

**Clinical trial results:**

A phase III, 12-week, multicentre, multinational, randomised, double-blind, double-dummy, 3 arm-parallel group study to test the efficacy of CHF 1535 50/6 microgram (fixed combination of beclomethasone dipropionate plus formoterol fumarate) versus a free combination of beclomethasone dipropionate 50 microgram plus formoterol fumarate 6 microgram and versus a monotherapy of beclomethasone dipropionate 50 microgram, in partly controlled asthmatic children.

Summary

EudraCT number	2009-016757-18
Trial protocol	DE FR HU SK ES BG IT Outside EU/EEA
Global end of trial date	28 September 2012

Results information

Result version number	v1 (current)
This version publication date	31 July 2016
First version publication date	31 July 2016

Trial information**Trial identification**

Sponsor protocol code	CCD-0807-PR-0024
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01475032
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici SpA
Sponsor organisation address	Via Palermo, 26/A, Parma, Italy, 43126
Public contact	Chiesi Clinical Trials, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com
Scientific contact	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)	EMA-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	28 September 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2012
Global end of trial reached?	Yes
Global end of trial date	28 September 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate that CHF 1535 50/6 µg pMDI (daily dose: BDP 200 µg/FF 24 µg) is superior to the corresponding monotherapy with beclomethasone dipropionate 50 µg pMDI (daily dose: BDP 200 µg) and non-inferior relative to the corresponding free combination of beclomethasone dipropionate 50 µg pMDI (daily dose: BDP 200 µg) plus formoterol fumarate 6 µg pMDI (daily dose: FF 24 µg) (all treatments administered via the AeroChamber Plus™ spacer device) in terms of pulmonary function (change from baseline in pre-dose morning FEV1 after a 12-week treatment period) in paediatric patients with "partly controlled" persistent asthma.

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP and FF

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 specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 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	Poland: 185
Country: Number of subjects enrolled	Slovakia: 35
Country: Number of subjects enrolled	Bulgaria: 111
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 108
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Ukraine: 77
Country: Number of subjects enrolled	Romania: 15

Worldwide total number of subjects	638
EEA total number of subjects	487

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)	638
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, 779 patients were screened; of these 638 patients were randomized.

Pre-assignment

Screening details:

Pre-screening visit was performed 3-7 days before screening visit. At screening visit, inclusion/exclusion criteria were assessed, followed by a Run-in period of 2 weeks when patients stopped their current asthma treatment and received BDP 100mcg pMDI.

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:

Placebo was provided to assure a complete double-blind, double-dummy design. The canisters/actuators of CHF 1535 and FF pMDI were of identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A - fixed combination CHF 1535 50/6 µg

Arm description:

Treatment A: CHF 1535 50/6 µg (total daily dose: BDP 200 µg/FF 24 µg)

- 2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device

- 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP 50µg and FF 6 µg

Arm type	Experimental
Investigational medicinal product name	CHF 1535 50/6 µg
Investigational medicinal product code	
Other name	BDP/FF, Fixed combination of beclomethasone dipropionate and formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device

- 2 inhalations twice a day

CHF 1535 50/6 µg=Fixed combination of BDPµg and FF 50µg/6 µg

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

pMDI=pressurised Metered Dose Inhaler

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Extrafine BDP placebo
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations twice a day

Arm title	Treatment B - free combination BDP + FF
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Arm description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)
- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate
FF=Formoterol fumarate

Arm type	Active comparator
Investigational medicinal product name	Beclomethasone dipropionate (BDP)
Investigational medicinal product code	
Other name	Beclomethasone dipropionate, Ventolair
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations twice a day

BDP=Beclomethasone dipropionate
pMDI=pressurised Metered Dose Inhaler

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

Dosage and administration details:

FF 6 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations twice a day.

FF=Formoterol fumarate
pMDI=pressurised Metered Dose Inhaler

Arm title	Treatment C - monotherapy BDP
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Arm description:

Treatment C: (total daily dose: BDP 200 µg)
- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

Arm type	Active comparator
Investigational medicinal product name	Beclomethasone dipropionate (BDP)
Investigational medicinal product code	
Other name	Beclomethasone dipropionate, Ventolair
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations twice a day

BDP=Beclomethasone dipropionate
pMDI=pressurised Metered Dose Inhaler

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	CHF 1535 placebo pMDI
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate
 FF=Formoterol fumarate
 CHF 1535=Fixed combination of BDP and FF
 pMDI=pressurised Metered Dose Inhaler

Number of subjects in period 1	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP
Started	211	213	214
Completed	208	205	204
Not completed	3	8	10
Consent withdrawn by subject	2	4	6
inclusion/exclusion criteria not met	-	2	2
Technical issues: metered dose inhaler & spacer	1	1	1
Lost to follow-up	-	1	-
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment A - fixed combination CHF 1535 50/6 µg
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Reporting group description:

Treatment A: CHF 1535 50/6 µg (total daily dose: BDP 200 µg/FF 24 µg)
 - 2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device
 - 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP 50µg and FF 6 µg

Reporting group title	Treatment B - free combination BDP + FF
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Reporting group description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)
 - 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
 - 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

Reporting group title	Treatment C - monotherapy BDP
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Reporting group description:

Treatment C: (total daily dose: BDP 200 µg)
 - 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
 - 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

Reporting group values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP
Number of subjects	211	213	214
Age categorical Units: Subjects			
5-8 years	98	95	95
9-12 years	112	113	114
not recorded	1	5	5
Gender categorical Units: Subjects			
Female	78	69	71
Male	132	139	138
not recorded	1	5	5
Race Units: Subjects			
White	208	207	207
Asian	0	0	1
Other	1	1	1
Not Available	1	0	0
Not part of ITT	1	5	5

Reporting group values	Total		
Number of subjects	638		

Age categorical Units: Subjects			
5-8 years	288		
9-12 years	339		
not recorded	11		
Gender categorical Units: Subjects			
Female	218		
Male	409		
not recorded	11		
Race Units: Subjects			
White	622		
Asian	1		
Other	3		
Not Available	1		
Not part of ITT	11		

End points

End points reporting groups

Reporting group title	Treatment A - fixed combination CHF 1535 50/6 µg
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Reporting group description:

Treatment A: CHF 1535 50/6 µg (total daily dose: BDP 200 µg/FF 24 µg)
- 2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day

BDP=Beclomethasone dipropionate

FF=Formoterol fumarate

CHF 1535=Fixed combination of BDP 50µg and FF 6 µg

Reporting group title	Treatment B - free combination BDP + FF
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Reporting group description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)
- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day

BDP = Beclomethasone dipropionate

FF=Formoterol fumarate

Reporting group title	Treatment C - monotherapy BDP
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Reporting group description:

Treatment C: (total daily dose: BDP 200 µg)
- 2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device
- 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day

Primary: 1_FEV1 change from baseline to end of treatment (week 12)

End point title	1_FEV1 change from baseline to end of treatment (week 12)
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End point description:

Pre-dose morning FEV1.

Shown value is the mean change from baseline, after 12 weeks of treatment.

End point type	Primary
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End point timeframe:

Baseline to end of treatment (Week 12).

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194 ^[1]	193 ^[2]	192 ^[3]	
Units: liters				
arithmetic mean (standard deviation)	0.153 (± 0.231)	0.194 (± 0.294)	0.135 (± 0.248)	

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

Statistical analysis title	Comparison between treatments (A vs C)
Statistical analysis description:	
Primary endpoint analysis: adjusted mean difference between treatments at week 12.	
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.482
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.07

Statistical analysis title	Comparison between treatments (A vs B)
Statistical analysis description:	
Primary endpoint analysis: adjusted mean difference between treatments at week 12.	
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.099
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	0.008

Secondary: 2a_FEV1 change from baseline to week 4, 8

End point title	2a_FEV1 change from baseline to week 4, 8
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to week 4, 8. For statistical analysis in relation to week12, see primary endpoint.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	210 ^[4]	208 ^[5]	209 ^[6]	
Units: liters				
arithmetic mean (standard deviation)				
Week 4	0.135 (± 0.245)	0.143 (± 0.233)	0.125 (± 0.244)	
Week 8	0.177 (± 0.232)	0.178 (± 0.239)	0.155 (± 0.249)	
Week 12	0.153 (± 0.231)	0.194 (± 0.294)	0.135 (± 0.248)	

Notes:

[4] - ITT population

For week 4 N=197

For week 8 N=197

For week 12 N=194

[5] - ITT population

For week 4 N=196

For week 8 N=193

For week 12 N=193

[6] - ITT population

For week 4 N=191

For week 8 N=192

For week 12 N=192

Statistical analyses

Statistical analysis title	Comparison between treatments at week 4 (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.527
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.063

Statistical analysis title	Comparison between treatments at week 8 (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.317
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.071

Statistical analysis title	Comparison between treatments at week 4 (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.965
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.046

Statistical analysis title	Comparison between treatments at week 8 (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.977
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	0.001

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.048

Secondary: 2b_FVC change from baseline to week 4, 8, 12

End point title	2b_FVC change from baseline to week 4, 8, 12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 4, 8, 12.	

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	210 ^[7]	208 ^[8]	209 ^[9]	
Units: liters				
arithmetic mean (standard deviation)				
Week 4	0.099 (± 0.256)	0.119 (± 0.22)	0.123 (± 0.265)	
Week 8	0.161 (± 0.274)	0.152 (± 0.232)	0.153 (± 0.24)	
Week 12	0.139 (± 0.261)	0.166 (± 0.275)	0.14 (± 0.25)	

Notes:

[7] - ITT population
For week 4 N=197
For week 8 N=197
For week 12 N=193
[8] - ITT population
For week 4 N=194
For week 8 N=191
For week 12 N=191
[9] - ITT population
For week 4 N=190
For week 8 N=191
For week 12 N=191

Statistical analyses

Statistical analysis title	Comparison between treatments at week 4 (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.477
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.031

Statistical analysis title	Comparison between treatments at week 8 (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.063

Statistical analysis title	Comparison between treatments at week 12 (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.994
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.052

Statistical analysis title	Comparison between treatments at week 4 (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.677
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	0.039

Statistical analysis title	Comparison between treatments at week 8 (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.066

Statistical analysis title	Comparison between treatments at week 12 (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.282
Method	Mixed Model for Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.023

Secondary: 3a_Morning PEF - change from baseline to end of treatment (week 12)

End point title	3a_Morning PEF - change from baseline to end of treatment (week 12)
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End point description:

Pre-dose morning PEF was recorded on the electronic peak flow meter during each inter-visit period in the randomised population.

End point type	Secondary
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End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199 ^[10]	199 ^[11]	199 ^[12]	
Units: liters/min				
arithmetic mean (standard deviation)	18.73 (± 27.28)	14.83 (± 31.38)	9.13 (± 30.6)	

Notes:

[10] - ITT population

[11] - ITT population

[12] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
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Statistical analysis description:

Only morning PEF measurements performed before morning study medication intake were considered.

Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
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Number of subjects included in analysis	398
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.002
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Method	ANCOVA
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Parameter estimate	Adjusted mean difference
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Point estimate	8.904
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	3.296
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upper limit	14.512
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Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.336
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	2.751
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.861
upper limit	8.362

Secondary: 3b_Evening PEF - change from baseline to end of treatment (week 12)

End point title	3b_Evening PEF - change from baseline to end of treatment (week 12)
End point description:	Pre-dose evening PEF was recorded on the electronic peak flow meter during each inter-visit period in the randomised population.
End point type	Secondary
End point timeframe:	Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199 ^[13]	199 ^[14]	199 ^[15]	
Units: liters/minute				
arithmetic mean (standard deviation)	12.4 (± 29.02)	11.37 (± 32.4)	6.7 (± 28.99)	

Notes:

[13] - ITT population

[14] - ITT population

[15] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Statistical analysis description:	Only evening PEF measurements performed before evening study medication intake were considered.
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	5.574
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.062
upper limit	11.21

Statistical analysis title	Change from baseline to entire treatment (A vs B)
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Statistical analysis description:

Only evening PEF measurements performed before evening study medication intake were considered.

Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.919
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.294
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.344
upper limit	5.932

Secondary: 4_PEF - change from baseline in daily variability

End point title	4_PEF - change from baseline in daily variability
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196 ^[16]	192 ^[17]	194 ^[18]	
Units: percent				
arithmetic mean (standard deviation)	-1.79 (± 6.73)	-1.01 (± 7.57)	-0.43 (± 6.39)	

Notes:

[16] - ITT population

[17] - ITT population

[18] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-1.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.051
upper limit	-0.184

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.454
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.292
upper limit	0.578

Secondary: 5a_Asthma symptom score - daytime - change from baseline

End point title	5a_Asthma symptom score - daytime - change from baseline
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End point description:

Asthma symptom score was recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening.

Shown value is the mean change from baseline, after 12 weeks of treatment.

End point type	Secondary
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End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208 ^[19]	205 ^[20]	207 ^[21]	
Units: asthma symptom score				
arithmetic mean (standard deviation)	-0.53 (± 1.12)	-0.48 (± 0.98)	-0.51 (± 1.07)	

Notes:

[19] - ITT population

[20] - ITT population

[21] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.646
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.227
upper limit	0.141

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF

Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.571
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.237
upper limit	0.131

Secondary: 5b_Asthma symptom score - evening - change from baseline

End point title	5b_Asthma symptom score - evening - change from baseline
End point description: Asthma symptom scores was recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. Shown value is the mean change from baseline, after 12 weeks of treatment.	
End point type	Secondary
End point timeframe: Baseline to end of treatment (week 12); entire treatment period.	

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	207 ^[22]	206 ^[23]	207 ^[24]	
Units: asthma symptom score				
arithmetic mean (standard deviation)	-0.41 (± 1.05)	-0.29 (± 0.92)	-0.36 (± 1)	

Notes:

[22] - ITT population

[23] - ITT population

[24] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.499
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.235
upper limit	0.114

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment B - free combination BDP + FF v Treatment A - fixed combination CHF 1535 50/6 µg
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.213
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.285
upper limit	0.064

Secondary: 6_Asthma symptom-free days - change from baseline

End point title	6_Asthma symptom-free days - change from baseline
End point description:	
Asthma symptom scores were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. An asthma symptom-free day is a day with total day-time and night-time asthma symptom scores = 0.	
Shown value is the mean change from baseline, after 12 weeks of treatment.	
End point type	Secondary
End point timeframe:	
Baseline to end of treatment (week 12); entire treatment period.	

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208 ^[25]	206 ^[26]	206 ^[27]	
Units: days				
arithmetic mean (standard deviation)	22.01 (± 33.35)	25.44 (± 30.71)	23.39 (± 31.19)	

Notes:

[25] - ITT population

[26] - ITT population

[27] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.734
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.353
upper limit	4.475

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.428
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-2.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.604
upper limit	3.226

Secondary: 7_Rescue medication use - change from baseline

End point title	7_Rescue medication use - change from baseline
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End point description:

Use of rescue medication (number of salbutamol puffs) were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. The recorded data was downloaded and checked by the investigator at each visit.

Shown value is the adjusted mean change from baseline (number of puffs per day), after 12 weeks of

treatment.

End point type	Secondary
End point timeframe:	Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	207 ^[28]	204 ^[29]	205 ^[30]	
Units: number of puffs per day				
arithmetic mean (standard deviation)	-0.18 (± 0.77)	-0.09 (± 0.71)	-0.17 (± 0.87)	

Notes:

[28] - ITT population

[29] - ITT population

[30] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.857
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.151
upper limit	0.126

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.402
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.059

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.198
upper limit	0.079

Secondary: 8_Rescue medication-free days - percentage - change from baseline

End point title	8_Rescue medication-free days - percentage - change from baseline
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End point description:

Use of rescue medication (number of salbutamol puffs) were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening. The recorded data was downloaded and checked by the investigator at each visit.

Shown value is the mean change from baseline (percentage of rescue medication use-free days), after 12 weeks of treatment.

End point type	Secondary
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End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208 ^[31]	206 ^[32]	206 ^[33]	
Units: days				
arithmetic mean (standard deviation)	16.41 (± 28.31)	13.17 (± 26.78)	11.76 (± 31.18)	

Notes:

[31] - ITT population

[32] - ITT population

[33] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.077
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	3.819

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.417
upper limit	8.054

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.21
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	2.704
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.529
upper limit	6.937

Secondary: 9_Asthma control days - change from baseline

End point title	9_Asthma control days - change from baseline
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End point description:

Asthma control days were recorded in the portable peak flow meter (used as an electronic diary) twice daily in the morning and in the evening.

An asthma control day is a day with total day-time and night-time asthma symptom scores = 0 and no puffs of rescue medication taken.

Shown value is the percentage asthma control days, presented as the adjusted mean change from baseline, after 12 weeks of treatment.

End point type	Secondary
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End point timeframe:

Baseline to end of treatment (week 12); entire treatment period.

End point values	Treatment A - fixed combination CHF 1535 50/6 µg	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208 ^[34]	206 ^[35]	206 ^[36]	
Units: days				
arithmetic mean (standard deviation)	22.25 (± 32.59)	26.48 (± 31.88)	22.44 (± 31.44)	

Notes:

[34] - ITT population

[35] - ITT population

[36] - ITT population

Statistical analyses

Statistical analysis title	Change from baseline to entire treatment (A vs C)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment C - monotherapy BDP
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.233
upper limit	5.801

Statistical analysis title	Change from baseline to entire treatment (A vs B)
Comparison groups	Treatment A - fixed combination CHF 1535 50/6 µg v Treatment B - free combination BDP + FF
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.338
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-2.695
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.216
upper limit	2.826

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Run-in phase (week -2) to Follow-up (week 14)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Treatment A - fixed combination BDP/FF
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Reporting group description:

Treatment A: (total daily dose: BDP 200 µg/FF 24 µg)

2 inhalations CHF 1535 50/6 µg pMDI via AeroChamber Plus spacer device + 2 inhalations of BDP placebo pMDI with AeroChamber Plus spacer device, twice a day.

Reporting group title	Treatment B - free combination BDP + FF
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Reporting group description:

Treatment B: (total daily dose: BDP 200 µg + FF 24 µg)

2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device + 2 inhalations of FF 6 µg pMDI with AeroChamber Plus spacer device, twice a day.

Reporting group title	Treatment C - monotherapy BDP
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Reporting group description:

Treatment C: (total daily dose: BDP 200 µg)

2 inhalations BDP 50 µg pMDI via AeroChamber Plus spacer device + 2 inhalations of CHF 1535 placebo pMDI with AeroChamber Plus spacer device, twice a day.

Serious adverse events	Treatment A - fixed combination BDP/FF	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 211 (0.95%)	2 / 210 (0.95%)	1 / 213 (0.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 211 (0.00%)	1 / 210 (0.48%)	0 / 213 (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
Head injury			
subjects affected / exposed	0 / 211 (0.00%)	1 / 210 (0.48%)	0 / 213 (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
Gastrointestinal disorders			

Enteritis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 210 (0.00%)	0 / 213 (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
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 211 (0.47%)	0 / 210 (0.00%)	0 / 213 (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
Renal and urinary disorders			
Post streptococcal glomerulonephritis			
subjects affected / exposed	0 / 211 (0.00%)	0 / 210 (0.00%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Tonsillitis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 210 (0.00%)	0 / 213 (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: 5 %

Non-serious adverse events	Treatment A - fixed combination BDP/FF	Treatment B - free combination BDP + FF	Treatment C - monotherapy BDP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 211 (29.86%)	61 / 210 (29.05%)	56 / 213 (26.29%)
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: "Asthma" is the Preferred Term of the event "asthma exacerbation".		
subjects affected / exposed	11 / 211 (5.21%)	7 / 210 (3.33%)	11 / 213 (5.16%)
occurrences (all)	12	8	12
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 211 (7.58%)	9 / 210 (4.29%)	11 / 213 (5.16%)
occurrences (all)	23	10	13
Pharyngitis			

subjects affected / exposed	5 / 211 (2.37%)	16 / 210 (7.62%)	8 / 213 (3.76%)
occurrences (all)	5	17	8

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.

None.

Notes: