian Federation: 113
Country: Number of subjects enrolled	Slovakia: 49
Country: Number of subjects enrolled	Ukraine: 119
Worldwide total number of subjects	448
EEA total number of subjects	216

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)	0
Adolescents (12-17 years)	448
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:

480 patients were screened; 32 patients failed screening. 448 patients were randomised and 438 patients completed the study.

Period 1

Period 1 title	overall trial (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

Blinding implementation details:

The study was double blind and double-dummy, but was open label for the spacer group.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A - fixed combination BDP/FF pMDI

Arm description:

CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg).

Arm type	Experimental
Investigational medicinal product name	CHF 1535
Investigational medicinal product code	
Other name	BDP/FF, beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg)

Arm title	Treatment B - BDP HFA pMDI

Arm description:

BDP HFA pMDI 250µg (Clenil® 250), 2 inhalations BID (daily dose: 1000 µg BDP)

Arm type	Active comparator
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	BDP, bemeclomethasone dipropionate, Clenil® 250
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

BDP HFA pMDI 250µg (Clenil® 250), 2 inhalations BID (daily dose: 1000 µg BDP)

Arm title	Treatment C - fixed combination BDP/FF by spacer device

Arm description:

CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg) administered by means of spacer device

Arm type	Experimental

Investigational medicinal product name	CHF 1535 by spacer device
Investigational medicinal product code	
Other name	BDP/FF, beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg) administered by means of spacer device

Number of subjects in period 1	Treatment A - fixed combination BDP/FF pMDI	Treatment B - BDP HFA pMDI	Treatment C - fixed combination BDP/FF by spacer device
Started	150	148	150
Completed	145	146	147
Not completed	5	2	3
Consent withdrawn by subject	1	1	-
unknown	1	-	1
asthma exacerbation	1	-	-
Adverse event, non-fatal	-	-	1
Protocol deviation	2	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A - fixed combination BDP/FF pMDI
Reporting group description:	
CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg).	
Reporting group title	Treatment B - BDP HFA pMDI
Reporting group description:	
BDP HFA pMDI 250µg (Clenil® 250), 2 inhalations BID (daily dose: 1000 µg BDP)	
Reporting group title	Treatment C - fixed combination BDP/FF by spacer device
Reporting group description:	
CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg) administered by means of spacer device	

Reporting group values	Treatment A - fixed combination BDP/FF pMDI	Treatment B - BDP HFA pMDI	Treatment C - fixed combination BDP/FF by spacer device
Number of subjects	150	148	150
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	14.6	14.5	14.4
standard deviation	± 1.73	± 1.72	± 1.71
Gender categorical Units: Subjects			
Female	59	46	51
Male	91	102	99
Weight Units: kg			
arithmetic mean	57.18	57.25	57.68
standard deviation	± 13.63	± 14.21	± 15.05

Reporting group values	Total		
Number of subjects	448		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		

Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	156		
Male	292		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	ITT population - Treatment A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population comprised all randomised patients who have received at least one administration of study medication and have at least one available evaluation of efficacy after baseline.	
Subject analysis set title	ITT population - Treatment B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population comprised all randomised patients who have received at least one administration of study medication and have at least one available evaluation of efficacy after baseline.	
Subject analysis set title	ITT population - Treatment C
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population comprised all randomised patients who have received at least one administration of study medication and have at least one available evaluation of efficacy after baseline.	
Subject analysis set title	safety population - Treatment A
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomised patients who will take at least one dose of study medication.	
Subject analysis set title	safety population - Treatment B
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomised patients who will take at least one dose of study medication.	
Subject analysis set title	Safety population - Treatment C
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomised patients who will take at least one dose of study medication.	

Reporting group values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C
Number of subjects	150	148	150
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	14.6	14.5	14.4
standard deviation	± 1.73	± 1.72	± 1.71
Gender categorical			
Units: Subjects			
Female	59	46	51
Male	91	102	99
Weight			
Units: kg			
arithmetic mean	57.18	57.25	57.68
standard deviation	± 13.63	± 14.21	± 15.05

Reporting group values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C
Number of subjects	150	148	150
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			

Weight Units: kg arithmetic mean standard deviation	± 	± 	±

End points

End points reporting groups

Reporting group title	Treatment A - fixed combination BDP/FF pMDI
Reporting group description:	
CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg).	
Reporting group title	Treatment B - BDP HFA pMDI
Reporting group description:	
BDP HFA pMDI 250µg (Clenil® 250), 2 inhalations BID (daily dose: 1000 µg BDP)	
Reporting group title	Treatment C - fixed combination BDP/FF by spacer device
Reporting group description:	
CHF 1535, 2 inhalations BID (daily dose: BDP 400 µg / formoterol fumarate 24 µg) administered by means of spacer device	
Subject analysis set title	ITT population - Treatment A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population comprised all randomised patients who have received at least one administration of study medication and have at least one available evaluation of efficacy after baseline.	
Subject analysis set title	ITT population - Treatment B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population comprised all randomised patients who have received at least one administration of study medication and have at least one available evaluation of efficacy after baseline.	
Subject analysis set title	ITT population - Treatment C
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population comprised all randomised patients who have received at least one administration of study medication and have at least one available evaluation of efficacy after baseline.	
Subject analysis set title	safety population - Treatment A
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomised patients who will take at least one dose of study medication.	
Subject analysis set title	safety population - Treatment B
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomised patients who will take at least one dose of study medication.	
Subject analysis set title	Safety population - Treatment C
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomised patients who will take at least one dose of study medication.	

Primary: Change from baseline in pre-dose morning PEF

End point title	Change from baseline in pre-dose morning PEF
End point description:	
Change from baseline in pre-dose morning PEF (L/min) [the mean of the last 7 available values during the run-in period and during the last 14 days of the treatment period will be considered].	
End point type	Primary
End point timeframe:	
Daily at home via SpirotelTM from Visit 1 to Visit 5	

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64	52	64	
Units: L/min				
arithmetic mean (standard deviation)	13.12 (± 45.826)	19.35 (± 58.997)	36.17 (± 48.328)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The primary analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator). To demonstrate the superiority of CHF 1535 vs BDP monotherapy, the primary endpoint (change from baseline in pre-dose morning PEF) has been submitted to an analysis of covariance (ANCOVA) model, using the baseline as covariate and treatment and country as factors.
This particular comparison is about Treatment B vs Treatment A

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.45
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	7.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.74
upper limit	26.33

Secondary: Pre-dose evening PEF

End point title	Pre-dose evening PEF

End point description:

Pre-dose evening PEF measured with the electronic peak flow meter in the last 14 days before each clinic visit.
Only changes from baseline to treatment phase are reported here. Entire treatment phase is the mean of all available values during the treatment period.

End point type	Secondary

End point timeframe:

Daily at home via SpirotelTM from Visit 1 to Visit 5

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	130	132	124	
Units: L/min				
arithmetic mean (standard deviation)	10.85 (± 41.715)	3.97 (± 43.654)	22.3 (± 38.707)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)
Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.223
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-6.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.12
upper limit	3.78

Notes:

[1] - The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Secondary: Daily PEF variability

End point title	Daily PEF variability

End point description:

For daily PEF variability the mean of the last seven available values during the run-in period was used as baseline and the mean of the last seven available values during the last 14 days before Visits 3, 4 and 5, respectively was to be used as post-baseline measurements.
Only changes from baseline to treatment phase are reported here. Entire treatment phase is the mean of all available values during the treatment period.

End point type	Secondary

End point timeframe:

Daily PEF variability from baseline to Visit 5

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	127	126	118	
Units: L/min				
arithmetic mean (standard deviation)	-1.05 (± 7.772)	-0.95 (± 7.765)	-2 (± 6.605)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)
Statistical analysis description:	
The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).	
Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.874
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	1.43

Secondary: Pre-dose FEV1	
End point title	Pre-dose FEV1
End point description:	
Only changes from baseline to treatment phase are reported here. Entire treatment phase is the mean of all available values during the treatment period.	
End point type	Secondary
End point timeframe:	
At each clinic visit from Visit 2 to Visit 5.	

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	148	146	150	
Units: liter				
arithmetic mean (standard deviation)	0.37 (± 0.408)	0.34 (± 0.414)	0.43 (± 0.466)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.376
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.05

Secondary: Post-dose FEV1

End point title	Post-dose FEV1

End point description:

Post-dose FEV1 at 10 min, 30 min, 1 hour at each clinic visit and relative 1h average (i.e. 1h AUC standardised by time).
Only absolute post-dose FEV1 AUC1hstd at Visit 5 is reported here.

End point type	Secondary

End point timeframe:

At each clinic visit from Visit 2 to Visit 5

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	147	
Units: liter				
arithmetic mean (standard deviation)	3.207 (± 0.7347)	3.066 (± 0.7772)	3.212 (± 0.802)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.012
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.241
upper limit	-0.029

Secondary: Pre-dose FVC

End point title	Pre-dose FVC
End point description:	
Only changes in pre-dose FVC from baseline at Visit 5 are reported here.	
End point type	Secondary
End point timeframe:	
At each clinic visit from Visit 2 to Visit 5	

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	148	
Units: liter				
arithmetic mean (standard deviation)	0.41 (± 0.516)	0.45 (± 0.555)	0.43 (± 0.536)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)
Statistical analysis description:	
The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).	
Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.555
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.15

Secondary: Post-dose FVC

End point title	Post-dose FVC

End point description:

Post-dose FVC at 10 min, 30 min, 1 hour at each clinic visit.
Only changes in post-dose FVC from baseline 1 hour after at Visit 5 are reported here.

End point type	Secondary

End point timeframe:

At each clinic visit from visit 2 to visit 5

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	147	
Units: liter				
arithmetic mean (standard deviation)	0.57 (± 0.535)	0.59 (± 0.593)	0.59 (± 0.556)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)
Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.757
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.14

Secondary: Pre-dose FEF25-75%

End point title	Pre-dose FEF25-75%

End point description: Only changes in pre-dose FEF25-75% from baseline at Visit 5 are reported here.
End point type: Secondary
End point timeframe: At each clinic visit from Visit 2 to Visit 5

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	148	
Units: L/sec				
arithmetic mean (standard deviation)	0.51 (± 0.836)	0.38 (± 0.823)	0.58 (± 0.973)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)
Statistical analysis description: The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).	
Comparison groups	ITT population - Treatment B v ITT population - Treatment A
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.104
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.03

Secondary: Post-dose FEF25-75%

End point title	Post-dose FEF25-75%
End point description: Post-dose FEF25-75% at 10 min, 30 min, 1 hour at each clinic visit and relative 1h average (i.e. 1h AUC standardised by time). Only changes in post-dose FEF25-75% from baseline 1 hour after at Visit 5 are reported here.	
End point type	Secondary
End point timeframe: at each clinic visit from Visit 2 to Visit 5	

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	144	146	147	
Units: L/min				
arithmetic mean (standard deviation)	1.01 (± 0.905)	0.54 (± 0.906)	1.07 (± 1.033)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.29

Secondary: Total morning asthma symptom score

End point title	Total morning asthma symptom score

End point description:

For the total asthma symptom scores the mean of the last seven available values during the run-in period were to be used as baseline and the mean of the last seven available values during the last 14 days before Visits 3, 4 and 5, respectively were to be used as post-baseline measurements.
Only change in total morning (night time symptoms) asthma symptom scores from baseline to "end of treatment" are reported here.

End point type	Secondary

End point timeframe:

Each day throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	138	130	139	
Units: integer				
arithmetic mean (standard deviation)	-0.76 (± 1.82)	-0.51 (± 1.586)	-0.33 (± 1.87)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.436
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.53

Secondary: Total evening asthma symptom score

End point title	Total evening asthma symptom score

End point description:

For the total asthma symptom scores the mean of the last seven available values during the run-in period were to be used as baseline and the mean of the last seven available values during the last 14 days before Visits 3, 4 and 5, respectively were to be used as post-baseline measurements.
Only change in total evening (day time symptoms) symptom scores from baseline to “end of treatment” are reported here.

End point type	Secondary

End point timeframe:

Each day throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	137	129	135	
Units: integer				
arithmetic mean (standard deviation)	-0.93 (± 2.037)	-0.72 (± 1.662)	-0.59 (± 2.066)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.485
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.56

Secondary: Total all day asthma symptom score

End point title	Total all day asthma symptom score

End point description:

For the total asthma symptom scores the mean of the last seven available values during the run-in period were to be used as baseline and the mean of the last seven available values during the last 14 days before Visits 3, 4 and 5, respectively were to be used as post-baseline measurements.
Only change in total all day asthma symptom scores from baseline to "end of treatment" are reported here.

End point type	Secondary

End point timeframe:

Each day throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	125	120	127	
Units: integer				
arithmetic mean (standard deviation)	-1.67 (± 3.765)	-1.12 (± 2.924)	-0.91 (± 3.867)	

Statistical analyses

Statistical analysis title	Comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.293
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	1.25

Secondary: Symptom-free days

End point title	Symptom-free days

End point description:

Symptom free days were defined as days with a daily evening total asthma score of 0.
For symptom free days, nights and complete days, the sum of all symptom free days, nights and complete days, respectively during the run-in period were to be used as baseline and the sum of symptom free days, nights and complete days, respectively during the entire treatment period were to be used as post-baseline measurement.
The percentage of symptom free days, nights and complete days were computed as follows: Sum of symptom free days, nights or complete days, respectively during a measurement period (baseline, post-baseline, respectively) divided by the duration (days) of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	149	144	148	
Units: percentage				
arithmetic mean (standard deviation)	17.36 (± 31.021)	23.89 (± 29.268)	19.27 (± 33.714)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.089
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	5.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	12.12

Secondary: Symptom-free nights

End point title	Symptom-free nights

End point description:

Symptom free nights were defined as nights with a daily morning total asthma score of 0.For symptom free days, nights and complete days, the sum of all symptom free days, nights and complete days, respectively during the run-in period were to be used as baseline and the sum of symptom free days, nights and complete days, respectively during the entire treatment period were to be used as post-baseline measurement.
The percentage of symptom free days, nights and complete days were computed as follows:
Sum of symptom free days, nights or complete days, respectively during a measurement period (baseline, post-baseline, respectively) divided by the duration (days) of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	150	145	149	
Units: percentage				
arithmetic mean (standard deviation)	14.66 (± 34.175)	14.63 (± 29.866)	16.89 (± 31.348)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.635
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.96
upper limit	8.12

Secondary: Symptom-free days and nights (complete day)

End point title	Symptom-free days and nights (complete day)

End point description:

Symptom free days and nights (complete days) were defined as days with a daily all day asthma score of 0.For symptom free days, nights and complete days, the sum of all symptom free days, nights and complete days, respectively during the run-in period were to be used as baseline and the sum of symptom free days, nights and complete days, respectively during the entire treatment period were to be used as post-baseline measurement.
The percentage of symptom free days, nights and complete days were computed as follows:
Sum of symptom free days, nights or complete days, respectively during a measurement period (baseline, post-baseline, respectively) divided by the duration (days) of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	148	143	148	
Units: percentage				
arithmetic mean (standard deviation)	19.65 (± 32.423)	23.78 (± 29.839)	21.48 (± 34.73)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.207
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	4.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.45
upper limit	11.26

Secondary: Day use of rescue salbutamol

End point title	Day use of rescue salbutamol

End point description:

The sum of all days with day, night or day and night salbutamol usage, respectively during the run-in period was to be used as baseline and the sum of all days with day, night or day and night salbutamol usage, respectively during the entire treatment period was to be used as post-baseline measurement.
The percentage of rescue salbutamol usage days was computed as follows:
Sum of all days with day, night, day and night and any rescue medication during a measurement period (baseline, post-baseline, respectively) divided by the duration [days] of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Each day throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	149	144	148	
Units: percentage				
arithmetic mean (standard deviation)	-13.38 (± 25.538)	-8.71 (± 22.319)	-13.68 (± 27.489)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.133
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	7.18

Notes:

[2] - Change in use of rescue salbutamol (absolute and relative) from baseline is reported here

Secondary: Night use of rescue salbutamol

End point title	Night use of rescue salbutamol

End point description:

The sum of all days with day, night or day and night salbutamol usage, respectively during the run-in period was to be used as baseline and the sum of all days with day, night or day and night salbutamol usage, respectively during the entire treatment period was to be used as post-baseline measurement.
The percentage of rescue salbutamol usage days was computed as follows:
Sum of all days with day, night, day and night and any rescue medication during a measurement period (baseline, post-baseline, respectively) divided by the duration [days] of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Each day throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	150	145	149	
Units: percentage				
arithmetic mean (standard deviation)	-10.62 (± 24.789)	-7.05 (± 21.813)	-10.85 (± 24.73)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.213
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	6.6

Notes:

[3] - Change in use of rescue salbutamol (absolute and relative) from baseline is reported here

Secondary: Day or night use of rescue salbutamol

End point title	Day or night use of rescue salbutamol

End point description:

The sum of all days with day, night or day and night salbutamol usage, respectively during the run-in period was to be used as baseline and the sum of all days with day, night or day and night salbutamol usage, respectively during the entire treatment period was to be used as post-baseline measurement.
The percentage of rescue salbutamol usage days was computed as follows:
Sum of all days with day, night, day and night and any rescue medication during a measurement period (baseline, post-baseline, respectively) divided by the duration [days] of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Each day throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	148	143	148	
Units: percentage				
arithmetic mean (standard deviation)	-15.46 (± 29.572)	-10.96 (± 26.18)	-16.9 (± 29.68)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.288
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.18
upper limit	7.31

Notes:

[4] - Change in use of rescue salbutamol (absolute and relative) from baseline is reported here

Secondary: Asthma control days

End point title	Asthma control days

End point description:

An asthma control day was defined as: An all day total asthma symptom score of 0 and all day without usage of rescue medication.
For the asthma control days the sum of all asthma control days during the run-in period was to be used as baseline and the sum of all asthma control days during the entire treatment period was to be used as post-baseline measurement.
The percentage of asthma control days was computed as follows:
Sum of asthma control days during a measurement period (baseline, post-baseline, respectively) divided by the duration [days] of the respective measurement period multiplied by 100.

End point type	Secondary

End point timeframe:

Throughout the run-in period and the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	148	143	148	
Units: percentage				
arithmetic mean (standard deviation)	20.44 (± 33.034)	24.34 (± 30.121)	22.54 (± 35.165)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator)

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.28
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	10.71

Notes:

[5] - Change in asthma control days (absolute and relative) from baseline is reported here

Secondary: Moderate/severe asthma exacerbations

End point title	Moderate/severe asthma exacerbations

End point description:

The total number of moderate/severe asthma exacerbations and the number of patients with moderate/severe asthma exacerbation during the treatment phase were evaluated

End point type	Secondary

End point timeframe:

Throughout the treatment period

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	150	148	150	
Units: number of subjects	3	1	0	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment B v ITT population - Treatment A
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.622
Method	Fisher exact

Secondary: Proportion of patients achieving the level of "controlled" asthma

End point title	Proportion of patients achieving the level of "controlled" asthma

End point description:

Asthma control was evaluated based on the relevant measurements for assessing asthma control recorded CRF and Spirotel™.
An assessment of asthma control was performed during the run-in period and during the last 14 days of treatment, according to the criteria defined by GINA Guidelines revised 2006.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	ITT population - Treatment A	ITT population - Treatment B	ITT population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	150	148	150	
Units: number of subject	46	45	62	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)

Statistical analysis description:

The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).

Comparison groups	ITT population - Treatment A v ITT population - Treatment B
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999 [6]
Method	Fisher exact

Notes:

[6] - p values are from Fisher's exact test comparing proportion of patients between groups

Secondary: Overnight 12-h urinary cortisol/creatinine ratios

End point title	Overnight 12-h urinary cortisol/creatinine ratios
End point description:	
Only data at Visit 5 are reported here. Data are from 50% of all randomized patients	
End point type	Secondary
End point timeframe:	
At Visit 2 and at Visit 5, in a subset of 50% of each group of patients	

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62	63	62	
Units: µmol/mol				
arithmetic mean (standard deviation)	33.1 (± 28.66)	25.7 (± 23.77)	28.1 (± 19.7)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)
Statistical analysis description:	
The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).	
Comparison groups	safety population - Treatment A v safety population - Treatment B
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.103
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.2
upper limit	1.3

Secondary: Morning serum cortisol

End point title	Morning serum cortisol
End point description:	
Only data at Visit 5 are reported here	
End point type	Secondary
End point timeframe:	
At Visit 2 and at Visit 5	

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	145	149	
Units: nmol/L				
arithmetic mean (standard deviation)	384.8 (± 152.112)	339.82 (± 163.236)	361.28 (± 139.476)	

Statistical analyses

Statistical analysis title	comparison between treatments (B vs A)
Statistical analysis description:	
The analysis is the comparison between CHF 1535 and BDP monotherapy (both administered via a pMDI standard actuator).	
Comparison groups	safety population - Treatment A v safety population - Treatment B
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.84
upper limit	-1.24

Secondary: Blood glucose

End point title	Blood glucose
End point description:	
Only data at Visit 5 are reported here	
End point type	Secondary
End point timeframe:	
At Visit 2 and at Visit 5	

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	149	
Units: mmol/L				
arithmetic mean (standard deviation)	5.01 (± 0.65)	4.97 (± 0.453)	4.99 (± 0.489)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum potassium

End point title	Serum potassium

End point description:

End point type	Secondary

End point timeframe:

At Visit 2 and at Visit 5

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	149	
Units: mmol/L				
arithmetic mean (standard deviation)	4.38 (± 0.412)	4.43 (± 0.43)	4.37 (± 0.387)	

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate

End point title	Heart rate

End point description:

Only post-dose change from baseline in HR, at visit 5, is reported here.

End point type	Secondary

End point timeframe:

At Visits 1, 2, 3, 4, 5

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	147	
Units: bpm				
arithmetic mean (standard deviation)	-1.8 (± 11.21)	-2.4 (± 9.21)	-1.1 (± 10.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic blood pressure

End point title	Systolic blood pressure

End point description:

Only post-dose change from baseline in SBP, at visit 5, is reported here.

End point type	Secondary

End point timeframe:

At each Visit

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	147	
Units: mmHg				
arithmetic mean (standard deviation)	-0.2 (± 7.87)	0.7 (± 9.13)	1.3 (± 8.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic blood pressure

End point title	Diastolic blood pressure

End point description:

Only post-dose change from baseline in DBP, at visit 5, is reported here.

End point type	Secondary

End point timeframe:

At each Visit

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	145	146	147	
Units: mmHg				
arithmetic mean (standard deviation)	0.1 (± 7.65)	0.4 (± 7.51)	0.3 (± 7.59)	

Statistical analyses

No statistical analyses for this end point

Secondary: QT interval by Bazett's

End point title	QT interval by Bazett's

End point description:

Only data 30 min post-dose at Visit 5 corrected by Bazett's formula are reported here

End point type	Secondary

End point timeframe:

pre-dose and 30 min post dose at Visit 2 and Visit 5

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	144	143	146	
Units: msec				
arithmetic mean (standard deviation)	413.3 (± 19.93)	404.5 (± 20.16)	412 (± 20.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: QT interval by Fridericia

End point title	QT interval by Fridericia

End point description:

Only data 30 post-dose at Visit 5 corrected by Fridericia formula are reported here

End point type	Secondary

End point timeframe:

Pre-dose and 30 min post-dose at Visit 2 and at Vist 5

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	144	143	146	
Units: msec				
arithmetic mean (standard deviation)	404.3 (± 15.61)	400.8 (± 15.34)	402.9 (± 15.85)	

Statistical analyses

No statistical analyses for this end point

Secondary: Standard haematology - Hematocrit

End point title	Standard haematology - Hematocrit

End point description:

Only data on Hematocrit at Visit 5 on safety population are reported here. All the other haematologic parameters (red cell count, white cell count, neutrophils, Total lymphocìytes, monocytes, eosinophils, basophils, neutrophils, platelets, hemoglobin) on safety population are comprised and tabulated in the study's results but are not reported here.

End point type	Secondary

End point timeframe:

At Visits 1 and 5

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	138	140	143	
Units: L/L				
arithmetic mean (standard deviation)	0.42 (± 0.031)	0.426 (± 0.034)	0.418 (± 0.033)	

Statistical analyses

No statistical analyses for this end point

Secondary: Standard biochemistry - sodium

End point title	Standard biochemistry - sodium

End point description:

Only sodium levels on Visit 5 are reported here. All the other biochemical parameters (chloride, urea, Creatinine, bilirubin, AST, ALT, GGT, AP, calcium, PHO, cholesterol, triglycerides, CRP) on safety population are comprised and tabulated in the study's results but are not reported here.

End point type	Secondary

End point timeframe:

At Visits 1 and 5

End point values	safety population - Treatment A	safety population - Treatment B	Safety population - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	149	
Units: mmol/l				
arithmetic mean (standard deviation)	140 (± 1.68)	140.1 (± 1.65)	140 (± 1.61)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Visit 2 to Visit 5 (treatment period)

Adverse event reporting additional description:

All adverse events, either reported by the patient, or observed by the Investigator, were recorded in source notes and transcribed into the CRF. The patient was also questioned about any adverse event(s) at each visit. Analysis of safety variables was performed in the safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Treatment A

Reporting group description:

Analysis of safety variables was performed in the safety population. The safety population included all randomised patients who took at least one dose of study medication.

Reporting group title	Treatment B

Reporting group description:

Analysis of safety variables was performed in the safety population. The safety population included all randomised patients who took at least one dose of study medication.

Reporting group title	Treatment C

Reporting group description:

Analysis of safety variables was performed in the safety population. The safety population included all randomised patients who took at least one dose of study medication.

Serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 150 (2.00%)	1 / 148 (0.68%)	0 / 150 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Mild abdominal pain due to alimentary reason		
subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids	Additional description: Mild anal haemorrhoids		
subjects affected / exposed	1 / 150 (0.67%)	0 / 148 (0.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Asthma exacerbation	Additional description: Moderate asthma exacerbation		
subjects affected / exposed	2 / 150 (1.33%)	0 / 148 (0.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 148 (0.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute respiratory viral infection			
subjects affected / exposed	1 / 150 (0.67%)	0 / 148 (0.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 150 (28.67%)	43 / 148 (29.05%)	51 / 150 (34.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 150 (2.67%)	3 / 148 (2.03%)	2 / 150 (1.33%)
occurrences (all)	4	7	2
Tremor			
subjects affected / exposed	2 / 150 (1.33%)	1 / 148 (0.68%)	3 / 150 (2.00%)
occurrences (all)	2	1	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 150 (0.67%)	2 / 148 (1.35%)	3 / 150 (2.00%)
occurrences (all)	1	2	3
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 150 (2.67%)	2 / 148 (1.35%)	2 / 150 (1.33%)
occurrences (all)	4	3	2
Cough			

subjects affected / exposed	3 / 150 (2.00%)	3 / 148 (2.03%)	1 / 150 (0.67%)
occurrences (all)	3	3	2
Infections and infestations			
Pharyngitis			
subjects affected / exposed	8 / 150 (5.33%)	8 / 148 (5.41%)	7 / 150 (4.67%)
occurrences (all)	8	8	7
Nasopharyngitis			
subjects affected / exposed	8 / 150 (5.33%)	7 / 148 (4.73%)	7 / 150 (4.67%)
occurrences (all)	8	8	7
Respiratory tract infection viral			
subjects affected / exposed	6 / 150 (4.00%)	3 / 148 (2.03%)	7 / 150 (4.67%)
occurrences (all)	7	4	7
Respiratory tract infection			
subjects affected / exposed	5 / 150 (3.33%)	6 / 148 (4.05%)	5 / 150 (3.33%)
occurrences (all)	5	7	5
Bronchitis			
subjects affected / exposed	4 / 150 (2.67%)	5 / 148 (3.38%)	6 / 150 (4.00%)
occurrences (all)	4	5	6
Rhinitis			
subjects affected / exposed	1 / 150 (0.67%)	2 / 148 (1.35%)	6 / 150 (4.00%)
occurrences (all)	1	2	7
Acute tonsillitis			
subjects affected / exposed	1 / 150 (0.67%)	1 / 148 (0.68%)	3 / 150 (2.00%)
occurrences (all)	1	1	3
Oral candidiasis			
subjects affected / exposed	1 / 150 (0.67%)	3 / 148 (2.03%)	0 / 150 (0.00%)
occurrences (all)	1	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No limitations or caveats are applicable to this summary of results

Notes: